PROTOCOL TP0001 AMENDMENT 3

A MULTICENTER, OPEN-LABEL, MULTIPLE-DOSE STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF UCB7665 IN SUBJECTS WITH PRIMARY IMMUNE THROMBOCYTOPENIA

PHASE 2

EudraCT Number: 2015-003984-12

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ADA	anti-drug antibodies
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUEC	area under the effect curve
BAFF	B cell activating factor
BP	blood pressure
CDMS	clinical data management system
CHMP	Committee for Medicinal Products for Human Use
CPM	Clinical Project Manager
CPMP	Committee for Proprietary Medicinal Products
CRO	contract research organization
CSF	cerebrospinal fluid
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCP	Data Cleaning Plan
DNA	deoxyribonucleic acid
DMC	Data Monitoring Committee
ECG	electrocardiogram
EDC	electronic data capture
EMA	European Medicines Agency
eCRF	electronic Case Report form
ES	Enrolled Set
EOS	End of Study
FAS	Full Analysis Set
FcRn	neonatal Fc receptor for IgG
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
[redacted]	[redacted]

HbA1c	glycosylated hemoglobin
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IGRA	interferon-gamma release assay
IMP	investigational medicinal product
INR	International Normalized Ratio
IRB	Institutional Review Board
ITP	immune thrombocytopenia
ITP-BAT	ITP-specific Bleeding Assessment Tool
iv	intravenous
IVIg	intravenous immunoglobulin
IXRS	interactive voice/web response system
LTB	latent tuberculosis
LLOQ	lower limit of quantification
LP	lumbar puncture
MCID	minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
miRNA	micro ribonucleic acid
NFI-MS	Neurological Fatigue Index for Multiple Sclerosis
NTMBI	nontuberculosis myobacterial infection
NOAEL	no observed adverse effect level
PD	pharmacodynamic(s)
PDILI	potential drug-induced liver injury
PD-PPS	Pharmacodynamic Per Protocol Set
PEF	peak expiratory flow
PK	pharmacokinetic(s)

PK-PPS	Pharmacokinetic Per Protocol Set
PLEX	plasma exchange
PPS	Per Protocol Set
PRO	Patient Reported Outcome
PS	Patient Safety
PTT	partial thromboplastin time
QTc	corrected QT interval
RNA	ribonucleic acid
[redacted]	[redacted]
SAE	serious adverse event
SAP	Statistical Analysis Plan
sc	subcutaneous
SD	standard deviation
SMOG	skin (S), visible mucosae (M), and organs (O), with gradation of severity
SOP	Standard Operating Procedure
SS	Safety Set
TB	tuberculosis
TEAE	treatment-emergent adverse event
TPO-R	thrombopoietin-receptor
ULN	upper limit of normal

1 SUMMARY

Primary immune thrombocytopenia (ITP) is a disease which is characterized by an isolated low platelet count (thrombocytopenia) and the absence of other causes of thrombocytopenia. It is an autoimmune disease which is characterized by specific autoantibodies directed against platelets. There is no causal treatment. Treatment options include immunosuppressive therapy, immunoglobulin therapy, and splenectomy. There is an unmet medical need for new treatment options due to significant side effects, significant risks, and significant complexity of existing therapy.

The neonatal major histocompatibility complex (MHC)-class-I-like neonatal Fc receptor for IgG (FcRn) binds immunoglobulin G (IgG), thereby preventing IgG from intracellular lysosomal degradation. UCB7665 is a humanized IgG4 monoclonal antibody that has been specifically designed to inhibit IgG binding to FcRn with the aim to reduce the concentration of pathogenic IgG in patients with IgG autoantibody mediated diseases, including ITP. Thereby, it represents a potential new mode of action to target the underlying pathomechanism of ITP and could enhance the still limited treatment options.

TP0001 is a Phase 2, multicenter, open-label, multiple-dose, multiple-arm study to evaluate the safety, tolerability, and efficacy of UCB7665 administered as subcutaneous (sc) doses of 4mg/kg, 7mg/kg, 10mg/kg, 15mg/kg, and 20mg/kg (resulting in cumulative doses of 20mg/kg, 21mg/kg, 20mg/kg, 15 mg/kg and 20mg/kg respectively), in subjects ≥18 years of age with persistent (>3 months up to 12 months after diagnosis) or chronic (more than 12 months after diagnosis) primary ITP.

The study is planned to be conducted at up to approximately 45 sites in Europe and Australia. A total of approximately 48 to 66 subjects (dependent on emerging safety data and corresponding DMC recommendation) are planned to enter the Dosing Period in the study. The maximum study duration for study participation for an individual subject is approximately 16 weeks.

The study is intended to evaluate 5 dose arms of UCB7665. Subjects in Dose Arm 1 will receive 5 doses of UCB7665 4mg/kg sc at 1 week intervals, subjects in Dose Arm 2 will receive 3 doses of UCB7665 7mg/kg sc at 1 week intervals, subjects in Dose Arm 3 will receive 2 doses of UCB7665 10mg/kg sc at 1 week intervals, Dose Arm 4 will receive 1 dose of UCB7665 15mg/kg sc and Dose Arm 5 will receive 1 dose of UCB7665 20mg/kg sc.

The study consists of a Screening Period (up to 4 weeks), Dosing Period of 1 day to 4 weeks where dosing arms are introduced sequentially, and an Observation Period of 8 weeks. The Screening Visit corresponds to Visit 1 of the study. The Dosing Period will commence at Visit 2 (Baseline Visit), with dosing visits scheduled at weekly intervals for Dose Arms 1, 2 and 3 and only one visit scheduled for Dose Arms 4 and 5. The Observation Period will start after the last dose administration (or only dose administration for Dose Arms 4 and 5) with a visit scheduled 3 days after the last dosing and weekly visits thereafter (ie, weekly after last or only dose) for a period of 8 weeks. The End-of-Study Visit will be performed at the end of the Observation Period, ie, 8 weeks after the last or only dose of investigational medicinal product (IMP).

The first 6 subjects will be enrolled in Dose Arm 1 only. While recruitment is ongoing, safety data for the first 3 subjects up to 7 days after the last dose of the third subject will be reviewed by the Data Monitoring Committee (DMC). During a second DMC meeting, all available safety data up to cut off date defined as 7 days after the last dose of the sixth subject will be reviewed.

Following this review, the DMC will make a recommendation on whether to open Dose Arm 2 for enrollment. Once the DMC has advocated the initiation of Dose Arm 2, the subsequent subjects for the first 2 arms will be randomly assigned in 1:1 ratio to either Dose Arm 1 or Dose Arm 2 using an interactive voice/web response system (IXRS). Once 15 subjects are enrolled in Dose Arm 1, the subsequently enrolled subjects will be enrolled in Dose Arm 2.

After the safety data review of at least 6 subjects in Dose Arm 2 is done, the DMC will make a recommendation on whether to open Dose Arm 3 for enrollment. Once the DMC has advocated the initiation of Dose Arm 3 and the enrollment of 15 subjects into Dose Arm 2 has been completed, the subsequent subjects will be assigned to Dose Arm 3 only. After every third subject has been enrolled, DMC will review all available safety data up to cut off date defined as 7 days after the last dose of the respective subject. Depending on the emerging safety data of 6 subjects in Dose Arm 3, the DMC will recommend whether to open Dose Arm 4 for enrollment or to include additional subjects in Dose Arm 3. If applicable, this procedure is planned to be repeated stepwise in groups of 3 subjects. A maximum of 12 subjects are planned for Dose Arm 3. The DMC will recommend to open Dose Arm 4 for enrollment in a subsequent DMC meeting, if applicable.

Once the DMC has advocated the initiation of Dose Arm 4, the enrollment of Dose Arm 3 will be closed and all subsequently enrolled subjects will be assigned to Dose Arm 4. After every third subject that has been enrolled, DMC will review all available safety data up to cut off date defined as 7 days after the last dose of the respective subject. Depending on the emerging safety data of 6 subjects in Dose Arm 4, the DMC will recommend whether to open Dose Arm 5 for enrollment or to include additional subjects in Dose Arm 4. If applicable, this procedure is planned to be repeated stepwise in groups of 3 subjects. A maximum of 12 subjects are planned for Dose Arm 4. The DMC will recommend to open Dose Arm 5 for enrollment in a subsequent meeting, if applicable.

Once the DMC has advocated the initiation of Dose Arm 5, the enrollment of Dose Arm 4 will be closed and the subsequently enrolled subjects will be assigned to Dose Arm 5. After every third subject is enrolled, the DMC will review all available safety data up to the cutoff date defined as 7 days after the dosing of the third subject in Dose Arm 4. Depending on the emerging safety data of 6 subjects in Dose Arm 5, the DMC will recommend to include additional subjects in Dose Arm 5. If applicable, this procedure is planned to be done stepwise in groups of 3 subjects. A maximum of 12 subjects may be enrolled in Dose Arm 5.

The DMC may also decide to reduce the number of doses dose arms, to stop a dose arm or not to open a dose arm based on review of safety data during the study. Safety data will also be reviewed on an ongoing basis by clinical research organization (CRO) medical monitor and UCB physician during the study so as to continuously evaluate the safety of subjects.

The primary objective of the study is to evaluate the safety and tolerability of UCB7665 administered by sc infusion in subjects with ITP.

The secondary objective of the study is to assess the clinical efficacy of UCB7665 as measured by the change in platelet count and to assess the pharmacodynamic (PD) effect of UCB7665 as measured by the change in total IgG concentrations in serum. The exploratory objectives include the following: [redacted] to evaluate the clinical efficacy as measured by

the change in ITP bleeding score; to evaluate the effect of UCB7665 on the concentrations of total protein, albumin, α-globulin and β-globulin, IgG subclasses, IgM, IgA, and IgE, and serum and plasma complement levels; to evaluate the emergence of anti-drug antibodies (ADA), ie, anti-UCB7665 antibodies with respect to immunogenicity and pharmacokinetics (PK)/PD; to evaluate the relationship between changes in platelet count and total IgG, IgG subclasses, ITP-specific autoantibodies; and to assess the plasma concentrations of UCB7665 administered by sc infusion.

The primary safety variable is the occurrence of treatment-emergent adverse events (TEAEs). Other safety variables are TEAEs leading to withdrawal of IMP, vital signs, 12-lead electrocardiogram (ECG), laboratory parameters (hematology including coagulation parameters, clinical chemistry, and urinalysis), and concentrations of total protein, albumin, α-globulin, and β-globulin in serum.

Other safety assessments are evaluation of potential drug-induced liver injury (PDILI), using pre-specified criteria for managing any PDILI events in accordance with the Drug Administration (FDA) Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation (Jul 2009).

The following efficacy variables will be assessed: Response (platelet count $\geq 30x10^9$/L and at least 2-fold increase of the Baseline count) during the study and by visit; Complete Response (platelet count $\geq 100x10^9$/L) during the study and by visit; platelet count $\geq 50x10^9$/L during the study and by visit; the maximum value and maximum increase from Baseline in platelet count during the study; value and change from Baseline in platelet count over time; Baseline-corrected area under the effect curve (AUEC) for platelet count; time to Response (time from starting treatment to achievement of Response); time to Complete Response (time from starting treatment to achievement of Complete Response); time to achieving platelet count $\geq 50x10^9$/L; duration of Response (measured from achievement of Response to loss of Response [defined as platelet count below $30x10^9$/L or less than 2-fold increase of Baseline platelet count]); duration of Complete Response (measured from achievement of Complete Response to loss of Complete Response [defined as platelet count below $100x10^9$/L]); duration of platelet count $\geq 50x10^9$/L (measured from achievement of platelet count $\geq 50x10^9$/L to reduction of platelet count below $50x10^9$/L); Clinical Response (defined as platelet count $\geq 30x10^9$/L and at least 2-fold increase from Baseline value and absence of bleeding); time to Clinical Response (time from starting treatment to achievement of Clinical Response); duration of Clinical Response (measured from achievement of Clinical Response to loss of Clinical Response [loss of Clinical Response defined as platelet count $<30x10^9$/L or less than 2-fold increase from Baseline platelet count or presence of bleeding]); Complete Clinical Response (defined as platelet count $\geq 100x10^9$/L and absence of bleeding); time to Complete Clinical Response (time from starting treatment to achievement of Complete Clinical Response); duration of Complete Clinical Response (measured from achievement of Complete Clinical Response to loss of Complete Clinical Response [loss of Complete Clinical Response defined as platelet count $<100x10^9$/L or presence of bleeding]); no Clinical Response (defined as platelet count $<30x10^9$/L and less than 2-fold increase from Baseline or presence of bleeding); ITP bleeding score over time; and Patient Reported Outcome (PRO), ie, Neurological Fatigue Index for Multiple Sclerosis (NFI-MS) summary score over time. Plasma concentration of UCB7665 over time will be assessed as the PK variable. The PD variables are minimum value and maximum decrease in total IgG concentration during the study; IgG subclass concentrations; and ITP-specific autoantibody

[redacted] in serum over time. Other immunological variables to be evaluated are total IgA, IgE, and IgM levels; serum (C3 and C4) and plasma (C3a and C5a) complement levels; ADA status (negative/positive) and relative mass units; exploratory safety biomarkers [redacted] and B cell activating factor (BAFF) levels; B and T lymphocytes; and cytokines (for subjects experiencing infusion reactions).

During this study, subjects will also have the option of providing additional informed consent for exploratory deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) (ie, messenger RNA [mRNA] and micro RNA [miRNA]) analyses. Participation in this additional portion of the study is optional and does not preclude subject's eligibility for participation in the main study. The additional genomic samples must not be collected if the subject has not consented to participate in this exploratory genomic substudy.

Prior to this amendment, a protocol amendment 2 with a dose arm 4mg/kg twice weekly was planned, however the corresponding protocol amendment 2 was not implemented. These changes are highlighted in Section 18.8.

2 INTRODUCTION

The neonatal MHC-class-I-like FcRn recycles immunoglobulin and albumin from most cells and transports it bi-directionally across epithelial barriers to affect systemic and mucosal immunity. It was shown that FcRn rescues both IgG and albumin from intracellular lysosomal degradation by recycling it from the sorting endosome to the cell surface (Anderson et al, 2006). With respect to IgG, this is achieved by interaction of IgG with the receptor, FcRn. Thus, in effect FcRn salvages IgG, saving it from degradation and returning it to circulation. Albumin is similarly recycled by FcRn, though via a different binding site on the FcRn molecule. It has been shown that knockout or blockade of FcRn removes this recycling resulting in endosomal catabolism of IgG and a marked reduction of IgG concentrations in both the vascular and extravascular (tissue) compartments. In effect, blockade of FcRn accelerates removal of endogenous IgG and, if the albumin binding site is also blocked, potentially of albumin.

Immune thrombocytopenia is a clinical disorder in which thrombocytopenia manifests as a bleeding tendency, purpura, or petechiae. Autoantibodies against platelet antigens are considered to be a hallmark of ITP. Production of pathogenic IgG autoantibodies by plasma cells is accepted as the central underlying pathophysiological mechanism in a number of IgG-mediated autoimmune diseases, which includes ITP. In some patients, antibodies recognize antigens derived from a single glycoprotein, whereas in others, antibodies recognize multiple glycoproteins. The spleen is the key organ in the pathophysiology of ITP, not only because platelet autoantibodies are formed in the white pulp, but also because mononuclear macrophages in the red pulp destroy immunoglobulin-coated platelets (Sandler, 2000).

Recently, new definitions for the phases of the disease were introduced (Rodeghiero et al, 2009). Based on the time from diagnosis, the first phase (up to 3 months) is the "newly-diagnosed ITP," phase 2 (>3 months up to 12 months) is the "persistent phase," and after 12 months the "chronic phase" starts. These phases also reflect the line of treatment.

The major goal for treatment of ITP is to achieve a platelet count that prevents major bleeding rather than correcting the platelet count to normal levels. The management of ITP should be

tailored to the individual patient and it is rarely indicated in those with platelet counts above $50x10^9$/L in the absence of bleeding, trauma, surgery, or high risk factors (eg, patients on anticoagulation therapy) (EMA/CHMP/153191/2013, 2014). However, there is general agreement that adults with a count of $<30x10^9$/L with bleeding at diagnosis require treatment.

The first line of treatment for newly-diagnosed ITP is generally agreed and based on the use of corticosteroids and intravenous immunoglobulin (IVIg). Patients who fail to respond or who relapse face the options of treatment with second line drug therapy or splenectomy but there is no clear evidence to support the best approach. Splenectomy can provide long-term efficacy in around 60% of cases and recent guidelines suggest considering a splenectomy after 12 months. Splenectomy is an invasive procedure associated with acute complications due to thrombocytopenia (like bleeding events) and long-term complications from loss of splenic functions. Asplenic subjects are at increased risk of life-threatening infections. Splenectomy may increase morbidity from venous thromboembolism or atherosclerosis (Ghanima et al, 2012). Second line drug therapies include high-dose dexamethasone or methylprednisolone; high-dose IVIg or anti-D Ig; vinca alkaloids; dapsone and danazol; the immunosuppressants cyclophosphamide, azathioprine, and cyclosporine; or mycophenolate mofetil and *Helicobacter pylori* eradication if applicable. The anti-CD20 monoclonal antibody rituximab - even if not licensed for the treatment of ITP - and the thrombopoietin-receptor (TPO-R) agonists are considered as second line as well as third line options.

Treatment-related morbidity is also a significant contributing factor; long-term courses of corticosteroids, other immunosuppressive medications, or splenectomy may be required to maintain a platelet count in a safe range in patients with chronic treatment-resistant ITP and morbidity and mortality can be related to treatment, reflecting the complications of therapy with corticosteroids or splenectomy. There thus remains a considerable unmet medical need for new therapeutic options in the treatment of ITP. UCB7665 may become the first targeted therapy to remove the autoantibodies to platelets providing a safe and tolerable alternative for patients with persistent or chronic ITP in acute or maintenance therapy.

UCB7665 is a humanized anti-FcRn monoclonal antibody that has been specifically designed to inhibit IgG binding to FcRn without inhibiting albumin binding to FcRn. UCB7665 is being developed as an inhibitor of FcRn activity with the aim to reduce the concentration of pathogenic IgG in patients with IgG autoantibody mediated diseases. UCB7665 was derived from a rat antibody with specificity for human FcRn by engineering the rat antibody into a humanized IgG4P format. The construct encoding UCB7665 was created by grafting the complementarity-determining region (CDRs) from the parental rat heavy and light chain variable regions onto a human IgG4P and kappa chain genetic background, respectively. The resulting UCB7665 contains only the original rat sequences that comprise the antigen binding site; all other sequences are human in origin.

UCB7665 is being evaluated in a study in healthy subjects (UP0018) with escalation of single intravenous (iv) and sc dosing. The outcomes are safety, tolerability, PK, and the PD effect on total IgG levels. Doses of UCB7665 1, 4, and 7mg/kg have been administered in 3 cohorts for the iv route and in 3 cohorts for the sc route. Preliminary information from the study is summarized below.

In the iv cohorts, the maximum tolerated dose was reached at UCB7665 4mg/kg. The most common TEAEs in all iv cohorts were mild to moderate gastrointestinal disturbances (nausea, vomiting, and diarrhea) and mild to severe headaches.

In the sc cohorts, a comparable tolerability profile was seen with UCB7665 7mg/kg sc and 4mg/kg iv. Adverse events of mild to moderate severity for headaches and gastrointestinal disturbances were observed. There were fewer cases of headache and gastrointestinal disturbances in the overall sc cohorts compared to overall iv cohorts.

In 4-week and 13-week toxicity studies with 8-week, treatment-free recovery periods in Cynomolgus monkeys, UCB7665 induced the expected large decreases (75% to 90%) in plasma IgG in all animals which was maintained for the duration of both studies in the majority of the animals, with only minor effects on albumin levels. UCB7665 was well tolerated at the highest dose levels tested of UCB7665 150mg/kg sc and UCB7665 150mg/kg iv administered every 3 days (there was no observed adverse effect level [NOAEL]).

Further information on the PK, PD, and safety profiles for UCB7665 from nonclinical studies, and preliminary safety information from clinical studies (including data from this study), can be obtained from the current version of the UCB7665 Investigator's Brochure.

Subjects will also have the option of providing additional informed consent for exploratory DNA and RNA (mRNA and miRNA) analyses as described in Section 5.1.1.

3 STUDY OBJECTIVE(S)

3.1 Primary objective

The primary objective of the study is:

- To evaluate the safety and tolerability of UCB7665 administered by sc infusion in subjects with ITP

3.2 Secondary objectives

The secondary objectives of this study are:

- To assess the clinical efficacy of UCB7665 as measured by the change in platelet count
- To assess the PD effect of UCB7665 as measured by the change in total IgG concentration in serum

3.3 Exploratory objectives

The exploratory objectives of this study are:

- [redacted]
- To evaluate the clinical efficacy as measured by the change in ITP bleeding score
- To evaluate the effect of UCB7665 on the concentrations of total protein, albumin, α-globulin and β-globulin, IgG subclasses, IgM, IgA, and IgE, and serum and plasma complement levels
- To evaluate the emergence of ADA with respect to immunogenicity and PK/PD

- To evaluate the relationship between changes in platelet count and total IgG, IgG subclasses, ITP-specific autoantibodies
- To assess the plasma concentrations of UCB7665 administered by sc infusion
- To evaluate the genomic components of ITP to understand the molecular etiology, progression, and treatment of the disease, applicable only for subjects consenting to participate in the optional genomic analyses substudy.
- [redacted]

4 STUDY VARIABLES

4.1 Primary variable

The primary safety variable is:

- Occurrence of TEAEs

4.2 Others and exploratory variables

4.2.1 Safety variables

The other safety variables are:

- Vital sign values and change from Baseline over time (systolic and diastolic blood pressure, temperature, pulse rate, respiratory rate, and body weight)
- 12-Lead ECG parameters and change from Baseline over time
- Laboratory values and change from Baseline over time (hematology including coagulation parameters, clinical chemistry, and urinalysis)
- Values and change from Baseline in concentrations of total protein, albumin, α-globulin, and β-globulin over time
- Change from Baseline in exploratory safety biomarkers over time
- TEAEs leading to withdrawal of IMP

4.2.2 Efficacy variables

The efficacy variables are:

- Response during the study: platelet count $\geq 30 \times 10^9$/L and at least 2-fold increase of the Baseline count
- Complete Response during the study: platelet count $\geq 100 \times 10^9$/L
- Platelet count $\geq 50 \times 10^9$/L during the study
- Response by visit
- Complete Response by visit
- Platelet count $\geq 50 \times 10^9$/L by visit

- The maximum value and maximum increase from Baseline in platelet count during the study
- Value and change from Baseline in platelet count over time
- Baseline-corrected AUEC for platelet count
- Time to Response: time from starting treatment to achievement of Response
- Time to Complete Response: time from starting treatment to achievement of Complete Response
- Time to achieving platelet count $\geq 50x10^9$/L
- Duration of Response: measured from achievement of Response to loss of Response (loss of Response defined as platelet count below $30x10^9$/L or less than 2-fold increase of Baseline platelet count)
- Duration of Complete Response: measured from achievement of Complete Response to loss of Complete Response (loss of Complete Response defined as platelet count below $100x10^9$/L)
- Duration of platelet count $\geq 50x10^9$/L: measured from achievement of platelet count $\geq 50x10^9$/L to reduction of platelet count below $50x10^9$/L
- Clinical Response: platelet count $\geq 30x10^9$/L and at least 2-fold increase from Baseline value and absence of bleeding
- Time to Clinical Response: time from starting treatment to achievement of Clinical Response
- Duration of Clinical Response: measured from achievement of Clinical Response to loss of Clinical Response (loss of Clinical Response defined as platelet count $<30x10^9$/L or less than 2-fold increase from Baseline platelet count or presence of bleeding)
- Complete Clinical Response: platelet count $\geq 100x10^9$/L and absence of bleeding
- Time to Complete Clinical Response: time from starting treatment to achievement of Complete Clinical Response
- Duration of Complete Clinical Response: measured from achievement of Complete Clinical Response to loss of Complete Clinical Response (loss of Complete Clinical Response defined as platelet count $<100x10^9$/L or presence of bleeding)
- No Clinical Response: platelet count $<30x10^9$/L or less than 2-fold increase from Baseline or presence of bleeding
- ITP bleeding score over time
- Value and change from Baseline in NFI-MS summary score over time

4.2.3 Pharmacokinetic variable

The PK variable is:

- Plasma concentration of UCB7665 over time

4.2.4 Pharmacodynamic variables

The PD variables are:

- Minimum value and maximum decrease from Baseline in total IgG concentration during the study
- Value and change from Baseline in total IgG concentrations over time
- Change from Baseline in ITP-specific autoantibody in serum over time: [redacted]
- Change from Baseline in IgG subclass concentrations over time

4.2.5 Other immunological variables

Other immunological variables are:

- Change from Baseline in serum immunoglobulin concentrations (total IgA, IgE, and IgM) over time
- Change from Baseline in serum (C3 and C4) and plasma (C3a and C5a) complement levels over time
- Change from Baseline in exploratory biomarkers relating to mechanism of action, disease activity, treatment response, and clinical outcome
- ADA (anti-UCB7665 antibodies) status (negative/positive) and change from Baseline in relative mass units over time
- Change from Baseline in cytokines over time (for subjects experiencing infusion reactions)
- Change from Baseline in serum BAFF levels over time
- Lymphocyte counts (B and T)

5 STUDY DESIGN

5.1 Study description

This is a Phase 2, multicenter, open-label, multiple-dose, multiple-arm study to evaluate the safety, tolerability, and efficacy of UCB7665 in subjects with primary persistent or chronic ITP.

Dose Arm 1 (15 subjects): UCB7665 4mg/kg sc (5 doses at an interval of 1 week)

Dose Arm 2 (15 subjects): UCB7665 7mg/kg sc (3 doses at an interval of 1 week)

Dose Arm 3 (6 to 12 subjects): UCB7665 10mg/kg sc (2 doses at an interval of 1 week)

Dose Arm 4 (6 to 12 subjects): UCB7665 15mg/kg sc (1 dose)

Dose Arm 5 (6 to 12 subjects): UCB7665 20mg/kg sc (1 dose)

The maximum duration of the study per subject is approximately 16 weeks, consisting of a Screening Period (1 to 28 days), a Dosing Period of 1 to 4 weeks, and an Observation Period of 8 weeks.

Screening Period: The purpose of the Screening Period is to evaluate and confirm the subject's eligibility. During the Screening Visit (Visit 1), subjects will sign a written Informed Consent

form prior to the conduct of any study-related procedures. The use of concomitant medication while in the study will be discussed, and the subject's eligibility will be determined on the basis of the inclusion/exclusion criteria. The Screening Period should not exceed 28 days.

Dosing Period: The first 6 subjects in the study will receive UCB7665 4mg/kg. These subjects in the Dose Arm 1 will not be randomized. While recruitment is still ongoing, safety data for the first 3 subjects up to 7 days after the last dose of the third subject in Dose Arm 1 will be reviewed by the DMC. During a second DMC meeting, all available safety data up to cut off date defined as 7 days after the last dose of the sixth subject in Dose Arm 1 will be reviewed. During these reviews recruitment in the dose arm will not be stopped. Following this review, the DMC will make a decision on whether to open Dose Arm 2 for enrollment. Once DMC has advocated the initiation of Dose Arm 2, the subsequent subjects will be randomly assigned in 1:1 ratio to either Dose Arm 1 or Dose Arm 2 using an IXRS. Once 15 subjects are enrolled in the Dose Arm 1, the remaining subjects will be enrolled in Dose Arm 2.

After the safety data review of at least 6 subjects in Dose Arm 2 is done, the DMC will make a recommendation on whether to open Dose Arm 3 for enrollment. Once the DMC has advocated the initiation of Dose Arm 3 and the enrollment of 15 subjects in Dose Arm 2 has been completed, the subsequent subjects will be assigned to Dose Arm 3 only. After every third subject has been enrolled, the DMC will review all available safety data up to cut off date defined as 7 days after the dosing. Depending on the emerging safety data of 6 subjects in Dose Arm 3, the DMC will recommend whether to open Dose Arm 4 for enrollment or to include additional subjects in Dose Arm 3. If applicable, this step is planned to be done stepwise in groups of 3 subjects. A maximum, 12 subjects will be enrolled in Dose Arm 3. The DMC will recommend to open Dose Arm 4 for enrollment in a subsequent DMC meeting, if applicable.

Once the DMC has advocated the initiation of Dose Arm 4, the enrollment of Dose Arm 3 will be closed and all subsequent subjects will be assigned to Dose Arm 4. After every third subject is enrolled, the DMC will review all available safety data up to the cutoff date defined as 7 days after the dosing. Depending on the emerging safety data of 6 subjects in Dose Arm 4, the DMC will recommend to include additional subjects in Dose Arm 4 or not. If applicable, this step is planned to be done stepwise in groups of 3 subjects. A maximum of 12 subjects may be enrolled in Dose Arm 4. The DMC will recommend to open Dose Arm 5 for enrollment in a subsequent meeting, if applicable.

Once the DMC has advocated the initiation of Dose Arm 5, the enrollment of Dose Arm 4 will be closed and all subsequent subjects will be assigned to Dose Arm 5. After every third subject is enrolled, the DMC will review all available safety data up to the cutoff date defined as 7 days after the dosing. Depending on the emerging safety data of 6 subjects in Dose Arm 5, the DMC will recommend to include additional subjects in Dose Arm 5. If applicable, this step is planned to be done stepwise in groups of 3 subjects. A maximum of 12 subjects may be enrolled in Dose Arm 5.

At least 11 interim analyses will be performed. Based on the interim analyses, the DMC will assess the safety of UCB7665, determine whether to initiate subsequent dose arms and may decide to adapt the dose regimen. Planned dosing may be discontinued for all subjects in a dose arm (see Section 6.5). Refer to Section 14.7 for details.

In case the DMC recommends reducing the number of doses (infusions) for any of the predefined dose arms (as applicable) based on review of safety data, then the additional dose arms receiving a reduced number of doses will be considered as additional new dose arms for the study.

Observation Period: Following the last dose (or only dose administration for Dose Arms 4 and 5), a visit will be scheduled 3 days postdose and weekly thereafter for 8 weeks to collect safety and efficacy data.

5.1.1 Exploratory genomic analyses

During this study, subjects will also have the option of providing additional informed consent for exploratory DNA and RNA analyses. Participation in this additional portion of the study is optional and does not preclude subject's eligibility for participation in the main study. The additional genomic samples must not be collected if the subject has not consented to participate in this exploratory genomic substudy.

Once subject provides consent, through a separate informed consent form, blood samples will be drawn as follows:

For DNA: Blood samples will be collected at Baseline (Visit 2) for all dose arms. Subsequent blood sample will be collected prior to the last dose (ie, Visit 7 for Dose Arm 1, Visit 5 for Dose Arm 2, and Visit 4 for Dose Arm 3).

For RNA: Blood samples will be collected at the following time points for different dose arms:

- Dose Arm 1: Baseline (Visit 2), 3 days after dose 1 (Visit 3), prior to the last dose (Visit 7), and End of Study Visit (Visit 15).
- Dose Arm 2: Baseline (Visit 2), 3 days after dose 1 (Visit 3), prior to the last dose (Visit 5), and End of Study Visit (Visit 13).
- Dose Arm 3: Baseline (Visit 2), 3 days after dose 1 (Visit 3), prior to the last dose (Visit 4), and End of Study Visit (Visit 12).
- Dose Arm 4: Baseline (Visit 2), 3 days after dosing (Visit 3) and End of Study Visit (Visit 10).
- Dose Arm 5: Baseline (Visit 2), 3 days after dosing (Visit 3) and End of Study Visit (Visit 10).

For each DNA blood sample a volume of 6mL whole blood is needed and for each RNA sample a volume of 2.5mL whole blood is needed.

Failure to provide consent to participate in this substudy will not impact subject's eligibility to participate in the main study.

Any exploratory biomarker or genomic analysis will only ever be related to the exploration of the underlying causes of ITP in patients, related biology, and drug response. Justification for additional genomic analyses is detailed in Section 5.4.6.

Details on the collection, storage, preparation, and shipping of samples will be presented in the Laboratory Manual provided separately.

Any results from this analysis will be reported separately and will not form a part of the main clinical study report.

5.1.2 Study duration per subject

The maximum duration of the study per subject is approximately 16 weeks.

Screening Period: 1 to 28 days (4 weeks)

Dosing Period: up to 4 weeks

Observation Period: 8 weeks

The end of the study is defined as the date of the last visit of the last subject in the study.

5.1.3 Planned number of subjects and sites

A total of up to approximately 48 to 66 subjects are planned to enter the Dosing Periods in the study (15 subjects in each of Dose Arms 1 and 2, and 6 to 12 subjects in Dose Arms 3, 4, and 5). To achieve the required number of eligible subjects to enter the Dosing Period, it is anticipated that approximately 90 subjects will need to be screened. These subjects will be enrolled at approximately 45 sites. First subject first visit is planned for Q1 2016, last subject last visit for Q2 2018.

5.1.4 Anticipated regions and countries

It is planned to recruit subjects in Europe and Australia for the study.

5.2 Schedule of study assessments

Table 5–1 presents the tabular scheme of study assessments for the weekly UCB7665 4mg/kg dose arm (Dose Arm 1), Table 5–2 presents the tabular scheme of study assessments for the weekly UCB7665 7mg/kg dose arm (Dose Arm 2), Table 5-3 presents the tabular scheme of study assessments for the weekly UCB7665 10mg/kg dose arm (Dose Arm 3), Table 5-4 presents the tabular scheme of study assessments for the one dose of UCB7665 15mg/kg, Table 5-5 presents the tabular scheme of study assessments for the one dose of UCB7665 20mg/kg and Table 5–6 presents the assessments to be performed on dosing days.

Table 5–1: Schedule of assessments for the UCB7665 4mg/kg weekly dose arm (Dose Arm 1)

Assessments		Screening Period	Dosing Period						Observation Period							
			Dose 1		Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a]	3	4[a]	5[a]	6[a]	7[a]	8	9	10[b]	11	12[b]	13	14[b]	15
			BL Visit													EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	22	29	32	36	43	50	57	64	71	85
	Week		1	1	2	3	4	5	5	6	7	8	9	10	11	13
	Visit Window			±1d	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Written informed consent[f]		X														
Demographic data		X														
Verification of inclusion/exclusion criteria		X	X													
Platelets for inclusion/ withdrawal check (local laboratory)[g]			X		X	X	X	X								
Randomization[h]			X													
Withdrawal criteria[i]			X	X	X	X	X	X								
General medical/procedures history		X														
ITP history		X														
Prior and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 5–1: Schedule of assessments for the UCB7665 4mg/kg weekly dose arm (Dose Arm 1)

Assessments		Screening Period	Dosing Period						Observation Period							
			Dose 1		Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a]	3	4[a]	5[a]	6[a]	7[a]	8	9	10[b]	11	12[b]	13	14[b]	15
			BL Visit													EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	22	29	32	36	43	50	57	64	71	85
	Week		1	1	2	3	4	5	5	6	7	8	9	10	11	13
	Visit Window			±1d	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Concomitant medical procedures			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight		X														X
Height		X														
Recording of AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[j]		X	X		X	X	X	X		X		X		X		X
12-lead ECG[k]		X	X		X	X	X	X		X						X
Karnofsky Performance Status		X														
Laboratory parameters (hematology, chemistry, urinalysis)		X[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serology test for HIV, hepatitis B, and hepatitis C		X														
IGRA TB test[m]		X														

Table 5–1: Schedule of assessments for the UCB7665 4mg/kg weekly dose arm (Dose Arm 1)

Assessments		Screening Period	Dosing Period						Observation Period							
			Dose 1		Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a] BL Visit	3	4[a]	5[a]	6[a]	7[a]	8	9	10[b]	11	12[b]	13	14[b]	15 EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	22	29	32	36	43	50	57	64	71	85
	Week		1	1	2	3	4	5	5	6	7	8	9	10	11	13
	Visit Window			±1d	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
TB signs and symptoms questionnaire		X														X
Blood sample for cytokines			X	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]
Whole blood sample for DNA (optional)			X					X								
Whole blood sample for RNA (optional)			X	X				X								X
Serum pregnancy test		X														
Urine pregnancy test			X		X	X	X	X								X
Call to IXRS for treatment kit number			X		X	X	X	X								
Administration of IMP			X		X	X	X	X								
Blood sampling for plasma concentration of UCB7665			X	X	X	X	X	X	X	X						
Anti-UCB7665 antibodies			X	X	X	X	X	X	X	X	X		X		X	X

Table 5–1: Schedule of assessments for the UCB7665 4mg/kg weekly dose arm (Dose Arm 1)

Assessments		Screening Period	Dosing Period						Observation Period							
			Dose 1		Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a]	3	4[a]	5[a]	6[a]	7[a]	8	9	10[b]	11	12[b]	13	14[b]	15
			BL Visit													EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	22	29	32	36	43	50	57	64	71	85
	Week		1	1	2	3	4	5	5	6	7	8	9	10	11	13
	Visit Window			±1d	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Serum complements (C3 and C4) and plasma complements (C3a and C5a)			X			X			X				X			
Blood collection for exploratory safety biomarkers			X	X[o]	X	X	X	X	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	
Serum BAFF levels			X		X	X	X	X			X				X	
Blood collection for exploratory biomarker analysis			X		X	X	X	X			X				X	
Immunoglobulins (total IgG, IgG subclasses)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IgA, IgM, IgE[p]			X					X		X					X	
ITP-specific autoantibodies [q]			X							X						X
ITP bleeding scale		X	X		X	X	X	X		X		X		X		X
NFI-MS			X							X		X		X		X

Table 5–1: Schedule of assessments for the UCB7665 4mg/kg weekly dose arm (Dose Arm 1)

Assessments		Screening Period	Dosing Period						Observation Period							
			Dose 1		Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a] BL Visit	3	4[a]	5[a]	6[a]	7[a]	8	9	10[b]	11	12[b]	13	14[b]	15 EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	22	29	32	36	43	50	57	64	71	85
	Week		1	1	2	3	4	5	5	6	7	8	9	10	11	13
	Visit Window			±1d	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Headache questionnaire[r]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject exit interview[s]																X

AE=adverse event; BAFF=B cell activating factor; BL=Baseline; CSF=cerebrospinal fluid; CT=computed tomography; d=day(s); DMC=Data Monitoring; DNA=deoxyribonucleic acid; Committee; ECG=electrocardiogram; EOS=End of Study; EW=Early Withdrawal; [redacted] HIV=human immunodeficiency virus; Ig=immunoglobulin; IMP=investigational medicinal product; ITP=immune thrombocytopenia; IXRS= interactive voice/web response system; LP=lumbar puncture; RNA=ribonucleic acid; MRI=magnetic resonance imaging; NFI-MS=Neurological Fatigue Index for multiple sclerosis; TB=tuberculosis.

[a] Frequency of assessments on dosing days is detailed in Table 5–6.

[b] Visits 10, 12, and 14 can be performed at home with a healthcare professional visiting the subject at his/her home.

[c] The End-of-Study Visit is 8 weeks following the final dose.

[d] A visit window of ±2 days is allowed for the dosing visits. The visit window of ±2 days is relative to the first dosing visit date. However, there should be a minimum interval of 5 days and maximum interval of 9 days as compared to the previous dose.

[e] The visit windows in the Observation Period are relative to the final dosing visit date.

[f] Additional informed consent is needed for participation in the exploratory genomic substudy. All samples will be collected prior to dosing with IMP.

[g] Prior to dosing at Visit 2, 2 platelet samples will be taken. One sample will be analyzed locally and the value will be used to check inclusion criteria. The other platelet sample will be sent to the central laboratory. At subsequent dosing visits, a platelet sample will be assessed locally prior to dosing to evaluate withdrawal criterion of platelet count >$350x10^9$/L.

[h] The first 6 subjects will be enrolled in the Dose Arm 1 group only. Safety data for these 6 subjects up to 7 days after the last dose will be reviewed by the DMC. Following this review the DMC will make a decision to open Dose Arm 2 for enrollment. If Dose Arm 2 is opened, the subsequent subjects will be randomly assigned in 1:1 ratio to either Dose Arm 1 or Dose Arm 2 using an IXRS. Once 15 subjects are enrolled in Dose Arm 1 and safety data review of at least 6 subjects in Dose Arm 2 is done, the subsequently enrolled subjects will be enrolled in Dose Arm 2 until a planned number of 15 subjects are enrolled.

[i] Subjects can withdraw at any time during the study, based on the criteria in Section 6.4 .

[j] A complete physical examination will be performed at Screening and EOS/EW Visit. At all other visits (where physical examination is performed), an abbreviated physical examination will be conducted.
[k] The ECG should be performed in triplicate prior to blood collection for assessment of laboratory parameters. Three ECGs should be recorded in a time frame of 5 minutes with at least 1 minute difference, 1-2 minutes between the ECGs.
[l] At the Screening Visit, 2 separate blood samples will be obtained on the same day for evaluation of platelet count.
[m] The IGRA test will be performed in a central laboratory. Any IGRA-positive subjects will be withdrawn from the study.
[n] Blood sample for cytokines will be obtained and analyzed at baseline for all subjects and at subsequent visits only in subjects with infusion reactions.
[o] Exploratory safety biomarker samples to be obtained on dosing days for all subjects. During non-dosing visits and during the visits in the Observation Period, the samples should be obtained only from subjects experiencing severe headaches or GI disturbances (only in case of Adverse Events of Interest, see Section 12.4).
[p] In case the number of infusions to be administered are reduced after DMC review of safety data, then the scheduled Visit 7 assessment for IgA, IgM, and IgE will be performed earlier at the last dosing visit.
[q] [redacted]
[r] This assessment is applicable only to subjects experiencing severe headaches and will be performed daily until resolution (ie, if headache becomes moderate or mild, normal collection of AEs should apply); this assessment will be followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.
[s] A semi-structured interview guide will be used and the interview will be recorded. In case of early withdrawal from the study, the subject exit interview should be performed at End-of-Study Visit only.

Table 5–2: Schedule of assessments for the UCB7665 7mg/kg weekly dose arm (Dose Arm 2)

Assessments		Screening Period	Dosing Period				Observation Period							
			Dose 1		Dose 2	Dose 3								
	Visit	**1**	**2**[a]	**3**	**4**[a]	**5**[a]	**6**	**7**	**8**[b]	**9**	**10**[b]	**11**	**12**[b]	**13**
			BL Visit											**EOS/ EW**[c]
	Day	**-28 to -1**	**1**	**4**	**8**	**15**	**18**	**22**	**29**	**36**	**43**	**50**	**57**	**71**
	Week		**1**	**1**	**2**	**3**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**11**
	Visit Window			**±1d**	**±2d**[d]	**±2d**[d]	**±1d**	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]
Written informed consent[f]		X												
Demographic data		X												
Verification of inclusion/exclusion criteria		X	X											
Platelets for inclusion/withdrawal check (local laboratory)[g]			X		X	X								
Randomization[h]			X											
Withdrawal criteria[i]			X	X	X	X								
General medical/procedures history		X												
ITP history		X												
Prior and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medical procedures			X	X	X	X	X	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight		X												X
Height		X												
Recording of AEs		X	X	X	X	X	X	X	X	X	X	X	X	X

Table 5–2: Schedule of assessments for the UCB7665 7mg/kg weekly dose arm (Dose Arm 2)

Assessments		Screening Period	Dosing Period				Observation Period							
			Dose 1		Dose 2	Dose 3								
	Visit	**1**	**2**[a]	**3**	**4**[a]	**5**[a]	**6**	**7**	**8**[b]	**9**	**10**[b]	**11**	**12**[b]	**13**
			BL Visit											**EOS/ EW**[c]
	Day	**-28 to -1**	**1**	**4**	**8**	**15**	**18**	**22**	**29**	**36**	**43**	**50**	**57**	**71**
	Week		**1**	**1**	**2**	**3**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**11**
	Visit Window			**±1d**	**±2d**[d]	**±2d**[d]	**±1d**	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]
Physical examination[j]		X	X		X	X		X		X		X		X
12-lead ECG[k]		X	X		X	X		X						X
Karnofsky Performance Status		X												
Laboratory parameters (hematology, chemistry, urinalysis)		X[l]	X	X	X	X	X	X	X	X	X	X	X	X
Serology test for HIV, hepatitis B, and hepatitis C		X												
IGRA TB test[m]		X												
TB signs and symptoms questionnaire		X												X
Blood sample for cytokines			X	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]
Whole blood sample for DNA (optional)			X			X								
Whole blood sample for RNA (optional)			X	X		X								X
Serum pregnancy test		X												
Urine pregnancy test			X		X	X								X
Call to IXRS for treatment kit number			X		X	X								

Table 5–2: Schedule of assessments for the UCB7665 7mg/kg weekly dose arm (Dose Arm 2)

Assessments		Screening Period	Dosing Period				Observation Period							
			Dose 1		Dose 2	Dose 3								
	Visit	**1**	**2**[a]	**3**	**4**[a]	**5**[a]	**6**	**7**	**8**[b]	**9**	**10**[b]	**11**	**12**[b]	**13**
			BL Visit											**EOS/ EW**[c]
	Day	**-28 to -1**	**1**	**4**	**8**	**15**	**18**	**22**	**29**	**36**	**43**	**50**	**57**	**71**
	Week		**1**	**1**	**2**	**3**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**11**
	Visit Window			**±1d**	**±2d**[d]	**±2d**[d]	**±1d**	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]
Administration of IMP			X		X	X								
Blood sampling for plasma concentration of UCB7665			X	X	X	X	X	X						
Anti-UCB7665 antibodies			X	X	X	X	X	X	X		X		X	X
Serum complements (C3 and C4) and plasma complements (C3a and C5a)			X			X	X				X			
Blood collection for exploratory safety biomarkers			X	X[o]	X	X	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	
Serum BAFF levels			X		X	X			X				X	
Blood collection for exploratory biomarker analysis			X		X	X			X				X	
Immunoglobulins (total IgG, IgG subclasses)		X	X	X	X	X	X	X	X	X	X	X	X	X
IgA, IgM, IgE[p]			X			X		X					X	
ITP-specific autoantibodies[q]			X					X						X
ITP bleeding scale		X	X		X	X		X		X		X		X
NFI-MS			X					X		X		X		X

Table 5–2: Schedule of assessments for the UCB7665 7mg/kg weekly dose arm (Dose Arm 2)

Assessments		Screening Period	Dosing Period				Observation Period							
			Dose 1		Dose 2	Dose 3								
	Visit	1	2[a] BL Visit	3	4[a]	5[a]	6	7	8[b]	9	10[b]	11	12[b]	13 EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	18	22	29	36	43	50	57	71
	Week		1	1	2	3	3	4	5	6	7	8	9	11
	Visit Window			±1d	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Headache questionnaire[r]			X	X	X	X	X	X	X	X	X	X	X	X
Subject exit interview[s]														X

AE=adverse event; BAFF=B cell activating factor; BL=Baseline; CSF=cerebrospinal fluid; CT=computed tomography; d=day(s); DMC=Data Monitoring Committee; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EOS=End of Study; EW=Early Withdrawal; [redacted] HIV=human immunodeficiency virus; Ig=immunoglobulin; IGRA= interferon-gamma release assay; IMP=investigational medicinal product; ITP=immune thrombocytopenia; IXRS= interactive voice/web response system; LP=lumbar puncture; RNA=ribonucleic acid; MRI=magnetic resonance imaging; NFI-MS=Neurological Fatigue Index for multiple sclerosis; TB=tuberculosis.

[a] Frequency of assessments on dosing days is detailed in Table 5–6.

[b] Visits 8, 10, and 12 can be performed at home with a healthcare professional visiting the subject at his/her home.

[c] The End-of-Study Visit is 8 weeks following the last dose.

[d] A visit window of ±2 days is allowed for the dosing visits. The visit window of ±2 days is relative to the first dosing visit date. However, there should be a minimum interval of 5 days and maximum interval of 9 days as compared to the previous dose.

[e] The visit windows in the Observation Period are relative to the final dosing visit date.

[f] Additional informed consent is needed for participation in the exploratory genomic substudy. All samples will be collected prior to dosing with IMP.

[g] Prior to dosing at Visit 2, 2 platelet samples will be taken. One sample will be analyzed locally and the value will be used to check inclusion criteria. The other platelet sample will be sent to the central laboratory. At subsequent dosing visits, a platelet sample will be assessed locally prior to dosing to evaluate withdrawal criterion of platelet count >350x109/L.

[h] The first 6 subjects will be enrolled in the Dose Arm 1 group. Safety data for these 6 subjects up to 7 days after the last dose will be reviewed by the DMC. Following this review the DMC will make a decision to open Dose Arm 2 for enrollment. If Dose Arm 2 is opened, the subsequent subjects will be randomly assigned in 1:1 ratio to either Dose Arm 1 or Dose Arm 2 using an IXRS. Once 15 subjects are enrolled in Dose Arm 1 and safety data review of at least 6 subjects in Dose Arm 2 is done, the subsequently enrolled subjects will be enrolled in Dose Arm 2 until a planned number of 15 subjects are enrolled.

[i] Subjects can withdraw at any time during the study, based on the criteria in Section 6.4.

[j] A complete physical examination will be performed at Screening and EOS/EW Visit. At all other visits (where physical examination is performed), an abbreviated physical examination will be conducted.

[k] The ECG should be performed in triplicate prior to blood collection for assessment of laboratory parameters. Three ECGs should be recorded in a time frame of 5 minutes with at least 1 minute difference, 1-2 minutes between the ECGs.

[l] At the Screening Visit, 2 separate blood samples will be obtained on the same day for evaluation of platelet count.

[m] The IGRA test will be performed in a central laboratory. Any IGRA-positive subjects will be withdrawn from the study.

[n] Blood sample for cytokines will be obtained and analyzed at baseline for all subjects and at subsequent visits only in subjects with infusion reactions.

[o] Exploratory safety biomarker samples to be obtained on dosing days for all subjects. During non-dosing visits and during the visits in the Observation Period, the samples should be obtained only from subjects experiencing severe headaches or GI disturbances (only in case of Adverse Events of Interest, see Section 12.4).

[p] In case the number of infusions to be administered are reduced after DMC review of safety data, then the scheduled Visit 5 assessment for IgA, IgM, and IgE will be performed earlier at the last dosing visit.

[q] [redacted]

[r] This assessment is applicable only to subjects experiencing severe headaches and will be performed daily until resolution (ie, if headache becomes moderate or mild, normal collection of AEs should apply); this assessment will be followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

[s] A semi-structured interview guide will be used and the interview will be recorded. In case of early withdrawal from the study, the subject exit interview should be performed at End-of-Study Visit only.

Table 5-3: Schedule of assessments for the UCB7665 10mg/kg once weekly dose arm (Dose Arm 3)

Assessments		Screening Period	Dosing Period							Observation Period							
			Dose 1				Dose 2										
	Visit	1	2[a]			3	4[a]			5	6	7[b]	8	9[b]	10	11[b]	12
			BL Visit														EOS/EW[c]
	Telephone Contact			1	2[d]			3	4[d]								
	Day	-28 to -1	1	2	3	4	8	9	10	11	15	22	29	36	43	50	64
	Week		1	1	1	1	2	2	2	2	3	4	5	6	7	8	10
	Visit Window					±1d	±2d[e]			±1d[f]	±2d[f]	±2d[f]	±2d[f]	±2d[f]	±2d[f]	±2d[f]	±2d[f]
Written informed consent[g]		X															
Demographic data		X															
Verification of inclusion/exclusion criteria		X	X														
Platelets for inclusion/ withdrawal check (local laboratory)[h]			X				X										
Withdrawal criteria[i]			X			X	X										
General medical/procedures history		X															
ITP history		X															
Prior and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medical procedures			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs		X	X			X	X			X	X	X	X	X	X	X	X

Table 5-3: Schedule of assessments for the UCB7665 10mg/kg once weekly dose arm (Dose Arm 3)

Assessments		Screening Period	Dosing Period							Observation Period							
			Dose 1				Dose 2										
	Visit	1	2[a]			3	4[a]			5	6	7[b]	8	9[b]	10	11[b]	12
			BL Visit														EOS/EW[c]
	Telephone Contact			1	2[d]			3	4[d]								
	Day	-28 to -1	1	2	3	4	8	9	10	11	15	22	29	36	43	50	64
	Week		1	1	1	1	2	2	2	2	3	4	5	6	7	8	10
	Visit Window					±1d	±2d[e]			±1d[f]	±2d[f]	±2d[f]	±2d[f]	±2d[f]	±2d[f]	±2d[f]	±2d[f]
Body weight		X															X
Height		X															
Recording of AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[j]		X	X				X				X		X		X		X
12-lead ECG[k]		X	X				X				X						X
Karnofsky Performance Status		X															
Laboratory parameters (hematology, chemistry, urinalysis)		X[l]	X			X	X			X	X	X	X	X	X	X	X
Serology test for HIV, hepatitis B, and hepatitis C		X															
IGRA TB test[m]		X															
TB signs and symptoms questionnaire		X															X
Blood sample for cytokines			X			X[n]	X[n]			X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]

Table 5-3: Schedule of assessments for the UCB7665 10mg/kg once weekly dose arm (Dose Arm 3)

Assessments		Screening Period	Dosing Period							Observation Period							
			Dose 1				Dose 2										
	Visit	1	2[a] BL Visit			3	4[a]			5	6	7[b]	8	9[b]	10	11[b]	12 EOS/EW[c]
	Telephone Contact			1	2[d]			3	4[d]								
	Day	-28 to -1	1	2	3	4	8	9	10	11	15	22	29	36	43	50	64
	Week		1	1	1	1	2	2	2	2	3	4	5	6	7	8	10
	Visit Window					±1d	±2d[e]			±1d[f]	±2d[f]	±2d[f]	±2d[f]	±2d[f]	±2d[f]	±2d[f]	±2d[f]
Whole blood sample for DNA (optional)			X				X										
Whole blood sample for RNA (optional)			X			X	X										X
Serum pregnancy test		X															
Urine pregnancy test			X				X										X
Call to IXRS for treatment kit number			X				X										
Administration of IMP			X				X										
Blood sampling for plasma concentration of UCB7665			X			X	X			X	X						
Anti-UCB7665 antibodies			X			X	X			X	X	X		X		X	X
Serum complements (C3 and C4) and plasma complements (C3a and C5a)			X							X				X			

Table 5-3: Schedule of assessments for the UCB7665 10mg/kg once weekly dose arm (Dose Arm 3)

Assessments		Screening Period	Dosing Period							Observation Period							
			Dose 1				Dose 2										
	Visit	1	2[a] BL Visit			3	4[a]			5	6	7[b]	8	9[b]	10	11[b]	12 EOS/EW[c]
	Telephone Contact			1	2[d]			3	4[d]								
	Day	-28 to -1	1	2	3	4	8	9	10	11	15	22	29	36	43	50	64
	Week		1	1	1	1	2	2	2	2	3	4	5	6	7	8	10
	Visit Window					±1d	±2d[e]			±1d[f]	±2d[f]	±2d[f]	±2d[f]	±2d[f]	±2d[f]	±2d[f]	±2d[f]
Blood collection for exploratory safety biomarkers			X			X[o]	X[o]			X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	
Serum BAFF levels			X				X					X				X	
Blood collection for exploratory biomarker analysis			X				X					X				X	
Immunoglobulins (total IgG, IgG subclasses)		X	X			X	X			X	X	X	X	X	X	X	X
IgA, IgM, IgE[p]			X				X				X					X	
ITP-specific autoantibodies[q]			X								X						X
ITP bleeding scale		X	X				X				X		X		X		X
NFI-MS			X								X		X		X		X
Headache questionnaire[r]			X			X	X			X	X	X	X	X	X	X	X
Subject exit interview[s]																	X

AE=adverse event; BAFF=B cell activating factor; BL=Baseline; CSF=cerebrospinal fluid; CT=computed tomography; d=day(s); DMC=Data Monitoring Committee; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EOS=End of Study; EW=Early Withdrawal; [redacted] HIV=human immunodeficiency virus; Ig=immunoglobulin; IGRA= interferon-gamma release assay; IMP=investigational medicinal product; ITP=immune thrombocytopenia; IXRS= interactive voice/web response system; LP=lumbar puncture; RNA=ribonucleic acid; MRI=magnetic resonance imaging; NFI-MS=Neurological Fatigue Index for multiple sclerosis; TB=tuberculosis.

[a] Frequency of assessments on dosing days is detailed in Table 5–6.

[b] Visits 7, 9, and 11 can be performed at home with a healthcare professional visiting the subject at his/her home.

[c] The End-of-Study Visit is 8 weeks following the last dose.

[d] If the TC is on the same day as an on-site visit, the TC may be skipped.

[e] A visit window of ±2 days is allowed for the dosing visits. The visit window of ±2 days is relative to the first dosing visit date. However, there should be a minimum interval of 5 days and maximum interval of 9 days as compared to the previous dose.

[f] The visit windows in the Observation Period are relative to the final dosing visit date.

[g] Additional informed consent is needed for participation in the exploratory genomic substudy. All samples will be collected prior to dosing with IMP.

[h] Prior to dosing at Visit 2, 2 platelet samples will be taken. One sample will be analyzed locally and the value will be used to check inclusion criteria. The other platelet sample will be sent to the central laboratory. At subsequent dosing visits, a platelet sample will be assessed locally prior to dosing to evaluate withdrawal criterion of platelet count >350x109/L.

[i] Subjects can withdraw at any time during the study, based on the criteria in Section 6.4.

[j] A complete physical examination will be performed at Screening and EOS/EW Visit. At all other visits (where physical examination is performed), an abbreviated physical examination will be conducted.

[k] The ECG should be performed in triplicate prior to blood collection for assessment of laboratory parameters. Three ECGs should be recorded in a time frame of 5 minutes with at least 1 minute difference, 1-2 minutes between the ECGs.

[l] At the Screening Visit, 2 separate blood samples will be obtained on the same day for evaluation of platelet count.

[m] The IGRA test will be performed in a central laboratory. Any IGRA-positive subjects will be withdrawn from the study.

[n] Blood sample for cytokines will be obtained and analyzed at baseline for all subjects and at subsequent visits only in subjects with infusion reactions.

[o] Exploratory safety biomarker samples to be obtained on dosing days for all subjects. During non-dosing visits and during the visits in the Observation Period, the samples should be obtained only from subjects experiencing severe headaches or GI disturbances (only in case of Adverse Events of Interest, see Section 12.4).

[p] In case the number of infusions to be administered are reduced after DMC review of safety data, then the scheduled Visit 6 assessment for IgA, IgM, and IgE will be performed earlier at the last dosing visit.

[q] [redacted]

[r] This assessment is applicable only to subjects experiencing severe headaches and will be performed daily until resolution (ie, if headache becomes moderate or mild, normal collection of AEs should apply); this assessment will be followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

[s] A semi-structured interview guide will be used and the interview will be recorded. In case of early withdrawal from the study, the subject exit interview should be performed at End-of-Study Visit only.

Table 5-4: Schedule of assessments for the UCB7665 15mg/kg once dose arm (Dose Arm 4)

Assessments		Screening Period	Dosing Period			Observation Period							
			Dose 1										
	Visit	**1**	**2**[a]			**3**	**4**	**5**[b]	**6**	**7b**	**8**	**9b**	**10**
			BL Visit										**EOS/EW**[c]
	Telephone Contact			**1**	**2**[d]								
	Day	**-28 to -1**	**1**	**2**	**3**	**4**	**8**	**15**	**22**	**29**	**36**	**43**	**57**
	Week		**1**	**1**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**9**
	Visit Window					**±1d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]
Written informed consent[f]		X											
Demographic data		X											
Verification of inclusion/exclusion criteria		X	X										
Platelets for inclusion/ withdrawal check (local laboratory)[g]			X										
Withdrawal criteria[h]			X										
General medical/procedures history		X											
ITP history		X											
Prior and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medical procedures			X	X	X	X	X	X	X	X	X	X	X
Vital signs		X	X			X	X	X	X	X	X	X	X
Body weight		X											X

Table 5-4: Schedule of assessments for the UCB7665 15mg/kg once dose arm (Dose Arm 4)

Assessments		Screening Period	Dosing Period			Observation Period							
			Dose 1										
	Visit	**1**	**2**[a]			**3**	**4**	**5**[b]	**6**	**7b**	**8**	**9b**	**10**
			BL Visit										**EOS/EW**[c]
	Telephone Contact			**1**	**2**[d]								
	Day	**-28 to -1**	**1**	**2**	**3**	**4**	**8**	**15**	**22**	**29**	**36**	**43**	**57**
	Week		**1**	**1**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**9**
	Visit Window					**±1d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]
Height		X											
Recording of AEs		X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[i]		X	X				X		X		X		X
12-lead ECG[j]		X	X				X						X
Karnofsky Performance Status		X											
Laboratory parameters (hematology, chemistry, urinalysis)		X[k]	X			X	X	X	X	X	X	X	X
Serology test for HIV, hepatitis B, and hepatitis C		X											
IGRA TB test[l]		X											
TB signs and symptoms questionnaire		X											X
Blood sample for cytokines			X			X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]
Whole blood sample for DNA (optional)			X										

Table 5-4: Schedule of assessments for the UCB7665 15mg/kg once dose arm (Dose Arm 4)

Assessments		Screening Period	Dosing Period			Observation Period							
			Dose 1										
	Visit	**1**	**2**[a]			**3**	**4**	**5**[b]	**6**	**7b**	**8**	**9b**	**10**
			BL Visit										**EOS/EW**[c]
	Telephone Contact			**1**	**2**[d]								
	Day	**-28 to -1**	**1**	**2**	**3**	**4**	**8**	**15**	**22**	**29**	**36**	**43**	**57**
	Week		**1**	**1**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**9**
	Visit Window					**±1d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]
Whole blood sample for RNA (optional)			X			X							X
Serum pregnancy test		X											
Urine pregnancy test			X										X
Call to IXRS for treatment kit number			X										
Administration of IMP			X										
Blood sampling for plasma concentration of UCB7665			X			X	X						
Anti-UCB7665 antibodies			X			X	X	X		X		X	X
Serum complements (C3 and C4) and plasma complements (C3a and C5a)			X			X				X			
Blood collection for exploratory safety biomarkers			X			X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	
Serum BAFF levels			X					X				X	

Table 5-4: Schedule of assessments for the UCB7665 15mg/kg once dose arm (Dose Arm 4)

Assessments		Screening Period	Dosing Period			Observation Period							
			Dose 1										
	Visit	1	2[a]			3	4	5[b]	6	7b	8	9b	10
			BL Visit										EOS/EW[c]
	Telephone Contact			1	2[d]								
	Day	-28 to -1	1	2	3	4	8	15	22	29	36	43	57
	Week		1	1	1	1	2	3	4	5	6	7	9
	Visit Window					±1d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Blood collection for exploratory biomarker analysis			X					X				X	
Immunoglobulins (total IgG, IgG subclasses)		X	X			X	X	X	X	X	X	X	X
IgA, IgM, IgE			X				X					X	
ITP-specific autoantibodies[o]			X				X						X
ITP bleeding scale		X	X				X		X		X		X
NFI-MS			X				X		X		X		X
Headache questionnaire[p]			X			X	X	X	X	X	X	X	X
Subject exit interview[q]													X

AE=adverse event; BAFF=B cell activating factor; BL=Baseline; CSF=cerebrospinal fluid; CT=computed tomography; d=day(s); DMC=Data Monitoring Committee; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EOS=End of Study; EW=Early Withdrawal; [redacted] HIV=human immunodeficiency virus; Ig=immunoglobulin; IGRA= interferon-gamma release assay; IMP=investigational medicinal product; ITP=immune thrombocytopenia; IXRS= interactive voice/web response system; LP=lumbar puncture; RNA=ribonucleic acid; MRI=magnetic resonance imaging; NFI-MS=Neurological Fatigue Index for multiple sclerosis; TB=tuberculosis.

[a] Frequency of assessments on dosing days is detailed in Table 5–6.

[b] Visits 5, 7, and 9 can be performed at home with a healthcare professional visiting the subject at his/her home.

[c] The End-of-Study Visit is 8 weeks following the dose.

[d] If the TC is on the same day as an on-site visit, the TC may be skipped.
[e] The visit windows in the Observation Period are relative to the dosing visit date.
[f] Additional informed consent is needed for participation in the exploratory genomic substudy. All samples will be collected prior to dosing with IMP.
[g] Prior to dosing at Visit 1, 2 platelet samples will be taken. One sample will be analyzed locally and the value will be used to check inclusion criteria. The other platelet sample will be sent to the central laboratory. At subsequent dosing visits, a platelet sample will be assessed locally prior to dosing to evaluate withdrawal criterion of platelet count >350x109/L.
[h] Subjects can withdraw at any time during the study, based on the criteria in Section 6.4.
[i] A complete physical examination will be performed at Screening and EOS/EW Visit. At all other visits (where physical examination is performed), an abbreviated physical examination will be conducted.
[j] The ECG should be performed in triplicate prior to blood collection for assessment of laboratory parameters. Three ECGs should be recorded in a time frame of 5 minutes with at least 1 minute difference, 1-2 minutes between the ECGs.
[k] At the Screening Visit, 2 separate blood samples will be obtained on the same day for evaluation of platelet count.
[l] IGRA test will be performed in a central laboratory. It is recommended that the QFT-GIT be the first test performed at Screening to reduce the number of screening procedures conducted for any IGRA-positive subjects that may need to be withdrawn from the study.
[m] Blood sample for cytokines will be obtained and analyzed at baseline for all subjects and at subsequent visits only in subjects with infusion reactions.
[n] Exploratory safety biomarker samples to be obtained on dosing days for all subjects. During non-dosing visits and during the visits in the Observation Period, the samples should be obtained only from subjects experiencing severe headaches or GI disturbances (only in case of Adverse Events of Interest, see Section 12.4).
[o] [redacted]
[p] This assessment is applicable only to subjects experiencing severe headaches and will be performed daily until resolution (ie, if headache becomes moderate or mild, normal collection of AEs should apply); this assessment will be followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.
[q] A semi-structured interview guide will be used and the interview will be recorded. In case of early withdrawal from the study, the subject exit interview should be performed at End-of-Study Visit only.

Table 5-5: Schedule of assessments for the UCB7665 20mg/kg once dose arm (Dose Arm 5)

Assessments		Screening Period	Dosing Period			Observation Period							
			Dose 1										
	Visit	**1**	**2**[a]			**3**	**4**	**5**[b]	**6**	**7**b	**8**	**9**b	**10**
			BL Visit										**EOS/EW**[c]
	Telephone Contact			**1**	**2**[d]								
	Day	**-28 to -1**	**1**	**2**	**3**	**4**	**8**	**15**	**22**	**29**	**36**	**43**	**57**
	Week		**1**	**1**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**9**
	Visit Window					**±1d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]
Written informed consent[f]		X											
Demographic data		X											
Verification of inclusion/exclusion criteria		X	X										
Platelets for inclusion/ withdrawal check (local laboratory)[g]			X										
Withdrawal criteria[h]			X										
General medical/procedures history		X											
ITP history		X											
Prior and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medical procedures			X	X	X	X	X	X	X	X	X	X	X
Vital signs		X	X			X	X	X	X	X	X	X	X
Body weight		X											X

Table 5-5: Schedule of assessments for the UCB7665 20mg/kg once dose arm (Dose Arm 5)

Assessments		Screening Period	Dosing Period			Observation Period							
			Dose 1										
	Visit	**1**	**2**[a]			**3**	**4**	**5**[b]	**6**	**7**b	**8**	**9**b	**10**
			BL Visit										**EOS/EW**[c]
	Telephone Contact			**1**	**2**[d]								
	Day	**-28 to -1**	**1**	**2**	**3**	**4**	**8**	**15**	**22**	**29**	**36**	**43**	**57**
	Week		**1**	**1**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**9**
	Visit Window					**±1d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]
Height		X											
Recording of AEs		X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[i]		X	X				X		X		X		X
12-lead ECG[j]		X	X				X						X
Karnofsky Performance Status		X											
Laboratory parameters (hematology, chemistry, urinalysis)		X[k]	X			X	X	X	X	X	X	X	X
Serology test for HIV, hepatitis B, and hepatitis C		X											
IGRA TB test[l]		X											
TB signs and symptoms questionnaire		X											X
Blood sample for cytokines			X			X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]
Whole blood sample for DNA (optional)			X										

Table 5-5: Schedule of assessments for the UCB7665 20mg/kg once dose arm (Dose Arm 5)

Assessments		Screening Period	Dosing Period			Observation Period							
			Dose 1										
	Visit	**1**	**2**[a]			**3**	**4**	**5**[b]	**6**	**7**b	**8**	**9**b	**10**
			BL Visit										**EOS/EW**[c]
	Telephone Contact			**1**	**2**[d]								
	Day	**-28 to -1**	**1**	**2**	**3**	**4**	**8**	**15**	**22**	**29**	**36**	**43**	**57**
	Week		**1**	**1**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**9**
	Visit Window					**±1d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]
Whole blood sample for RNA (optional)			X			X							X
Serum pregnancy test		X											
Urine pregnancy test			X										X
Call to IXRS for treatment kit number			X										
Administration of IMP			X										
Blood sampling for plasma concentration of UCB7665			X			X	X						
Anti-UCB7665 antibodies			X			X	X	X		X		X	X
Serum complements (C3 and C4) and plasma complements (C3a and C5a)			X			X				X			
Blood collection for exploratory safety biomarkers			X			X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	
Serum BAFF levels			X					X				X	

Table 5-5: Schedule of assessments for the UCB7665 20mg/kg once dose arm (Dose Arm 5)

Assessments		Screening Period	Dosing Period			Observation Period							
			Dose 1										
	Visit	**1**	**2**[a]			**3**	**4**	**5**[b]	**6**	**7b**	**8**	**9b**	**10**
			BL Visit										**EOS/EW**[c]
	Telephone Contact			**1**	**2**[d]								
	Day	**-28 to -1**	**1**	**2**	**3**	**4**	**8**	**15**	**22**	**29**	**36**	**43**	**57**
	Week		**1**	**1**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**9**
	Visit Window					**±1d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]
Blood collection for exploratory biomarker analysis			X					X				X	
Immunoglobulins (total IgG, IgG subclasses)		X	X			X	X	X	X	X	X	X	X
IgA, IgM, IgE			X				X					X	
ITP-specific autoantibodies[o]			X				X						X
ITP bleeding scale		X	X				X		X		X		X
NFI-MS			X				X		X		X		X
Headache questionnaire[p]			X			X	X	X	X	X	X	X	X
Subject exit interview[q]													X

AE=adverse event; BAFF=B cell activating factor; BL=Baseline; CSF=cerebrospinal fluid; CT=computed tomography; d=day(s); DMC=Data Monitoring Committee; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EOS=End of Study; EW=Early Withdrawal; [redacted] HIV=human immunodeficiency virus; Ig=immunoglobulin; IGRA= interferon-gamma release assay; IMP=investigational medicinal product; ITP=immune thrombocytopenia; IXRS= interactive voice/web response system; LP=lumbar puncture; RNA=ribonucleic acid; MRI=magnetic resonance imaging; NFI-MS=Neurological Fatigue Index for multiple sclerosis; TB=tuberculosis.

[a] Frequency of assessments on dosing days is detailed in Table 5–6.

[b] Visits 5, 7, and 9 can be performed at home with a healthcare professional visiting the subject at his/her home.

[c] The End-of-Study Visit is 8 weeks following the dose.

[d] If the TC is on the same day as an on-site visit, the TC may be skipped.
[e] The visit windows in the Observation Period are relative to the dosing visit date.
[f] Additional informed consent is needed for participation in the exploratory genomic substudy. All samples will be collected prior to dosing with IMP.
[g] Prior to dosing at Visit 1, 2 platelet samples will be taken. One sample will be analyzed locally and the value will be used to check inclusion criteria. The other platelet sample will be sent to the central laboratory. At subsequent dosing visits, a platelet sample will be assessed locally prior to dosing to evaluate withdrawal criterion of platelet count >350x109/L.
[h] Subjects can withdraw at any time during the study, based on the criteria in Section 6.4.
[i] A complete physical examination will be performed at Screening and EOS/EW Visit. At all other visits (where physical examination is performed), an abbreviated physical examination will be conducted.
[j] The ECG should be performed in triplicate prior to blood collection for assessment of laboratory parameters. Three ECGs should be recorded in a time frame of 5 minutes with at least 1 minute difference, 1-2 minutes between the ECGs.
[k] At the Screening Visit, 2 separate blood samples will be obtained on the same day for evaluation of platelet count.
[l] The IGRA test will be performed in a central laboratory. Any IGRA-positive subjects will be withdrawn from the study.
[m] Blood sample for cytokines will be obtained and analyzed at baseline for all subjects and at subsequent visits only in subjects with infusion reactions.
[n] Exploratory safety biomarker samples to be obtained on dosing days for all subjects. During non-dosing visits and during the visits in the Observation Period, the samples should be obtained only from subjects experiencing severe headaches or GI disturbances (only in case of Adverse Events of Interest, see Section 12.4).
[o] [redacted]
[p] This assessment is applicable only to subjects experiencing severe headaches and will be performed daily until resolution (ie, if headache becomes moderate or mild, normal collection of AEs should apply); this assessment will be followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.
[q] A semi-structured interview guide will be used and the interview will be recorded. In case of early withdrawal from the study, the subject exit interview should be performed at End-of-Study Visit only.

Table 5–6: Schedule of investigations on the dosing days

	Predose	End of infusion	2h after end of infusion	4h after end of infusion	6h after end of infusion[a]
Withdrawal criteria	X				
Platelet count (local laboratory) for inclusion check at Visit 2 and for withdrawal criterion at other dosing visits	X				
Prior and concomitant medications	X				
Concomitant medical procedures	X				
Vital signs[b]	X	X	X	X	X
Physical examination	X				
12-lead ECG[c]	X				
Hematology	X				
Clinical chemistry	X				
Urinalysis	X				
Urine pregnancy test	X				
Immunoglobulins[d]	X				
ITP-specific autoantibodies[e]	X				
Blood sampling for UCB7665 plasma concentration	X				
Anti-UCB7665 antibodies	X				
Serum (C3 and C4) and plasma complements (C3a and C5a)[f]	X				
Blood collection for exploratory safety biomarkers[g]	X		X	X	
Serum BAFF levels	X				

Table 5–6: Schedule of investigations on the dosing days

	Predose	End of infusion	2h after end of infusion	4h after end of infusion	6h after end of infusion[a]
Blood collection for exploratory biomarker analysis	X				
Blood sampling for cytokines	X[h]			X[i]	
Whole blood sample for DNA and RNA (optional)[j]	X				
ITP bleeding scale	X				
AEs	X	X	X	X	X
NFI-MS[k]	X				

AE=adverse event; BAFF=B cell activating factor; DNA=deoxyribonucleic acid; ECG=electrocardiogram; h=hours; Ig=immunoglobulin; IMP=investigational medicinal product; ITP=immune thrombocytopenia; NFI-MS=Neurological Fatigue Index for multiple sclerosis; PRO=Patient Reported Outcomes; RNA=ribonucleic acid; [redacted]

[a] For Dose Arms 3, 4 and 5 only

[b] In addition to time points mentioned, vital signs will be evaluated every 15 minutes during infusion. Respiratory rate will be assessed only once predose.

[c] The ECG should be performed in triplicate prior to blood collection for assessment of laboratory parameters. Three ECGs should be recorded in a time frame of 5 minutes with at least 1 minute difference, 1-2 minutes between the ECGs.

[d] Total IgG and IgG subclasses.

[e] Evaluation of ITP-specific autoantibodies will be performed prior to dose 1 only.

[f] Serum and plasma complements (C3a and C5a) will be assessed prior to dose 1 and dose 3 only.

[g] [redacted]

[h] Blood sample for Baseline cytokine values will be obtained and analyzed at Baseline (Visit 2) pre-dose for all subjects. Also for all subjects on Dose Arm 3, the blood sample for cytokine values will be obtained and analyzed at Visit 4 pre-dose.

[i] Additional cytokine blood sample to be taken at 4h after end of infusion only in subjects with infusion reaction.

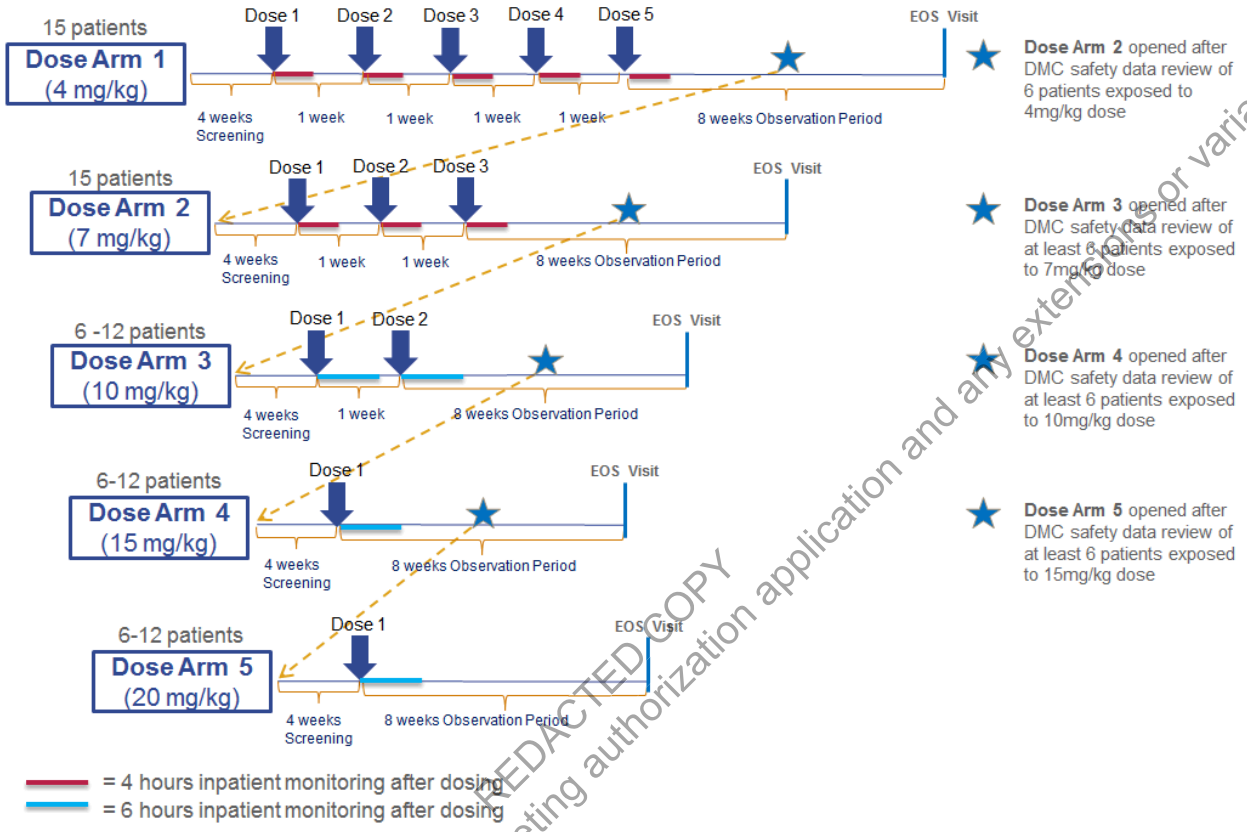
[j] For DNA, samples are taken at Baseline (Visit 2) and last dose only. For RNA, samples are taken at Baseline (Visit 2), Visit 3, at last dose, and End of Study Visit. All samples collected prior to dosing (if applicable for visit).

[k] PRO endpoint (NFI-MS) will be assessed prior to dose 1 only.

5.3 Schematic diagram

Figure 5–1 presents a schematic diagram for the study design.

Figure 5–1: Schematic diagram



DMC=Data Monitoring Committee; EOS=End of Study

5.4 Rationale for study design and selection of dose

5.4.1 Pathophysiology of ITP

Production of pathogenic autoantibodies is a major feature of a number of autoimmune diseases often associated with a specific pathomechanism. Autoantibodies against platelet antigens are considered to be a hallmark of ITP. Production of pathogenic IgG autoantibodies by plasma cells is accepted as the central underlying pathophysiological mechanism in a number of IgG-mediated autoimmune diseases, which includes ITP. In some patients, antibodies recognize antigens derived from a single glycoprotein; whereas in others, antibodies recognize multiple glycoproteins. The spleen is the key organ in the pathophysiology of ITP, not only because platelet autoantibodies are formed in the white pulp, but also because mononuclear macrophages in the red pulp destroy immunoglobulin-coated platelets.

Treatments aimed at reducing the quantity of circulating IgG autoantibodies are being used for primary and secondary therapy of autoimmune diseases, particularly where corticosteroid-based immune suppression is not or no longer effective. The therapeutic approach of these treatments is based on lowering levels of pathogenic autoantibodies, which represents rational and effective treatment modalities of autoimmune diseases.

5.4.2 Mechanism of action of UCB7665

UCB7665 is a humanized IgG4 monoclonal antibody that is being developed as an inhibitor of the activity of FcRn. The FcRn receptor recycles IgG and albumin and transports it bidirectionally across epithelial barriers. Recent studies have shown that FcRn rescues both IgG and albumin from intracellular lysosomal degradation by recycling it from the sorting endosome to the cell surface (Anderson et al, 2006). UCB7665 has been specifically designed to block IgG binding to FcRn without blocking the binding and recycling of albumin.

By blocking the activity of FcRn, UCB7665 accelerates the catabolism of IgG antibodies, including IgG autoantibodies. The aim is to reduce the concentration of pathogenic IgG in patients with autoimmune diseases mediated by the action of IgG autoantibodies.

5.4.3 Choice of study design and endpoints

The primary objective of the study is evaluation of safety and tolerability of UCB7665 administered as an sc infusion in subjects with ITP. The study utilizes a sequential adaptive design with at least 11 interim analyses as described in Section 14.7. This design was chosen to permit adequate monitoring of the safety of the subjects in the study.

The study will evaluate the platelet count as a surrogate marker for clinical efficacy in ITP in accordance with the European Medicines Agency (EMA) guidance for clinical development of medicinal products for chronic ITP (EMA/CHMP/153191/2013, 2014). The platelet count measures treatment activity and is believed to be a reliable predictor of clinical benefit. Endpoints related to Response and Complete Response as defined in the guidance will be evaluated. In addition, a platelet response of $>50x10^9$/L will be evaluated in the study.

5.4.4 Safety of UCB7665

Safety and tolerability of UCB7665 7mg/kg sc dose has been evaluated in healthy subjects. The most common TEAEs were mild to moderate gastrointestinal disturbances (nausea, vomiting,

and diarrhea) and headaches ranging from mild to moderate intensity. Details of AEs seen with UCB7665 7mg/kg administered by the iv route are presented in Section 5.4.5.

5.4.5 Rationale for dose selection

A single ascending dose study in healthy subjects (UP0018) explored the dose range of UCB7665 (between 1 and 7mg/kg) and characterized the PK and PD effect on total IgG. Preliminary data indicate that mean absolute decreases in IgG and mean percent change from Baseline IgG were greater in the active dose groups (n=6 each) compared to the pooled iv and sc placebo group (n=12) with maximum decreases of 49.3% (range: 44.6% to 55.9%) observed on Day 6 for a UCB7665 7mg/kg iv dose and 42.8% (range: 39.6% to 48.6%) on Day 9 for a UCB7665 7mg/kg sc dose.

The dose-exposure-response relationship, with total IgG as primary endpoint, was determined using non-linear mixed effects modeling. The derived population PK-PD (structural PK-PD model based on that of Lowe [Lowe et al, 2010]) was then used to guide, through simulation, the selection of appropriate repeat dose regimens that would mimic decreases achieved by plasmapheresis paradigms and result in IgG reductions of 70% or greater.

The model-based simulations demonstrate that weekly doses of UCB7665 4mg/kg for 5 consecutive weeks are expected to produce maximum mean IgG reductions of >70%. Similar reductions are predicted to be achieved following 3 consecutive weekly doses of UCB7665 7mg/kg.

Following iv administration in UP0018, the maximum tolerated dose was identified as UCB7665 4mg/kg due to AEs seen at the higher dose of 7mg/kg with severe headache and moderate diarrhea being reported. The tolerability profile of UCB7665 7mg/kg given as an sc infusion was more favorable than the equivalent iv dose and similar to the UCB7665 4mg/kg iv dose with mild to moderate cases of gastrointestinal disturbances and headaches being reported at a lower incidence.

Therefore, doses of UCB7665 4mg/kg given once weekly for 5 weeks(Dose Arm 1) and UCB7665 7mg/kg given once weekly for 3 weeks (Dose Arm 2) have been selected as the initial doses to evaluate the safety, tolerability and effect on platelet count in subjects with primary persistent or chronic ITP. Both dose regimens have the same cumulative dose of approximately UCB7665 20mg/kg.

Preliminary data from the current study indicates that the current dose regimens of UCB7665 4mg/kg and UCB7665 7mg/kg have been well tolerated. Hence the additional dose regimens of UCB7665 10mg/kg given once weekly for 2 weeks (Dose Arm 3) and of UCB7665 20mg/kg given once only (Dose Arm 5) are planned to further investigate the safety, tolerability and effect on platelet count of the same cumulative dose of UCB7665 20mg/kg but administered in dose regimes with higher dosages given in less infusions. The dose of UCB7665 15mg/kg given once only (Dose Arm 4) has been selected in addition as a risk mitigation as it is bridging the dose of UCB7665 10mg/kg given once weekly for 2 weeks (Dose Arm 3) and the dose of UCB7665 20mg/kg given once only (Dose Arm 5).

5.4.6 Justification for additional genomic analyses

DNA analysis

A genetic component in ITP has long been suspected to predispose some persons to develop ITP when exposed to a provocative event.

Further, the hypothesis of underlying genetic risk for ITP is supported by rare anecdotal and case reports of familial ITP. Affected members of these families present with ITP that meets the clinical criteria for primary ITP, but demonstrates a convincing pattern of inheritance. A 2006 review of the Pediatric and Adult Registry of Chronic ITP (PARC-ITP) (Johnsen, 2012) found that 10 of 445 (2.2%) of pediatric patients reported a positive family history of ITP. However, identification of susceptibility genes in ITP, via family linkage studies or genome wide association studies, have not yet been forthcoming, likely due to the rarity of familial ITP families available for study and the heterogeneity of ITP sporadic cases. Identification and characterization of a genetic and/or epigenetic component of familial ITP will lead to important clues into the pathogenesis of more common forms of ITP and possibly advance understanding of drug response phenotypes.

RNA analysis

Gene expression (mRNA) analyses have identified distinct gene transcription signatures from whole blood associated with many autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus, and ITP. Such signatures have provided molecular insight into disease biology and can facilitate patient stratification via gene expression panels predictive of therapeutic response and clinical outcomes.

Collection of blood for RNA analysis will enable identification of candidate markers for treatment effect and safety, and determine the feasibility of patient stratification.

MicroRNA analysis

MicroRNA are short (19-25 nucleotides) evolutionarily conserved single-stranded RNA molecules that regulate the expression of genes involved in diverse biological processes. The effect of miRNA on mRNA is mediated through the binding of the miRNA to the target mRNA ribonucleoprotein complex resulting in altered expression and decreased protein translation.

Regulated miRNA in ITP significantly affect both gene and protein expression in T cells, indicating that they may be important regulatory molecules involved in the loss of immune tolerance in ITP.

In summary, the genetic, epigenetic, and genomic elements of ITP are complex and require further elucidation to understand the cause, progression, and appropriate treatment of ITP. Through the voluntary collection of blood DNA/and RNA samples from consenting subjects, this substudy will help enable further investigation of this complex disease.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Inclusion criteria

To be eligible to participate in this study, all of the following criteria must be met:

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the subject.

2. Subject is considered reliable and capable of adhering to the protocol, visit schedule, or medication intake according to the judgment of the investigator.
3. Subject is male or female, ≥18 years of age at Visit 1 (Screening).
4. Subject has a diagnosis of primary ITP for a minimum of 3 months prior to Screening Visit.
5. Subject has a platelet count <$30x10^9$/L at Screening and <$35x10^9$/L at Baseline (Visit 2).

   Measured as follows: At Screening Visit, 2 separate blood collections for platelet count to be performed on the same day with at least 1 value below $30x10^9$/L and both values below $35x10^9$/L. At Baseline Visit (Visit 2), a platelet measure will be taken locally and the value should be below $35x10^9$/L.
6. Subject has a current or history of a peripheral blood smear consistent with ITP (thrombocytopenia with normal size or only slightly enlarged platelets and normal red and white blood cell morphology).
7. Female subjects of childbearing potential must have a negative serum pregnancy test at the Screening Visit, which is confirmed to be negative by urine testing prior to the first dose of IMP at Week 1 (Visit 2) and prior to further dosing at each study visit thereafter.

   Female subjects of childbearing potential must agree to use a highly effective method of birth control, during the study and for a period of 2 months after their final dose of IMP. Highly effective forms of birth control are methods which achieve a failure rate of less than 1% per year when used consistently and correctly. Highly effective methods of birth control include:

   – Combined (estrogen- and progesterone-containing) hormonal contraception (oral, implant, injectable) associated with inhibition of ovulation (which must be stable for at least 1 full month prior to Screening [Visit 1], and should remain stable during the study).
   – Progesterone-only hormonal contraceptives (oral, implant, injectable) associated with inhibition of ovulation (which must be stable for at least 1 full month prior to Screening [Visit 1], and should remain stable during the study).
   – Progesterone-releasing intrauterine systems or the TCu 380A intrauterine device.
   – Vasectomized partner (provided sole partner and partner has medical proof of surgical success).
   – True heterosexual sexual abstinence is an acceptable form of contraception when this is in line with the preferred and usual lifestyle of the person. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception.

   Women not agreeing to use birth control must be of nonchildbearing potential, defined as being:

   – Postmenopausal (for at least 2 years before the Screening Visit), verified by serum follicle-stimulating hormone level >40mIU/mL at the Screening Visit, or
   – Permanently sterilized (eg, bilateral tubal occlusion, hysterectomy, bilateral salpingectomy), or
   – Congenitally sterile

8. Contraception methods for male subjects and their female partners:
   - Male subject with a partner of childbearing potential must be willing to use a condom when sexually active during the study and for 3 months after the final administration of IMP.
   - In addition the female partner of childbearing potential of a male subject must be willing to use a highly effective method of contraception (as above), during the study period and for 3 months after the final administration of IMP.
9. Subject has adequate peripheral venous access.
10. Subject has responded to previous ITP therapy (according to the judgment of the investigator).

6.2 Exclusion criteria

Subjects are not permitted to enroll in the study if any of the following criteria are met:

1. Subject has participated in another study of an IMP (or a medical device) within the previous 30 days of Screening Visit or is currently participating in another study of an IMP (or a medical device).
2. Subject has a known hypersensitivity to any components of the IMP.

6.2.1 Exclusion criteria related to health status

3. Subject has a Karnofsky Performance Status (Appendix 18.1) rating <60% at Screening Visit.
4. Subject has an IgG level ≤6g/L at Screening Visit.
5. Subject has a partial thromboplastin time (PTT) ≥1.5x upper limit of normal (ULN) or International Normalized Ratio (INR) ≥1.5 at Screening Visit.
6. Subject has any medical condition (acute or chronic illness) or psychiatric condition that, in the opinion of the investigator, could harm the subject or would compromise the subject's ability to participate in this study.
7. Subject has 12-lead ECG with changes considered to be clinically significant upon medical review.
8. Subject has a glycosylated hemoglobin (HbA1c) value >8% at Screening Visit.
9. Subject has renal impairment, defined as:
   - Serum creatinine level of ≥1.4mg/dL for females and ≥1.5mg/dL for males at Screening Visit.
10. Subject has 2xULN of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP), or >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If the subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

For subjects with a Baseline result >ULN for ALT, AST, ALP, or total bilirubin, a Baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the electronic Case Report form (eCRF).

If subject has >ULN for ALT, AST, or ALP that does not meet the exclusion limit at screening, repeat the tests, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the subject must be discussed with the Medical Monitor.

Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. This includes rescreening (see Section 6.3).

11. Female subject who is pregnant or lactating.
12. Subject has planned an elective surgical procedure in the coming 6 months.

6.2.2 Exclusion criteria related to medical history

13. Subject has a history of chronic alcohol or drug abuse within the previous 12 months of Screening Visit.
14. Subject has evidence of a secondary cause of immune thrombocytopenic purpura from the past medical history (eg, bacterial or viral infection, past medical history of leukemia, lymphoma, common variable immunodeficiency, systemic lupus erythematosus, auto-immune thyroid disease) or to drug treatments (eg, heparin, quinine, antimicrobials, anticonvulsants) or subject has a multiple immune cytopenia, eg, Evan's syndrome.
15. Subject has a history of clinically relevant ongoing chronic infections including but not limited to human immunodeficiency virus (HIV), hepatitis B, hepatitis C, active or latent tuberculosis, or is tested positive for HIV, hepatitis B, or hepatitis C at the Screening Visit.
16. Subject has a family history of primary immunodeficiency.
17. Subject has a clinically relevant active infection (eg, sepsis, pneumonia, abscess) or has had a serious infection (resulting in hospitalization or requiring parenteral antibiotic treatment) within 6 weeks prior to the first dose of IMP.
18. Subject has active neoplastic disease or history of neoplastic disease within 5 years of Screening Visit (except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the uterine cervix which has been definitively treated with standard of care approaches).
19. Subject has a history of a major organ transplant or hematopoietic stem cell/marrow transplant.
20. Subject has a history of known inflammatory bowel disease, diverticular disease, or has a history of confirmed, duodenal, gastric or esophageal ulceration in the past 6 months.
21. Subject has experienced a clinically symptomatic gastrointestinal bleed (positive hemoccult tests without any signs and symptoms of gastrointestinal bleedings will not be considered as "clinically symptomatic") in the last 6 months prior to Screening Visit and/or has current gastritis or esophagitis and/or has a known risk for clinically relevant gastrointestinal bleeding beyond ITP.
22. Subject has experienced intracranial bleed in the last 6 months prior to Screening Visit.

23. Subject has a medical history of thrombosis within the past 5 years or a history of thrombosis with unknown cause at any time or a significant known risk for thrombosis.
24. Subject has a history of coagulopathy disorders other than ITP.
25. Subjects with known tuberculosis (TB) infection, at high risk of acquiring TB infection, or with latent TB (LTB) infection or current history of nontuberculous mycobacterial infection (NTMBI) are excluded.

a. Known TB infection whether present or past is defined as:

- Active TB infection or clinical signs and symptoms suggestive of TB (pulmonary or extrapulmonary).
- History of active TB infection involving any organ system or findings in other organ systems consistent with TB infection.
- Any historical evidence by radiography or other imaging modalities consistent with previously active TB infection.

b. High risk of acquiring TB infection is defined as:

- Known exposure to another person with active TB infection within the 3 months prior to Screening.
- Time spent in a healthcare delivery setting or institution where individuals infected with TB are housed and where the risk of transmission of infection is high.

c. LTB infection (refer to Section 12.8.1 for further details and instructions).

d. NTMBI is defined as a group of lung infections caused by mycobacteria different from mycobacterium tuberculosis infections.

26. Subjects with known TB infection, at high risk of acquiring TB infection, or LTB infection, or current/history of NTMBI are excluded.

6.2.3 Exclusion criteria related to concomitant medications/procedures

27. Subject has received a live vaccination within 8 weeks prior to the Baseline Visit; or intends to have a live vaccination during the course of the study or within 7 weeks following the final dose of IMP.
28. Subject has received any experimental biological agent within or outside of a clinical study in the past 3 months or within 5 half-lives prior to Baseline (whichever is longer).
29. Subject has had prior treatment with rituximab in the 6 months prior to the Baseline Visit or subject has had prior treatment with rituximab in the 12 months prior to Baseline and B cells are not within the normal range.
30. Subject has not completed the washout period for the immunosuppressants, biologics and other therapies as detailed in Table 6–1. Medications as presented in Table 6–1 are prohibited during the study.

    Subject is currently receiving any of the prohibited medications listed in Section 7.8.2 or receiving immunosuppressant medications in doses higher than the maximum permissible dose for the study as per Section 7.8.1.

Table 6–1: Washout periods for immunosuppressants, biologics and other therapies

Generic name (most common commercial/trade names)	Washout period relative to Baseline Visit (regardless of route)
Immunosuppressants	
Cyclophosphamide	6 months
Pimecrolimus (Elidel®)	4 weeks
Vinca alkaloids (vincristine, vinblastine)	12 weeks
Biologics (mAbs and fusion proteins)	
Abatacept (CTLA 4-Ig) (Orencia®)	6 months
Belimumab (Benlysta™)	6 months
Golimumab (Simponi™)	6 months
Natalizumab (Tysabri®)	6 months
Ofatumumab (Arzerra)	6 months
Rituximab (Rituxan®) and ocrelizumab	6 months
TACI-Ig (Atacicept)	10 months
Veltuzumab	6 months
Other biologics	3 months
Others	
Intravenous immunoglobulin	4 weeks
IPP-201101 (Lupuzor™)	3 months
Plasma exchange (PLEX)	4 weeks
TPO-R agonists (eltrombopag, romiplostim)	4 weeks
Anti-D	4 weeks
Antiplatelets and Anticoagulants (Vitamin K antagonists)	
Warfarin	2 weeks
Fenprocoumon	2 weeks
Acenocoumarol	2 weeks
Heparin	1 week
Clopidogrel	1 week
Salicylates (Aspirin)	1 week
Dipyramidole	1 week

Table 6–1: Washout periods for immunosuppressants, biologics and other therapies

Generic name (most common commercial/trade names)	Washout period relative to Baseline Visit (regardless of route)
Prasugrel	1 week
Ticagrelor	1 week
Tirofiban	1 week
Abciximab	1 week

31. Subject has undergone a splenectomy in the 3 months prior to the Baseline Visit or subject was splenectomized >3 months prior to Baseline but was not vaccinated following local recommendations.
32. Subject has received IVIg in the 4 weeks prior to the Baseline Visit.
33. Subject has received TPO-R agonists in the 4 weeks prior to Baseline Visit.
34. Subject has received cyclophosphamide in the 6 months prior to the Baseline Visit.
35. Subject has received anti-D immunoglobulin in the 4 weeks prior to the Baseline Visit.

6.3 Rescreening

Subjects with isolated test results that are outside the specified ranges and that are deemed potentially as clinically non-significant can be enrolled without retesting at the discretion of the investigator, following discussion and agreement with the Medical Monitor/study physician, if appropriate. If a subject has 1 isolated test result outside the specific range which is deemed clinically significant, retesting may be allowed at the discretion of the investigator, following discussion and agreement with the Medical Monitor/study physician. If the normalization of the test result occurs within the Screening Period, then no other screening procedures need to be repeated.

6.4 Withdrawal criteria

Subjects are free to withdraw from the study at any time, without prejudice to their continued care.

Subjects should be withdrawn from the study if any of the following events occur:

1. Subject withdraws his/her consent.
2. Subject develops an illness or has a change in health status that would interfere with his/her continued participation, including but not limited to:
   - Subject has a serious infective episode requiring hospitalization or iv antibiotic therapy (including but not limited to bacteremia or sepsis, bacterial meningitis, osteomyelitis or septic arthritis, bacterial pneumonia, or visceral abscess).
   - Subject experiences a severe AE of gastrointestinal disturbance or headache which is considered related to the IMP in the opinion of the investigator.

- Subject has a severe infusion reaction requiring corticosteroid and/or epinephrine therapy.
- Subject has an anaphylactic reaction requiring corticosteroid and/or epinephrine therapy.
- Subject has a life threatening bleeding event.
- Subject has a TB test that is confirmed positive or any further evidence suggestive of potential TB infection (eg, close exposure) and further examinations result in a diagnosis of active TB or LTB. Refer to Section 12.8.1 for further details and instructions.
- If an NTMBI infection is identified during a study, the same withdrawal procedures as those used for an active TB infection identified during the study should be followed.

3. Subject requires rescue therapy (Section 7.8.3).
4. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
5. The sponsor or a regulatory agency requests withdrawal of the subject.

Subjects MAY be withdrawn from the study if any of the following events occur:

1. Subject is noncompliant with the study procedures or medications in the opinion of the investigator.
2. Subject takes prohibited concomitant medications as defined in this protocol that could compromise subject's safety.

Subjects MUST stop treatment with the IMP if the platelet count is >350x10^9/L during the Dosing Period. Subjects should continue in the study and attend the protocol defined visits in the Observation Period.

6.4.1 Potential drug induced liver injury IMP discontinuation criteria

Subjects with PDILI must be assessed to determine if IMP must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

The PDILI criteria below require **immediate and permanent** discontinuation of IMP:

- Subjects with either of the following:
  - ALT or AST ≥5xULN
  - ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN

The PDILI criterion below requires immediate discontinuation of IMP:

- Subjects with ALT or AST ≥3xULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, right upper quadrant pain or tenderness. Hypersensitivity symptoms include fever (without clear alternative cause), rash, or eosinophilia (ie, >5%).

If a nondrug-related cause for the symptoms can be confirmed, these subjects may resume IMP administration after discussion with responsible UCB physician, but only when the requirements for rechallenge with IMP as provided in Section 12.7.1.2.1 are followed.

The PDILI criterion below allows for subjects to continue on IMP at the discretion of the investigator.

- Subjects with ALT or AST ≥3xULN (and ≥2x Baseline) and <5xULN, total bilirubin <2xULN, and no eosinophilia (ie, ≤5%), with no fever, rash, or symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain, or tenderness).

Evaluation of PDILI must be initiated as described in Section 12.7.1. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

- For all other withdrawal criteria, investigators should contact the Medical Monitor, whenever possible, to discuss the withdrawal of a subject in advance. Subjects who are withdrawn will not be replaced.

Subjects who decide to withdraw from the study will be encouraged to return to the clinic for all visits during the Observation Period and to complete the End-of-Study Visit (scheduled 8 weeks after final dose of IMP). If a subject is unwilling to complete the Observation Period, then subjects will be encouraged to complete at least 2 more study visits: Early Withdrawal Visit and End-of-Study Visit.

Investigators should attempt to obtain information on subjects in the case of withdrawal or discontinuation. For subjects considered as lost to follow up, the investigator should make an effort (at least 1 phone call and 1 written message to the subject), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the subject, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal or discontinuation. In case the subject is early terminated due to withdrawal of consent, the reason why the subject withdrew consent should be added to the eCRF.

6.5 Study stopping rules

During the clinical study, planned dosing may be discontinued for all subjects on a dose level, but subjects will be required to attend all visits during the Observation Period. Possible reasons for discontinuation of a dose level include (but are not limited to):

- In the opinion of the DMC, a clinically significant event or a pattern of events occur that contraindicate the dosing of any more subjects.
- If the DMC judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP).

More detailed criteria for stopping a dose arm will be defined in the DMC charter.

7 STUDY TREATMENT

7.1 Description of investigational medicinal product

UCB7665 product is supplied as a lyophilized powder in a 10mL Type I glass vial with a rubber stopper, sealed with an aluminum overseal and flip-off overcap. Prior to use, the lyophilized vials have to be reconstituted with 4mL of diluent ([redacted]). [redacted]

[redacted]

7.2 Treatment to be administered

Subjects in Dose Arm 1 will receive 5 sc doses of UCB7665 4mg/kg at 1-week intervals.
Subjects in Dose Arm 2 will receive 3 sc doses of UCB7665 7mg/kg at 1-week intervals.
Subjects in Dose Arm 3 will receive 2 sc doses of UCB7665 10mg/kg at a 1-week interval.
Subjects in Dose Arm 4 will receive 1 sc dose of UCB7665 15mg/kg.
Subjects in Dose Arm 5 will receive 1 sc dose of UCB7665 20mg/kg.

The IMP will be administered as a sc infusion using an infusion pump:

The perfusor will be programmed at a constant flow rate of 20mL/h for all subjects. In the case of any blockage of the infusion, a suitable flush (eg, 0.9% sodium chloride) is allowed.

The subject's body weight at Screening Visit will be used for the dose calculation. The dose will be constant for a subject throughout the duration of the study, and will not be adjusted during the treatment.

The exact procedure for dose preparation according to dose arm and body weight will be provided in a pharmacy manual.

The infusion rate may be reduced at any time at the discretion of the investigator. If an infusion is interrupted, it can be restarted if the investigator considers it appropriate to do so. The chronology of these events should be recorded accurately in the source data and eCRF.

In the event of a severe infusion reaction, the subject must permanently discontinue IMP (see Section 12.1.10).

7.3 Packaging

The IMP is manufactured, packaged, and labeled according to Good Manufacturing Practice (GMP) guidelines and applicable laws or regulations. The IMP is suitably packaged in such a way as to protect the IMP from deterioration during transport and storage.

7.4 Labeling

Clinical drug supplies will be labeled in accordance with the current International Council for Harmonisation (ICH) guidelines on GCP and GMP and will include any locally required statements. If necessary, labels will be translated into the local language.

7.5 Handling and storage requirements

The investigator (or designee) is responsible for the safe and proper storage of IMP at the site. Investigational medicinal product stored by the investigator is to be kept in a secured area with limited access.

Appropriate storage conditions must be ensured either by controlled fridge temperature or by completion of a temperature log in accordance with local requirements on a regular basis (eg, once a day), showing minimum and maximum temperatures reached over the time interval.

In case an out-of-range temperature is noted, it must be immediately communicated to the Clinical Project Manager (CPM) (or designee) before further use of the IMP.

The CPM (or designee) will transmit the out-of-range temperature (copy of the temperature log and duration of the out-of-range temperature, if available) to the Clinical Supply Manager or designee. Based on discussion with a UCB Quality Assurance representative, the Clinical Supply Manager or designee will then provide the CPM (or designee) with instructions for the site regarding use of the IMP.

7.6 Drug accountability

A Drug Accountability form will be used to record IMP dispensing and return information on a by-subject basis and will serve as source documentation during the course of the study. Details of any IMP lost (due to breakage or wastage), not used, disposed of at the study site, or returned to the sponsor or designee must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

The investigator (or designee) is responsible for retaining all used, unused, and partially used containers of IMP until returned or destroyed.

The investigator may assign some of the investigator's duties for drug accountability at the study site to an appropriate pharmacist/designee.

The investigator must ensure that the IMP is used only in accordance with the protocol.

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers) and unused IMP containers must be reconciled and returned to UCB (or designee), preferably in their original package or destroyed on site. Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

7.7 Procedures for monitoring subject compliance

Drug accountability is ensured by administering the IMP as sc infusion by designated personnel. Drug accountability must be recorded on the Drug Accountability form.

7.8 Concomitant medication/treatment

7.8.1 Permitted immunosuppressant medications

The following concomitant immunosuppressant medications are permitted during the course of the study at a stable dose.

Table 7–1: Permitted immunosuppressant medications

Permitted medications	Dose	Comment
Oral corticosteroids (prednisolone)	≤10mg/day	Stable dose for 2 weeks prior to Baseline
Methotrexate	≤30mg/week	Stable dose for 2 months prior to Baseline
Mycophenolate mofetil	≤3g/day	Stable dose for 2 months prior to Baseline
Cyclosporin	≤5mg/kg/day	Stable dose for 2 months prior to Baseline
Azathioprine	≤3mg/kg/day	Stable dose for 2 months prior to Baseline
Danazol	≤15mg/kg/day	Stable dose for 2 months prior to Baseline
Dapsone	100mg/day	Stable dose for 2 months prior to Baseline

In the event of a subject developing an infection during the course of the study, samples for culture will be taken prior to commencing antimicrobial treatment. Antimicrobial treatment may be modified accordingly when the identity of the infective organism is known.

Vaccines (with the exception of live vaccines) and prophylactic antibiotics are permitted in splenectomized subjects.

7.8.2 Prohibited concomitant treatments (medications and therapies)

The following concomitant medications are prohibited during the study:

- IVIg
- All biologics including rituximab
- Cyclophosphamide
- Pimecrolimus
- IPP-201101 (Lupuzor™)
- PLEX
- Immunoadsorption
- Anti-D
- TPO-R agonists (eltrombopag, romiplostim)
- Dexamethasone
- Vinca alkaloids (vincristine, vinblastine)
- Anticoagulants and antiplatelets (warfarin, heparin, clopidogrel, aspirin, salicylics, dipyramidole, prasugrel, tricagrelor, tirofiban, abciximab)

If a subject needs or takes any prohibited medication (except IVIg, PLEX, dexamethasone or rituximab), the investigator will (where possible) discuss with the Medical Monitor and a decision will be made whether the subject can continue in the study or must be withdrawn. If

subject needs IVIg, PLEX, dexamethasone or rituximab, the subject must be withdrawn from the study.

7.8.3 Rescue medication

In the case of prolonged hypogammaglobulinemia the subject will be considered for treatment with prophylactic antimicrobial therapy. Subjects will be followed up until immunoglobulin levels return to within the normal range.

In case of lack of efficacy and/or severe bleeding events and where appropriate, platelet substitution or treatment with a commercially available iv immunoglobulin may be considered.

If such rescue medication must be given when the subject is still in the dosing period, the subject should be withdrawn from the study treatment and complete all Observation visits, if possible.

If such rescue medication is given when the subject has completed the study treatment, the subject should continue the Observation Visits, as per schedule of study assessments (Section 5.2).

7.9 Blinding

This is an open-label study and blinding is not applicable.

7.10 Randomization and numbering of subjects

An IXRS will be used for assigning eligible subjects to a treatment regimen based on a predetermined production randomization and/or packaging schedule provided by PAREXEL Informatics. The IXRS will generate individual assignments for subject kits of IMP, as appropriate, according to the dose arm and subject's weight.

The first 6 subjects (and those treated before DMC assessment after the 6 subjects) will not be randomized. Once the DMC has advocated the initiation of Dose Arm 2 for enrollment, subsequent subjects will be randomly assigned to 1 of the 2 dose arms (ie, Dose Arm 1 and Dose Arm 2) in a 1:1 ratio. Once 15 subjects are enrolled in the Dose Arm 1, the remaining subjects will be enrolled in Dose Arm 2 until Dose Arm 2 is completed with 15 subjects.

After Dose Arm 2, there will be no randomization between dose arms.

To enroll a subject (Visit 1), the investigator or designee will contact the IXRS and provide brief details about the subject to be enrolled. Each subject will receive a 5-digit number assigned at screening that serves as the subject identifier throughout the study. The subject number will be required in all communication between the investigator or designee and the IXRS regarding a particular subject. Subject numbers and kit numbers will be tracked via the IXRS.

To randomize a subject, the investigator or designee will contact the IXRS and provide brief details about the subject to be randomized. The IXRS will automatically inform the investigator or designee of the subject's kit number. The IXRS will allocate kit numbers to the subject based on the subject number or randomization during the course of the study.

8 STUDY PROCEDURES BY VISIT

A detailed tabular schedule of study procedures is provided in Section 5.2.

8.1 Screening Period

8.1.1 Visit 1 (Day -28 to -1) Screening Visit (all Dose Arms)

At Visit 1, subjects will be evaluated for their suitability for enrollment. Prior to the conduct of any study-related procedures, a complete explanation (both verbal and written) of the nature and purpose of the study will be given to the subject by the investigator (or designee). The subject is required to sign and date the IRB/IEC-approved Informed Consent form if he/she decides to participate in the study.

Subjects will also have the option of providing additional voluntary informed consent for collection of whole blood samples for exploratory DNA and RNA analyses.

The subject's eligibility for the study will be determined on the basis of the inclusion/exclusion criteria and signature of an informed consent prior to any study-related procedures or evaluations. The following assessments and procedures will be performed during Visit 1 of TP0001:

- Obtain written informed consent
- Obtain informed consent for substudy involving DNA and RNA analyses
- Assessment of inclusion/exclusion criteria
- Demographic data (includes date of birth, gender, and race/ethnicity)
- General medical and procedure history
- ITP history
- Prior and concomitant medications
- Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate)
- Body weight
- Height
- Physical examination (complete)
- 12-lead ECG (triplicate)
- Karnofsky Performance Status
- Recording of AEs
- Urine sample for urinalysis
- Blood sample for the following:
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry (two blood samples for assessment of platelet count to be obtained via 2 separate blood collections)
  - Serum pregnancy test for women of childbearing potential
  - Serum total IgG and IgG subclasses concentration

  - Serum HbA1c
  - Serology tests for HIV, hepatitis B, and hepatitis C
  - IGRA TB test
- ITP bleeding scale
- TB signs and symptoms questionnaire

8.2 Dosing Period for all Dose Arms

8.2.1 Visit 2 (Week 1/Day 1) Baseline Visit

Visit 2 can occur at any time after Visit 1, but no later than 28 days after Visit 1. Prior to dosing at Visit 2, 2 platelet samples will be taken. One sample will be analyzed locally and the value will be used to check inclusion criterion. The other platelet sample will be sent to the central laboratory.

Eligible subjects will be treated with IMP at Visit 2.

Subjects allocated to Dose Arm 1 (UCB7665 4mg/kg weekly sc) will receive a total of 5 doses of IMP at Visit 2 (Day 1, Week 1), Visit 4 (Week 2), Visit 5 (Week 3), Visit 6 (Week 4), and Visit 7 (Week 5).

Subjects allocated to Dose Arm 2 (UCB7665 7mg/kg weekly sc) will receive a total of 3 doses of IMP at Visit 2 (Day 1, Week 1), Visit 4 (Week 2), and Visit 5 (Week 3).

Subjects allocated to Dose Arm 3 (UCB7665 10mg/kg weekly sc) will receive a total of 2 doses of IMP at Visit 2 (Day 1, Week 1) and Visit 4 (Day 8, Week 2).

Subjects allocated to Dose Arm 4 (UCB7665 15mg/kg) will receive 1 dose of IMP at Visit 2 (Day 1, Week 1).

Subjects allocated to Dose Arm 5 (UCB7665 20mg/kg) will receive 1 dose of IMP at Visit 2 (Day 1, Week 1).

The following assessments will be performed at this visit (predose unless stated otherwise):

- Reconfirm inclusion/exclusion criteria
- Serum platelets for inclusion/exclusion check
- Call IXRS to obtain treatment kit number(s)
- Concomitant medications
- Concomitant medical procedures
- Vital signs (systolic and diastolic blood pressure, pulse rate, and temperature) assessed prior to dosing, every 15 minutes during infusion, end of infusion, and 2 and 4 hours after end of infusion; respiratory rate to be assessed only once prior to dosing
- Recording of AEs (assessed predose, at end of infusion, and at 2 and 4 hours after end of infusion)
- Subjects in Dose Arms 1 and 2 will stay on site for 4 hours after the end of infusion for inpatient observation at the site.

- Subjects in Dose Arms 3, 4 and 5 will stay on site for 6 hours after the end of infusion for inpatient observation at the site.
- Physical examination (abbreviated)
- 12-lead ECG (triplicate)
- Urine pregnancy test for women of childbearing potential
- Urine sample for urinalysis
- Blood sample for the following:
  - Plasma concentration of UCB7665
  - Anti-UCB7665 antibodies
  - Serum total IgG and IgG subclasses concentration
  - Serum IgA, IgM, and IgE concentration
  - ITP-specific autoantibodies [redacted]
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Additional platelet sample for analysis in local laboratory for evaluation of the inclusion criteria of platelet count <$35x10^9$/L at Baseline
  - Serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a)
  - Exploratory safety biomarkers [redacted]. Blood samples are taken prior to dosing, 2 and 4 hours after end of infusion for exploratory safety biomarkers
  - Serum BAFF levels
  - Exploratory biomarker analysis
  - Serum cytokines mandatory for all subjects at pre-dose, and only in case of infusion reactions at 4 hours after end of infusion
- Collection of whole blood for exploratory DNA and RNA analyses
- ITP bleeding scale
- NFI-MS
- Administration of IMP
- Review withdrawal criteria
- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to computed tomography (CT) scan, magnetic resonance imaging (MRI) and/or lumbar puncture (LP) for cerebrospinal fluid (CSF) collection to be performed

if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

8.2.2 Visit 3 (Week 1/Day 4) [UCB7665 4mg/kg, UCB7665 7mg/kg, and UCB7665 10mg/kg]

This is a nondosing visit. A visit window of ±1 day relative to Dose 1 at the Visit 2 date is allowed for this visit. The following assessments will be performed at this visit:

- Concomitant medications
- Concomitant medical procedures
- Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate)
- Recording of AEs
- Urine sample for urinalysis
- Blood sample for the following:
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Plasma concentration of UCB7665
  - Anti-UCB7665 antibodies
  - Serum total IgG and IgG subclasses concentration
  - Exploratory safety biomarkers [redacted] only from subjects experiencing severe headaches or GI disturbances (only in case of Adverse Events of Interest, see Section 12.4)
- Review withdrawal criteria
- Serum cytokines, only in case of late infusion reactions visible during the visit
- For Dose Arm 1, 2, and 3 collection of whole blood for exploratory RNA analyses
- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

8.2.3 Visit 4 (Week 2/Day 8) [UCB7665 4mg/kg, UCB7665 7mg/kg and UCB7665 10mg/kg]

This is the second dosing visit and a window of ±2 days is allowed for this visit, relative to Dose 1 at the Visit 2 date. However, there should be a minimum of 5 days and a maximum of 9 days since the last dosing day. The following assessments will be performed at this visit (predose unless stated otherwise):

- Concomitant medications

- Concomitant medical procedures
- Vital signs (systolic and diastolic blood pressure, pulse rate, and temperature) assessed prior to dosing, every 15 minutes during infusion, end of infusion, and 2 and 4 hours after end of infusion; respiratory rate to be assessed only once prior to dosing
- Recording of AEs (assessed predose, at end of infusion, and at 2 and 4 hours after end of infusion)
- Subjects in Dose Arms 1 and 2 will stay on site for 4 hours after the end of infusion for inpatient observation at the site.
- Subjects in Dose Arms 3, 4 and 5 will stay on site for 6 hours after the end of infusion for inpatient observation at the site.
- Physical examination (abbreviated)
- 12-lead ECG (triplicate)
- Urine pregnancy test for women of childbearing potential
- Urine sample for urinalysis
- Call IXRS to obtain treatment kit number(s)
- Blood sample for the following:
  - Plasma concentration of UCB7665
  - Anti-UCB7665 antibodies
  - Serum total IgG and IgG subclasses concentration
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Additional platelet sample for analysis in local laboratory for evaluation of the withdrawal criteria of platelet count >350x10^9/L
  - Exploratory safety biomarkers [redacted] Blood samples are taken prior to dosing, 2 and 4 hours after end of infusion for exploratory serum biomarkers
  - Serum BAFF levels
  - Exploratory biomarker analysis
  - Serum cytokines at pre-dose mandatory for subjects on Dose Arm 3 (10mg/kg), and at 4 hours after end of infusion (for all dose arms)
- For Dose Arm 3, only collection of whole blood for exploratory DNA and RNA analyses
- ITP bleeding scale
- Administration of IMP
- Review withdrawal criteria

- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

8.2.4 Visit 5 (Week 3/Day 15) [UCB7665 4mg/kg and UCB7665 7mg/kg]

This is the third dosing visit and a window of ±2 days is allowed for this visit, relative to Dose 1 at the Visit 2 date. However, there should be a minimum of 5 days and a maximum of 9 days since the last dosing day. The following assessments will be performed at this visit (predose unless stated otherwise):

- Concomitant medications
- Concomitant medical procedures
- Vital signs (systolic and diastolic blood pressure, pulse rate, and temperature) assessed prior to dosing, every 15 minutes during infusion, end of infusion, and 2 and 4 hours after end of infusion; respiratory rate to be assessed only once prior to dosing
- Recording of AEs (assessed predose, at end of infusion, and at 2 and 4 hours after end of infusion)
- Physical examination (abbreviated)
- 12-lead ECG (triplicate)
- Urine pregnancy test for women of childbearing potential
- Urine sample for urinalysis
- Call IXRS to obtain treatment kit number(s)
- Blood sample for the following:
  - Plasma concentration of UCB7665
  - Anti-UCB7665 antibodies
  - Serum total IgG and IgG subclasses concentration
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Additional platelet sample for analysis in local laboratory for evaluation of the withdrawal criteria of platelet count >350x10^9/L
  - Serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a)
  - Serum IgA, IgM, and IgE concentration (UCB7665 7mg/kg only)
  - Exploratory safety biomarkers (may include but not limited to: [redacted] Blood samples are taken prior to dosing, 2 and 4 hours after end of infusion for exploratory safety biomarkers

  - Serum BAFF levels
  - Exploratory biomarker analysis
- For Dose Arm 2 only, collection of whole blood for exploratory DNA and RNA analyses
- ITP bleeding scale
- Administration of IMP
- Review withdrawal criteria
- Serum cytokines, only in case of late infusion reactions visible during the visit
- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

8.2.5 Visit 6 for Dose Arm 1 (Week 4/Day 22) [UCB7665 4mg/kg only]

This is the fourth dosing visit (UCB7665 4mg/kg only) and a window of ±2 days is allowed for this visit, relative to Dose 1 at the Visit 2 date. However, there should be a minimum of 5 days and a maximum of 9 days since the last dosing day. The following assessments will be performed at this visit (predose unless stated otherwise):

- Concomitant medications
- Concomitant medical procedures
- Vital signs (systolic and diastolic blood pressure, pulse rate, and temperature) assessed prior to dosing, every 15 minutes during infusion, end of infusion, and 2 and 4 hours after end of infusion; respiratory rate to be assessed only once prior to dosing
- Recording of AEs (assessed predose, at end of infusion, and at 2 and 4 hours after end of infusion)
- Physical examination (abbreviated)
- 12-lead ECG (triplicate)
- Urine pregnancy test for women of childbearing potential
- Urine sample for urinalysis
- Call IXRS to obtain treatment kit number(s)
- Blood sample for the following:
  - Plasma concentration of UCB7665
  - Anti-UCB7665 antibodies
  - Serum total IgG and IgG subclasses concentration
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry

  - Additional platelet sample for analysis in local laboratory for evaluation of the withdrawal criteria of platelet count >350x10^9/L
  - Exploratory safety biomarkers [redacted] Blood samples are taken prior to dosing, 2 and 4 hours after end of infusion for exploratory safety biomarkers
  - Serum BAFF levels
  - Exploratory biomarker analysis
- ITP bleeding scale
- Administration of IMP
- Review withdrawal criteria
- Serum cytokines, only in case of late infusion reactions visible during the visit
- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

8.2.6 Visit 7 for Dose Arm 1 (Week 5/Day 29) [UCB7665 4mg/kg only]

This is the fifth dosing visit (UCB7665 4mg/kg only) and a window of ±2 days is allowed for this dosing visit, relative to Dose 1 at the Visit 2 date. However, there should be a minimum of 5 days and a maximum of 9 days since the last dosing day. The following assessments will be performed at this visit (predose unless stated otherwise):

Following assessments will be performed:

- Concomitant medications
- Concomitant medical procedures
- Vital signs (systolic and diastolic blood pressure, pulse rate, and temperature) assessed prior to dosing, every 15 minutes during infusion, end of infusion, and 2 and 4 hours after end of infusion; respiratory rate to be assessed only once prior to dosing
- Recording of AEs (assessed predose, at end of infusion, and at 2 and 4 hours after end of infusion)
- Physical examination (abbreviated)
- 12-lead ECG (triplicate)
- Urine pregnancy test for women of childbearing potential
- Urine sample for urinalysis
- Call IXRS to obtain treatment kit number(s)
- Blood sample for the following:

  - Plasma concentration of UCB7665
  - Anti-UCB7665 antibodies
  - Serum total IgG and IgG subclasses concentration
  - Serum IgA, IgM, and IgE concentration
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Additional platelet sample for analysis in local laboratory for evaluation of the withdrawal criteria of platelet count >350x10^9/L
  - Exploratory safety biomarkers [redacted] Blood samples are taken prior to dosing, 2 and 4 hours after end of infusion for exploratory safety biomarkers
  - Serum BAFF levels
  - Exploratory biomarker analysis
- For Dose Arm 1 only, collection of whole blood for DNA and RNA analyses
- ITP bleeding scale
- Administration of IMP
- Review withdrawal criteria
- Serum cytokines, only in case of late infusion reactions visible during the visit
- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

8.3 Telephone Contacts

For Dose Arms 3, 4 and 5 the site must make a phone call to the subject on Day 1 and Day 2 after dosing as a safety measure.

8.3.1 Telephone Contact 1 (Week 1/Day 2) [UCB7665 10mg/kg, UCB7665 15mg/kg, UCB7665 20mg/kg]

- Concomitant medications
- Concomitant medical procedures
- Recording of AEs

8.3.2 Telephone Contact 2 (Week 1/Day 3) [UCB7665 10mg/kg, UCB7665 15mg/kg, UCB7665 20mg/kg]

- Concomitant medications

- Concomitant medical procedures
- Recording of AEs

8.3.3 Telephone Contact 3 (Week 2/Day 9) [UCB7665 10mg/kg only]

- Concomitant medications
- Concomitant medical procedures
- Recording of AEs

8.3.4 Telephone Contact 4 (Week 2/Day 10) [UCB7665 10mg/kg only]

- Concomitant medications
- Concomitant medical procedures
- Recording of AEs

8.4 Observation Period

The Observation Period will last for 8 weeks following the final dose administration. The first visit in the Observation Period will be performed 3 days after the final dose administration and subsequent visits will be performed at weekly intervals (except for a 2-week interval before the final visit).

For UCB7665 4mg/kg weekly dose (Dose Arm 1), the following visits will be performed: Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13, Visit 14, and Visit 15, corresponding to UCB7665 7mg/kg weekly dose (Dose Arm 2) on Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, and Visit 13.

For the UCB7665 10mg/kg weekly dose (Dose Arm 3), the following visits will be performed: Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, and Visit 12.

For the UCB7665 15 mg/kg dose (Dose Arm 4) and the UCB7665 20mg/kg dose (Dose Arm 5), the following visits will be performed: Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8, Visit 9 and Visit 10.

8.4.1 Visit 8 (Week 5/Day 32) [UCB7665 4mg/kg]/ Visit 6 (Week 3/Day 18) [UCB7665 7mg/kg]/ Visit 5 (Week 2/Day 11) [UCB7665 10mg/kg] Visit 3 (Week 1/Day 4) [UCB7665 15mg/kg and UCB7665 20mg/kg]

This is the first visit in the Observation Period and will be performed 3 days after the final dose of the IMP. A visit window of ±1 day relative to the final dosing visit is allowed for this visit. The following assessments will be performed at this visit:

- Concomitant medications
- Concomitant medical procedures
- Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate)
- Recording of AEs

- Urine sample for urinalysis
- Blood sample for the following:
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Plasma concentration of UCB7665
  - Anti-UCB7665 antibodies
  - Serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a)
  - Exploratory safety biomarkers [redacted] only from subjects experiencing severe headaches or GI disturbances (only in case of Adverse of Interest, see Section 12.4).
  - Serum total IgG and IgG subclasses concentration
- Serum cytokines, only in case of late infusion reactions visible during the visit
- For Dose Arm 4 and 5 collection of whole blood for exploratory RNA analyses
- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

8.4.2 Visit 9 (Week 6/Day 36) [UCB7665 4mg/kg]/ Visit 7 (Week 4/Day 22) [UCB7665 7mg/kg]/ Visit 6 (Week 3/Day 15) [UCB7665 10mg/kg] Visit 4 (Week 2/Day 8) [UCB7665 15mg/kg and UCB7665 20mg/kg]

This is the second visit in the Observation Period. A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. The following assessments will be performed at this visit:

- Concomitant medications
- Concomitant medical procedures
- Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate)
- Recording of AEs
- Physical examination (abbreviated)
- 12-lead ECG (triplicate)
- Urine sample for urinalysis

- Blood sample for the following:
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Plasma concentration of UCB7665
  - Anti-UCB7665 antibodies
  - Exploratory safety biomarkers [redacted] only from subjects experiencing severe headaches or GI disturbances (only in case of Adverse Events of Interest, see Section 12.4).
  - Serum total IgG and IgG subclasses concentration
  - Serum IgA, IgM, and IgE concentration
  - ITP-specific autoantibodies [redacted]
- ITP bleeding scale
- NFI-MS
- Serum cytokines, only in case of late infusion reactions visible during the visit
- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

8.4.3 Visit 10 (Week 7/Day 43) [UCB7665 4mg/kg]/ Visit 8 (Week 5/Day 29) [UCB7665 7mg/kg]/ Visit 7 (Week 4/Day 22) [UCB7665 10mg/kg] Visit 5 (Week 3/Day 15) [UCB7665 15mg/kg and UCB7665 20mg/kg]

This is the third visit in the Observation Period. A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. This visit can be performed at home with a healthcare professional visiting the subject at his/her home. The following assessments will be performed at this visit:

- Concomitant medications
- Concomitant medical procedures
- Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate)
- Recording of AEs
- Urine sample for urinalysis

- Blood sample for the following:
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Anti-UCB7665 antibodies
  - Exploratory safety biomarkers [redacted], only from subjects experiencing severe headaches or GI disturbances (only in case of Adverse Events of Interest, see Section 12.4)
  - Serum BAFF levels
  - Exploratory biomarker analysis
  - Serum total IgG and IgG subclasses concentration
- Serum cytokines, only in case of late infusion reactions visible during the visit
- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

8.4.4 Visit 11 (Week 8/Day 50) [UCB7665 4mg/kg]/ Visit 9 (Week 6/Day 36) [UCB7665 7mg/kg]/ Visit 8 (Week 5/Day 29) [UCB7665 10mg/kg] Visit 6 (Week 4/Day 22) [UCB7665 15mg/kg and UCB7665 20mg/kg]

This is the fourth visit in the Observation Period. A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. The following assessments will be performed at this visit:

- Concomitant medications
- Concomitant medical procedures
- Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate)
- Recording of AEs
- Physical examination (abbreviated)
- Urine sample for urinalysis
- Blood sample for the following:
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Exploratory safety biomarkers [redacted] only from

subjects experiencing severe headaches or GI disturbances (only in case of Adverse Events of Interest, see Section 12.4)

- Serum total IgG and IgG subclasses concentration

- ITP bleeding scale
- NFI-MS
- Serum cytokines, only in case of late infusion reactions visible during the visit
- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

8.4.5 Visit 12 (Week 9/Day 57) [UCB7665 4mg/kg]/ Visit 10 (Week 7/Day 43) [UCB7665 7mg/kg]/ Visit 9 (Week 6/Day 36) [UCB7665 10mg/kg] Visit 7 (Week 5/Day 29) [UCB7665 15mg/kg and UCB7665 20mg/kg]

This is the fifth visit in the Observation Period. A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. This visit can be performed at home with a healthcare professional visiting the subject at his/her home. The following assessments will be performed at this visit:

- Concomitant medications
- Concomitant medical procedures
- Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate)
- Recording of AEs
- Urine sample for urinalysis
- Blood sample for the following:
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Anti-UCB7665 antibodies
  - Serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a)
  - Exploratory safety biomarkers [redacted], only from subjects experiencing severe headaches or GI disturbances (only in case of Adverse Events of Interest, see Section 12.4)
  - Serum total IgG and IgG subclasses concentration
- Serum cytokines, only in case of late infusion reactions visible during the visit

- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

8.4.6 Visit 13 (Week 10/Day 64) [UCB7665 4mg/kg]/ Visit 11 (Week 8/Day 50) [UCB7665 7mg/kg]/ Visit 10 (Week 7/Day 43) [UCB7665 10mg/kg] Visit 8 (Week 6/Day 36) [UCB7665 15mg/kg and UCB7665 20mg/kg]

This is the sixth visit in the Observation Period. A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. The following assessments will be performed at this visit:

- Concomitant medications
- Concomitant medical procedures
- Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate)
- Recording of AEs
- Physical examination (abbreviated)
- Urine sample for urinalysis
- Blood sample for the following:
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Serum total IgG and IgG subclasses concentration
  - Exploratory safety biomarkers [redacted], only from subjects experiencing severe headaches or GI disturbances (only in case of Adverse Events of Interest, see Section 12.4)
- ITP bleeding scale
- NFI-MS
- Serum cytokines, only in case of late infusion reactions visible during the visit
- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

8.4.7 Visit 14 (Week 11/Day 71) [UCB7665 4mg/kg]/ Visit 12 (Week 9/Day 57) [UCB7665 7mg/kg]/ Visit 11 (Week 8/Day 50) [UCB7665 10mg/kg] Visit 9 (Week 7/Day 43) [UCB7665 15mg/kg and UCB7665 20mg/kg]

This is the seventh visit in the Observation Period. A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. This visit can be performed at home with a healthcare professional visiting the subject at his/her home. The following assessments will be performed at this visit:

- Concomitant medications
- Concomitant medical procedures
- Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate)
- Recording of AEs
- Urine sample for urinalysis
- Blood sample for the following:
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Anti-UCB7665 antibodies
  - Exploratory safety biomarkers [redacted] only from subjects experiencing severe headaches or GI disturbances (only in case of Adverse Events of Interest, see Section 12.4)
  - Serum BAFF levels
  - Exploratory biomarker analysis
  - Serum total IgG and IgG subclasses concentration
  - Serum IgA, IgM, and IgE concentration
- Serum cytokines, only in case of late infusion reactions visible during the visit
- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

8.4.8 End-of-Study Visit: Visit 15 (Week 13/Day 85) [UCB7665 4mg/kg]/ Visit 13 (Week 11/Day 71) [UCB7665 7mg/kg]/ Visit 12 (Week 10/Day 64) [UCB7665 10mg/kg] Visit 10 (Week 9/Day 57) [UCB7665 15mg/kg and UCB7665 20mg/kg]

The End-of-Study Visit will be conducted 8 weeks after the final dose. A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. The following assessments will be performed at this visit:

- Concomitant medications
- Concomitant medical procedures
- Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate)
- Body weight
- Recording of AEs
- Physical examination (complete)
- 12-lead ECG (triplicate)
- Urine pregnancy test for women of childbearing potential
- Urine sample for urinalysis
- Blood sample for the following:
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Anti-UCB7665 antibodies
  - Serum total IgG and IgG subclasses concentration
  - ITP-specific autoantibodies [redacted]
- For all dose arms, collection of whole blood for exploratory RNA analyses
- ITP bleeding scale
- NFI-MS
- Subject exit interview
- Serum cytokines, only in case of late infusion reactions visible during the visit
- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.
- TB signs and symptoms questionnaire

8.5 Early Withdrawal Visit

All subjects who withdraw early from the study treatment should attend an Early Withdrawal Visit which will be scheduled as close as possible to the date of the decision for the study or treatment withdrawal. Subjects are encouraged to return to the clinic for all visits of the Observation Period following the Early Withdrawal Visit. The subjects will have their End-of-Study Visit scheduled 8 weeks after their final dose.

In case a subject is not willing to attend the visits in the Observation Period, the subjects should still be strongly encouraged to attend at least the Early Withdrawal Visit and End-of-Study Visit. The End-of-Study Visit should be scheduled 8 weeks after their last dose of IMP.

The assessments to be done at both the Early Withdrawal Visit as well as the End-of-Study Visit are the same as those at Visit 15 for the UCB7665 4mg/kg weekly (Dose Arm 1) group, Visit 13 for the UCB7665 7mg/kg weekly (Dose Arm 2) group, Visit 12 for the UCB7665 10mg/kg weekly (Dose Arm 3) group, or Visit 10 for the UCB7665 15mg/kg (Dose Arm 4) and UCB7665 20mg/kg (Dose Arm 5) groups, except for the subject exit interview which will be performed at the End-of-Study Visit only.

8.6 Unscheduled Visit

Unscheduled visits may include the following assessments or other assessments deemed necessary by the investigator:

- Concomitant medication
- Concomitant medical procedures
- Recording of AEs
- Vital signs (systolic and diastolic blood pressure, pulse rate, and temperature)
- Serum cytokines, only in case of late infusion reactions visible during the visit
- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment. Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

Other safety assessments (eg, physical examination, 12-lead ECG, laboratory assessments) may be performed at the discretion of the investigator.

In the event of a subject developing an infection during the course of the study, samples for culture will be taken prior to commencing antimicrobial treatment.

9 ASSESSMENT OF EFFICACY

9.1 Platelet counts

For assessment of platelet counts, blood samples will be collected by qualified site personnel at the same time that samples are collected for standard clinical laboratory assessments. The time and date of the blood draws will be recorded in medical source data and the eCRF. Assessment will be performed according to the schedule of study assessments (Section 5.2).

Platelet counts will be determined by a central laboratory and the following variables will be computed in the statistical database for the purpose of analysis:

- Response by visit and Response at least once during the study
- Complete Response by visit and Complete Response at least once during the study
- Platelet count $\geq 50x10^9$/L by visit and at least once during the study
- Value and change from Baseline in platelet count by visit
- Baseline-corrected AUEC for platelet count calculated from Baseline to the end of study visit
- Maximum value and maximum increase from Baseline
- Time to Response
- Time to Complete Response
- Time to achieving platelet count $\geq 50x10^9$/L
- Duration of Response
- Duration of Complete Response
- Duration of platelet count $\geq 50x10^9$/L
- Clinical Response: platelet count $\geq 30x10^9$/L and at least 2-fold increase from Baseline value and absence of bleeding
- Time to Clinical Response: time from starting treatment to achievement of Clinical Response
- Duration of Clinical Response: measured from achievement of Clinical Response to loss of Clinical Response (loss of Clinical Response defined as platelet count $<30x10^9$/L or less than 2-fold increase from Baseline platelet count or presence of bleeding)
- Complete Clinical Response: platelet count $\geq 100x10^9$/L and absence of bleeding
- Time to Complete Clinical Response: time from starting treatment to achievement of Complete Clinical Response
- Duration of Complete Clinical Response: measured from achievement of Complete Clinical Response to loss of Complete Clinical Response (loss of Complete Clinical Response defined as platelet count $<100x10^9$/L or presence of bleeding)
- No Clinical Response: platelet count $<30x10^9$/L or less than 2-fold increase from Baseline or presence of bleeding

The clinical response variables will be assessed only for visits for which both platelet counts and the ITP bleeding score are assessed (with the exception of the confirmatory platelet assessments which may be obtained at any visit [scheduled or unscheduled] provided that they meet the criteria below). In order to define a clinical response, the platelet count must be confirmed on 2 separate occasions at least 7 days apart (ie, the second assessment should be ≥168 hours after the first assessment). The time to response will be taken as the time to the first platelet assessment (obtained at the same time as the corresponding ITP bleeding score assessment). If the second assessment does not fulfill the required criteria for a clinical response, the subject will be

considered as a nonresponder at the respective visits. In order to define a clinical response (or no clinical response), the platelet count must be confirmed on 2 separate occasions; further details will be provided in the SAP. Absence of bleeding is indicated by Grade 0 for all domains of the SMOG. Presence of bleeding is indicated by a Grade of 1 or above, for at least one domain of the SMOG.

Refer to Section 14 for details of statistical analysis of these variables.

9.2 ITP bleeding score

The International Working Group on ITP now proposes a consensus-based ITP-specific Bleeding Assessment Tool (ITP-BAT), based on a precise definition of bleeding manifestations and on the grading of their severity (Rodeghiero et al, 2013). The ITP bleeding score will be assessed using the ITP-BAT tool version 1.0. Assessment will be performed according to the schedule of study assessments (Section 5.2).

For the ITP-BAT, bleeding manifestations were grouped into 3 major domains: skin (S), visible mucosae (M), and organs (O), with gradation of severity (SMOG). Each bleeding manifestation is assessed at the time of examination. Severity is graded from 0 to 3 or 4, with grade 5 for any fatal bleeding. Bleeding reported by the subject without medical documentation is graded 1. Within each domain, the same grade is assigned to bleeding manifestations of similar clinical impact. The "worst" bleeding manifestation since the last Observation Period visit is graded, and the highest grade within each domain is recorded. The SMOG system provides a consistent description of the bleeding phenotype in ITP.

A standardized data collection form will be used to facilitate collection of information and communication among physicians and investigators. The grading of bleeding symptoms at presentation and at each subsequent evaluation is presented in Appendix 18.2.

9.3 Patient reported outcomes

Subjects will complete 1 questionnaire (NFI-MS) and 1 subject exit interview as per time points mentioned in the schedule of study assessments in Section 5.2. Administration of the questionnaire and the subject exit interview should be performed by study personnel other than the treating physician. The questionnaire and the subject exit interview should be completed in a quiet place and by the subject themselves.

The questionnaire and the subject exit interview should be completed in the following order: NFI-MS followed by the subject exit interview which will be performed only at last visit. The questionnaire and the subject exit interview should only be checked for completeness. On dosing days, the NFI-MS questionnaire will be completed prior to dosing.

9.3.1 NFI-MS

The NFI-MS was developed in multiple sclerosis and consists of 23 items in 4 subscales of Physical (8 items), Cognitive (4 items), Relief by diurnal sleep or rest (6 items) and Abnormal nocturnal sleep and sleepiness (5 items). A summary score is available comprising items from the Physical and Cognitive subscales. The measurement properties have been established using Rasch analysis (Mills et al, 2013; Mills et al, 2010).

Each item has a 4 point, Likert response option. There is a single sentence instruction at the start of the scale asking respondents to consider their experience over the previous 2 weeks.

Using the interval level NFI-MS scores, the largest minimal clinically important difference (MCID) equated to 2.49 points on the Summary scale, 2.36 points on the Physical scale, 0.84 points on the Cognitive scale, 0.97 on the Diurnal Sleep scale and 1.95 on the Nocturnal Sleep scale (Mills et al, 2013). The NFI-MS questionnaire is available as Appendix 18.3.

9.4 Subject exit interview

At the last clinic visit, subject interview will be conducted using a semi-structured interview guide by a study nurse/study personnel. The aim is to collect the subject's experience with living with ITP in terms of symptoms and impact on daily activities, and the perceived changes during the course of the study. In addition, the relevance of the NFI-MS in ITP will be assessed. The interviews will be recorded. If a subject leaves the study prematurely, he/she will also be invited to participate in an exit interview.

10 ASSESSMENT OF PHARMACOKINETIC/ PHARMACODYNAMIC VARIABLES

10.1 Pharmacokinetic variables

The plasma concentration of UCB7665 will be characterized. Blood samples will be drawn according to the schedule of study assessments Section 5.2

All blood samples will be collected before dosing with UCB7665 at the dosing visits, and will be drawn at the same time of the sampling for standard clinical laboratory tests. The time and date of collection will be recorded in the eCRF.

Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual for this study.

10.2 Pharmacodynamic variables

For all PD assessments, blood samples will be collected predose (at dosing visits) by qualified site personnel at the same time that samples are collected for standard clinical laboratory assessments. Blood samples for PD analyses will be drawn according to the schedule of study assessments (Section 5.2). The time and date of collection will be recorded in the eCRF. Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual for this study.

- Serum IgG concentrations
- Serum IgG subclass concentrations
- Serum ITP-specific autoantibody

[redacted]

11 ASSESSMENT OF OTHER IMMUNOLOGICAL VARIABLES

For all immunological assessments, blood samples will be collected predose (at dosing visits) by qualified site personnel at the same time that samples are collected for standard clinical laboratory. The time and date of the blood draws will be recorded in the eCRF. The following

immunological assessments will be performed according to the schedule of study assessments (Section 5.2).

- Serum immunoglobulin concentration over time
  - IgA
  - IgE
  - IgM
- Serum complement levels over time
  - C3
  - C4
- Plasma complement levels over time
  - C3a
  - C5a
- Exploratory safety biomarkers levels over time
- Serum BAFF levels
- Lymphocyte counts (B and T)
- Anti-UCB7665 antibodies
- Cytokines

  Cytokine samples will be taken at Baseline Visit for all subjects. At subsequent visits, cytokine samples will be taken only when the subject experiences infusion reactions.

12 ASSESSMENT OF SAFETY

12.1 Adverse events

12.1.1 Definition of adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the Informed Consent form), including any pretreatment and posttreatment periods required by the protocol, must be reported in the eCRF even if no IMP was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs that recurred or worsened after the initial visit.

Signs or symptoms of the condition/disease for which the IMP is being studied should be recorded as AEs only if their nature changes considerably or their frequency or intensity

increases in a clinically significant manner as compared to the clinical profile known to the investigator from the subject's history or the Baseline Period.

Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or 2 bleeding events should not be reported as an AE since these events will be assessed and reported during the ITP-BAT assessment; CTCAE grade 3 or more bleeding events should be reported as AEs.

Treatment-emergent AEs are defined as AEs starting after the time of first IMP administration up to and including 8 weeks after the final dose.

12.1.2 Procedures for reporting and recording adverse events

The subject will be given the opportunity to report AEs spontaneously. A general prompt will also be given at each study visit to detect AEs. For example:

"Did you notice anything unusual about your health (since your last visit)?"

12.1.3 Description of adverse events

When recording an AE, the investigator should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The eCRF and source documents should be consistent. Signs and symptoms should only be documented as AEs in case the underlying disease or condition is unknown or they are considered as clinically significant independent of the underlying disease or condition in the discretion of the investigator. Any discrepancies between the subject's own words on his/her own records (eg, diary card) and the corresponding medical terminology should be clarified in the source documentation.

For recording an AE, CTCAE will be used, and only if it is impossible to assess severity using CTCAE, then AE intensity will be assessed using a scale of mild, moderate, or severe.

Details for completion of the AE eCRF (including judgment of relationship to IMP) are described in the CRF Completion Guidelines.

12.1.4 Follow up of adverse events

An AE should be followed until it has resolved, has a stable sequelae, the investigator determines that it is no longer clinically significant, or the subject is lost to follow up.

If an AE is ongoing at the end of the study for a subject, follow up should be provided until resolution/stable level of sequelae is achieved, or until the investigator no longer deems that it is clinically significant, or until the subject is lost to follow up. If no follow up is provided, the investigator must provide a justification. The follow up will usually be continued for 8 weeks after the subject has discontinued his/her IMP.

12.1.5 Rule for repetition of an adverse event

An increase in the intensity of an AE should lead to the repetition of the AE being reported with:

- The outcome date of the first AE that is not related to the natural course of the disease being the same as the start date of the repeated AE, and the outcome of "worsening"
- The AE verbatim term being the same for the first and repeated AE, so that the repeated AE can be easily identified as the worsening of the first one

12.1.6 Pregnancy

If an investigator is notified that a subject has become pregnant after the first intake of any IMP, the investigator must immediately notify UCB's Patient Safety (PS) department by providing the completed Pregnancy Report and Outcome form (for contact details see Serious Adverse Event reporting information at the beginning of this protocol). The subject should be withdrawn from the study as soon as pregnancy is known (by positive pregnancy test), and the following should be completed:

- The subject should return for an Early Withdrawal Visit.
- No further IMP will be administered.
- An End-of-Study Visit should be scheduled 8 weeks after the subject has discontinued her IMP.

The investigator must inform the subject of information currently known about potential risks and about available treatment alternatives.

The pregnancy will be documented on the Pregnancy Report and Outcome form provided to the investigator. The progression of the pregnancy and the eventual birth (if applicable) must be followed up using the Pregnancy Report and Outcome form in which the investigator has to report on the health of the mother and of the child. Every reasonable attempt should be made to follow the health of the child for 30 days after birth for any significant medical issues. In certain circumstances, UCB may request that follow up is continued for a period longer than 30 days. If the subject is lost to follow up and/or refuses to give information, written documentation of attempts to contact the subject need to be provided by the investigator and filed at the site. UCB's PS department is the primary contact for any questions related to the data collection for the pregnancy, eventual birth, and follow up.

In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, the investigator or designee is asked to contact the subject to request consent of the partner via the Partner Pregnancy Consent form that has been approved by the responsible IRB/IEC and should be available in the investigator site file. In case of questions about the consent process, the investigator may contact the UCB/contract research organization (CRO) contract monitor for the study. The investigator will complete the Pregnancy Report and Outcome form and send it to UCB's PS department (for contact details see Serious Adverse Event reporting information at the beginning of this protocol) only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form. UCB's PS department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow up.

A pregnancy becomes a serious adverse event (SAE) in the following circumstances: miscarriage, abortion (elective or spontaneous), unintended pregnancy after hormonal contraceptive failure (if the hormonal contraceptive was correctly used), ectopic pregnancy, fetal demise, or any congenital anomaly/birth defect of the baby. Those SAEs must be additionally reported using the Investigator SAE Report form.

12.1.7 Suspected transmission of an infectious agent via a medicinal product

For the purposes of reporting, any suspected transmission of an infectious agent via a medicinal product should be considered as an SAE; such cases must be reported immediately, recorded in the AE module of the CRF, and followed as any other SAE. Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

12.1.8 Overdose of investigational medicinal product

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the appropriate module of the eCRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or nonserious AE. These events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess medicine itself is an AE or SAE (eg, suicide attempt).

12.1.9 Safety signal detection

The safety variables and ADA results available after 7 days of the final dose of 3 and 6 subjects in the UCB7665 4mg/kg weekly group (Dose Arm 1) will be reviewed by the DMC (interim analysis 1 and 2) comprising at least 1 external expert, the UCB study physician, the UCB PS representative, and a biostatistician and will be summarized on an ongoing basis during the study so as to continuously evaluate the safety of subjects. The DMC will meet and reach a decision on whether or not the study can continue as planned, and whether or not Dose Arm 2 can be started. Subsequently, safety variables and ADA results available after 7 days of the final dose of 3 and 6 subjects in the UCB7665 7mg/kg weekly (Dose Arm 2) (together with all available data from Dose Arm 1 and 2) will be reviewed by the DMC (interim analysis 3 and 4). The DMC will also meet and review safety data to add additional subjects to subsequent dose arms or to open subsequent dose arms. Further details are described in Section 5.1.

The DMC may also decide to reduce the number of doses in each of the dose arms, to stop a dose arm or not to open a dose arm based on review of data during the study.

Thus, selected data from this study will be reviewed periodically to detect as early as possible any safety concern(s) related to the IMP so that investigators, clinical study subjects, regulatory authorities, and IRBs/IECs will be informed appropriately and as early as possible.

The Study Physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the PS representative.

As appropriate for the stage of development and accumulated experience with the IMP, medically qualified personnel at UCB may identify additional safety measures (eg, AEs, vital signs, laboratory or ECG results) for which data will be periodically reviewed during the course of the study.

12.1.10 Hypersensitivity and adverse reactions

In the event of a severe infusion reaction, the subject must permanently discontinue IMP and be managed as described in Appendix 18.4.

In case of occurrence of a hypersensitivity reaction (except for local injection site reaction) and depending upon its severity, appropriate countermeasures will immediately be taken by the investigator. The cytokine samples must be taken for infusion reactions.

If the investigator does not initially choose to discontinue the infusion of IMP and symptoms persist or escalate during continued infusion, the infusion should be stopped. In case of any severe infusion reaction(s), the infusion of IMP must be stopped immediately and appropriate treatment initiated, as necessary, at the discretion of the investigator and in accordance with the standard of care.

Suspected anaphylactic reactions should be diagnosed using Sampson's Criteria (Sampson et al, 2006) as described in Appendix 18.5. In the event of an anaphylactic reaction the infusion must be discontinued immediately and emergency resuscitation measures implemented.

12.1.11 Management of severe headache

Severe headache is defined as severe pain limiting self-care activities of daily living (ADL) or new/prolonged hospitalization for management of headache or life-threatening consequences requiring urgent medical intervention. Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications. Treatment of headache will be provided as clinically indicated according to the local guidelines.

Subjects experiencing severe headache will complete the Headache Questionnaire and will complete the questionnaire daily until resolution (ie, if headache becomes moderate or mild, normal collection of AEs should apply); this assessment will be followed by a neurological assessment (including fundoscopy). Further workup will be performed at the discretion of the investigator and may include eg, a CT scan, MRI and/or a LP for CSF collection, considering the local guidelines for performing LP in patients with ITP. These investigations will be performed in order to further understand the mechanism of headache in these subjects.

Details of neurological examination to be performed are provided in Section 12.8.5. The Headache Questionnaire is available in Appendix 18.6.

12.1.12 Management of moderate or severe diarrhea

Moderate or severe diarrhea is defined as an increase of ≥4 stools per day over Baseline or incontinence due to urgency of diarrhea or new/prolonged hospitalization for management of diarrhea or limiting self-care ADL or life-threatening consequences requiring urgent medical intervention.

Stool collection and analysis will be performed for subjects reporting moderate or severe diarrhea. The frequency of stool sampling will be as clinically indicated in the opinion of the investigator. Analysis of stool samples will be performed locally.

Treatment of diarrhea will be provided as clinically indicated according to the local guidelines.

12.2 Serious adverse events

12.2.1 Definition of serious adverse event

Once it is determined that a subject experienced an AE, the seriousness of the AE must be determined. An SAE must meet 1 or more of the following criteria:

- Death

- Life-threatening

  (Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form.)

- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect (including that occurring in a fetus)
- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definition of serious

  (Important medical events may include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)

- Initial inpatient hospitalization or prolongation of hospitalization

  (A subject admitted to a hospital, even if he/she is released on the same day, meets the criteria for the initial inpatient hospitalization. An emergency room visit that results in admission to the hospital would also qualify for the initial inpatient hospitalization criteria. However, emergency room visits that do not result in admission to the hospital would not qualify for this criteria and, instead, should be evaluated for 1 of the other criteria in the definition of serious [eg, life-threatening adverse experience, important medical event].

  Hospitalizations for reasons not associated with the occurrence of an AE [eg, preplanned surgery or elective surgery for a pre-existing condition that has not worsened or manifested in an unusual or uncharacteristic manner] do not qualify for reporting. For example, if a subject has a condition recorded on his/her medical history and later has a preplanned surgery for this condition, it is not appropriate to record the surgery or hospitalization as an SAE, since there is no AE upon which to assess the serious criteria. Please note that, if the pre-existing condition has worsened or manifested in an unusual or uncharacteristic manner, this would then qualify as an AE and, if necessary, the seriousness of the event would need to be determined.)

12.2.2 Procedures for reporting serious adverse events

If an SAE is reported, UCB must be informed within 24 hours of receipt of this information by the site (see contact information for SAE reporting listed in the Serious Adverse Event Reporting section at the front of the protocol). The investigator must forward to UCB (or its representative) a duly completed "Investigator SAE Report Form for Development Drug" (SAE Report form) provided by UCB, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions. Information recorded on this form will be entered into the global safety database.

An Investigator SAE Report form will be provided to the investigator. The Investigator SAE Report form must be completed in English.

It is important for the investigator, when completing the SAE Report form, to include the assessment as to a causal relationship between the SAE and the IMP administration. This insight from the investigator is very important for UCB to consider in assessing the safety of the IMP

and in determining whether the SAE requires reporting to the regulatory authorities in an expedited manner.

Additional information (eg, autopsy or laboratory reports) received by the investigator must be provided within 24 hours. All documents in the local language must be accompanied by a translation in English, or the relevant information included in the same document must be summarized in the Investigator SAE Report form.

The investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the investigator is certain that they are in no way associated with the IMP), up to 30 days from the end of the study for each subject, and to also inform participating subjects of the need to inform the investigator of any SAE within this period. Serious AEs that the investigator thinks may be associated with the IMP must be reported to UCB regardless of the time between the event and the end of the study.

Upon receipt of the SAE Report form, UCB will perform an assessment of expectedness of the reported SAE. The assessment of the expectedness of the SAE is based on the Investigator's Brochure.

12.2.3 Follow up of serious adverse events

An SAE should be followed until it has resolved, has a stable sequelae, the investigator determines that it is no longer clinically significant, or the subject is lost to follow up.

Information on SAEs obtained after clinical database lock will be captured through the PS database without limitation of time.

12.3 Adverse events of special interest

An AE of special interest is any AE that a regulatory authority has mandated to be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound.

Adverse event of special interest for UCB7665 is:

- Potential Hy's law cases

Potential Hy's law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality, must always be reported to UCB as an AE of special interest (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the subject.

12.4 Adverse events of interest

For UCB7665, AEs of interest that require immediate reporting to UCB are:

- Severe headache
- Moderate to severe diarrhea
- Moderate to severe abdominal pain
- Moderate to severe vomiting

12.5 Immediate reporting of adverse events

The following AEs must be reported immediately using the SAE Report Form according to the procedure in Section 12.2.2:

- SAE: AE that the investigator classifies as serious by the above definitions regardless of causality
- Suspected transmission of an infectious agent via a medicinal product
- AE of special interest (see Section 12.3)
- AE of interest (see Section 12.4)
- Confirmed LTB, active TB, and NTBI (see Section 12.8.1)

12.6 Anticipated serious adverse events

The following list of Anticipated SAEs has been identified, as these events are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure. This original list will remain in effect for the duration of the protocol.

This list does not change the investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 12.2.2.

Table 12–1: Anticipated serious adverse events for ITP population

Headache
Infections
Bleeding events

12.7 Laboratory measurements

Blood and urine specimens for routine assay of hematology including coagulation parameters, clinical chemistry, urinalysis testing, and pregnancy testing as well as serology testing will be performed according to the Schedule of assessments (Section 5.2) to monitor the safety of subjects. All clinical chemistry, hematology, and urinalysis parameters will be assessed by the designated central laboratory with the exception of platelet count and the urine pregnancy test prior to each dose. Specific details regarding the handling and processing of serum chemistry, hematology, and urinalysis samples are provided in the study laboratory manuals.

Prior to dosing at Visit 2, 2 platelet samples will be taken. One sample will be analyzed locally and the value will be used to check inclusion criteria. The other platelet sample will be sent to the central laboratory. At subsequent dosing visits, an additional platelet sample will be obtained prior to dosing and analyzed locally to evaluate withdrawal criterion of platelet count $>350x10^9$/L. The urinalysis for pregnancy testing will be performed with a dipstick.

The following laboratory parameters will be measured:

Table 12–2: Laboratory measurements

Hematology	Chemistry	Coagulation parameters	Urinalysis	Pregnancy test
Basophils[a]	Calcium	INR	pH	Urine[b] HCG
Eosinophils[a]	Phosphate	Prothrombin time	Protein	Serum[c] HCG
Neutrophils[a]	Chloride	aPTT	Creatinine	
Lymphocytes[a]	Magnesium	Fibrinogen	Glucose	**Others**
Monocytes[a]	Potassium		Ketones	HbA1c
Hematocrit	Sodium		Urobilinogen	HIV
Hemoglobin	BUN		Bilirubin	Hepatitis B (HBsAg, anti-HBs, anti-HBc)
Platelet count	AST		Blood	Hepatitis C (anti-HCV)
RBC count	ALT		Nitrite	Tuberculosis[d]
WBC count	GGT		Albumin	
	Total bilirubin		Leucocytes	**Safety Biomarkers**[e]
	Direct bilirubin (if indicated)			[redacted]
	LDH			[redacted]
	Total cholesterol			[redacted]
	Triglycerides			[redacted]
	ALP			[redacted]
	Total protein			
	Albumin			
	α1-globulin, α2-globulin, β-globulin, γ-globulin			
	Creatinine			
	hs-CRP			
	Amylase			

[a] Absolute as well as percentages for the differential leucocyte counts will be performed.
ALP=alkaline phosphatase; ALT=alanine aminotransferase; anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; anti-HCV=hepatitis C virus antibody; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen;GGT=gamma-glutamyltransferase; HbA1c=glycosylated hemoglobin; HBsAg=hepatitis B surface antigen; HCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; hs-CRP=high-sensitivity C-reactive protein; INR=International Normalized Ratio; LDH=lactate dehydrogenase; RBC=red blood cell; WBC=white blood cell

[b] Urine pregnancy test will be performed predose on dosing days and at End-of-Study Visit.
[c] Serum pregnancy test is done at Visit 1 (Screening) and to confirm results of positive urine test if applicable.
[d] Interferon-gamma release assay by central laboratory.
[e] May include but not limited to the biomarkers listed in the table. Samples collected for safety biomarkers at Baseline (Visit 2) and 4 hours post dosing (Visit 2) for all subjects and during follow up only in subjects with severe headache and/or moderate to severe GI disturbances. The Baseline samples will only be analysed in case he subject experienced a severe headache and/or moderate to severe GI disturbance.

12.7.1 Evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 6.4, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's law must be reported as an AE of special interest (see Section 12.3), and, if applicable, also reported as an SAE (see Section 12.2.2).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 12-3 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 12.7.1.1). The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 12.7.1.4).

The results of all monitoring, including laboratory testing and other testing, should be made available to the study site and sponsor.

All initial tests resulting in abnormal hepatic laboratory values need to be repeated, but appropriate medical action must not be delayed waiting for the repeat result.

If tests are done locally for more rapid results, a concurrent sample should also be sent to the central laboratory whenever possible. Medical care decisions are to be made initially using the most rapidly available results and a conservative approach must be taken if the results from the 2 laboratory tests are significantly different. Data from the local and central laboratory are to be recorded on the applicable CRF pages.

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. In these cases, the investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

When IMP is stopped due to PDILI (as described in Section 6.4), IMP must be permanently discontinued unless a subsequent alternative diagnosis fully explains the hepatic findings. If a subsequent alternative diagnosis fully explains the hepatic findings, and the requirements provided in Section 12.7.1.2.1 are met, rechallenge with IMP may be appropriate.

Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

The table below summarizes the approach to investigate PDILI.

Table 12-3: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN[b]	NA	Hepatology consult[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 12.7.1.3); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline values.[d]
≥3xULN	NA	Yes		Immediate, temporary or permanent, IMP discontinuation.		
≥3xULN (and ≥2x Baseline) and <5xULN	<2xULN	No	Discussion with Medical Monitor required if the criterion that allows for IMP continuation is met.	Further investigation – immediate IMP discontinuation not required (see Section 12.7.1.2).	Not required unless otherwise medically indicated (at discretion of investigator).	
≥5xULN (and ≥2x Baseline)	<2xULN	No	Discussion with Medical Monitor required. Hepatology consult required if ALT or AST ≥8xULN.	Immediate, permanent IMP discontinuation.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 12.7.1.3).	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline values.[d]

Table 12-3: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**

ALP=alkaline phosphatase; ALT=alanine aminotransferase; ASAP=as soon as possible; AST=aspartate aminotransferase; HCP=healthcare practitioner; IMP=investigational medicinal product; NA=not applicable; PDILI=potential drug-induced liver injury; ULN=upper limit of normal

[a] Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

[b] If the subject also has ≥2xULN ALP, the possibility of an indication of biliary obstruction should be discussed with the Medical Monitor.

[c] Details provided in Section12.7.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

[d] Unless an alternative monitoring schedule is agreed by the investigator and UCB responsible physician. Determination of stabilization is at the discretion of the investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

12.7.1.1 Consultation with Medical Monitor and local hepatologist

Potential drug-induced liver injury events require notification of the Medical Monitor within 24 hours (eg, by laboratory alert), and the subject must be discussed with the Medical Monitor as soon as possible. If required, the subject must also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section 12.7.1.3) and SAE report (if applicable).

12.7.1.2 Immediate action: determination of IMP discontinuation

All PDILI events require immediate action, testing, and monitoring.

The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and ranges from continuation of IMP (followed by immediate investigation) to immediate and permanent discontinuation (see Section 6.4 and Table 12-3 for details).

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. The investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

12.7.1.2.1 IMP restart/rechallenge (if applicable)

Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

Subjects who are immediately discontinued from IMP due to having met certain criteria for PDILI (as described in Section 6.4 and Table 12-3), but for whom an alternative diagnosis is confirmed, can rarely restart IMP. Rechallenge with IMP can occur only if ALL of the following requirements are met:

- The results of additional testing and monitoring described in Section 12.7.1.3 and Section 12.7.1.4 confirm a nondrug-related cause for the abnormal hepatic laboratory parameters and any associated symptoms (ie, a subsequent alternative diagnosis fully explains the hepatic findings).
- No alternative treatment options are available to the subject.
- The subject has shown clear therapeutic benefit from the IMP.
- Subject's ALT or AST elevations do not exceed ≥3xULN.
- Subject's total bilirubin is < 1.5xULN.
- Subject has no signs or symptoms of hypersensitivity.
- The rechallenge is approved by the UCB responsible physician, DMC, and a hepatologist. The hepatologist must be external to UCB but may be a member of the DMC. It is recommended that the hepatologist be a local hepatology expert or the hepatologist treating the subject.
- Subject agrees to the investigator-recommended monitoring plan.

12.7.1.3 Testing: identification/exclusion of alternative etiology

The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are detailed in Table 12-4 (laboratory measurements) and Table 12-5 (additional information). Results of the laboratory measurements and information collected are to be submitted to the sponsor on the corresponding CRF. If the medical history of the subject indicates a requirement for other assessments not included below, these should be completed and submitted, as applicable.

All blood samples should be stored, if possible. If tests are done locally for more rapid results, a concurrent sample must also be sent to the central laboratory.

The following measurements are to be assessed:

Table 12-4: PDILI laboratory measurements

Virology-related	**Hematology**
Hepatitis A IgM antibody	Eosinophil count
HBsAg	**Urinalysis**
Hepatitis E IgM antibody	Toxicology screen
HBcAb-IgM	**Chemistry**
Hepatitis C RNA	Amylase
Cytomegalovirus IgM antibody	If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophile antibody or monospot testing)	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
Immunology	**Additional**
Anti-nuclear antibody (qualitative and quantitative)	Prothombin time/INR[a]
Anti-smooth muscle antibody (qualitative and quantitative)	Serum pregnancy test
Type 1 anti-liver-kidney microsomal antibodies (qualitative and quantitative)	PK sample

ALT=alanine aminotransferase; CPK=creatine phosphokinase; HBcAb-IgM=hepatitis B core antibody-IgM; HBsAg=hepatitis B surface antigen; IgM=immunoglobulin; INR=international normalized ratio; LDH=lactate dehydrogenase; PDILI=potential drug-induced liver injury; PK=pharmacokinetic; RNA=ribonucleic acid; ULN=upper limit of normal

a. Measured only for subjects with ALT or AST >5 xULN, elevations in total bilirubin, and symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

The following additional information is to be collected:

Table 12-5: PDILI information to be collected

New or updated information
Concomitant prescription and over-the-counter medications (eg, acetaminophen, herbal remedies, vitamins); dosages and dates should be included.
Pertinent medical history, including the following: • History of liver disease (eg, autoimmune hepatitis, nonalcoholic steatohepatitis or other "fatty liver disease") • Adverse reactions to drugs • Allergies • Relevant family history or inheritable disorders (eg, Gilbert's syndrome, alpha-1 antitrypsin deficiency) • Recent travel • Progression of malignancy involving the liver (Note: Metastatic disease to the liver, by itself, should not be used as an explanation for significant AST and/or ALT elevations.)
The appearance or worsening of clinical symptoms of hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, decreased appetite, abdominal pain, jaundice, fever, or rash)
Recent clinically significant hypotension or hypoxemia with compromised cardiopulmonary function
Alcohol and illicit drug use; include dates where available
Results of liver imaging or liver biopsy, if done
Results of any specialist or hepatology consult, if done
Any postmortem/pathology reports

ALT=alanine aminotransferase; AST=aspartate aminotransferase; PDILI=potential drug-induced liver injury

12.7.1.4 Follow-up evaluation

Potential drug-induced liver injury events require follow-up monitoring as described in Table 12-3. Monitoring should continue until liver chemistry values normalize, stabilize, or return to Baseline. Determination of stabilization is at the discretion of the investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

12.8 Other safety measurements

12.8.1 Assessment and management of TB and TB risk factors

With the currently available data, TB is not considered as an important potential or identified risk for treatment with UCB7665. As immunomodulation may carry a risk of new or activation of latent TB, UCB has conservatively developed TB detection and management procedures taking into account the most current recommendations of international guidelines (2010 WHO) and most recent literature, covering any infection by the mycobacteria tuberculosis complex.

Appropriate rigorous precautions are being taken within this protocol to monitor for the risk of TB infection prior to study entry and during the study (see Section 6.2.2 (Exclusion Criterion #25) and Section 6.4. Following are the key considerations of these procedures:

12.8.1.1 TB Tests at Screening

The IGRA and TB questionnaire are required as indicated in Schedule of Assessments.

- TB screening is mandatory both before study entry and during the conduct of the study. The preferred screening test is **IGRA performed at a Central Laboratory**.
  - The IGRA result must be negative for subjects to enroll in this study
  - Subjects who test positive for IGRA test should be excluded from the study and referred for appropriate medical evaluation according to the local medical practice guidelines.
  - If the result of the IGRA test is indeterminate, the particular IGRA test previously performed may be repeated once; if positive or indeterminate on retest, the subject may not be randomized to study drug and, if already randomized, must undergo appropriate study specified withdrawal procedures. The retest must be done during the protocol-defined Screening window.

12.8.1.2 Monitoring for TB during the study

Subjects will be monitored for signs/symptoms of TB using routine pharmacovigilance measures for Adverse Events. Subjects reporting AEs related to signs/symptoms of TB will be evaluated for LTB and active TB according to the local medical practice guidelines.

Subjects with confirmed LTB or active TB or NTMBI will be immediately withdrawn from the study as described in Withdrawal Criteria. Confirmed LTB, active TB and NTMBI must be reported to the Sponsor immediately regardless of seriousness using the SAE Report Form. Additional information received by the Investigator should be provided within 24 hours of awareness.

Once withdrawn from study treatment, subjects should return for the End of Study (EOS), complete all early withdrawal assessments, and complete the follow-up visits.

12.8.1.3 TB tests at Final /End of Study Visit

Subjects will be evaluated for signs and symptoms of latent or active TB infection and for risk factors of exposure to TB, using the TB questionnaire, at the Final/EOS Visit. See the 'TB signs and symptoms questionnaire' section for further instructions on using the questionnaire.

12.8.1.4 Signs and symptoms of Tuberculosis

The Investigator should consider all potential sites of infection when assessing for TB during the physical examination, and other evaluations, and based on the subject's history.

Common symptoms with which the subject may present with include cough, blood in sputum, night sweats, lymphadenitis, joint pain/swelling, spinal deformity, headache/confusion, abdominal pain mimicking inflammatory bowel disease, frequent or painful urination, scrotal mass in men and pelvic inflammatory disease in women as well as other symptoms, or

nonspecific symptoms. This is not an exhaustive list and unusual presentations should always be considered.

12.8.1.4.1 TB signs and symptoms questionnaire

The questionnaire "Evaluation of signs and symptoms of tuberculosis" should be used as a source document. The questionnaire will assist with the identification of subjects who may require therapy for TB. A subject who answers "Yes" to the question [redacted] at Screening is excluded. A "Yes" response to any of the other questions within the questionnaire at Screening should trigger further careful assessment to determine if subject has latent or active TB (see Section 6.2.2 (Exclusion Criterion #25). A "Yes" response to any of the questions during/end of the study should trigger further assessments as per local medical guidelines to determine if the subject has either LTB or active TB infection.

12.8.1.4.2 LTB infection, active TB or other NTMBI identified during study

During the study, subjects who develop evidence of LTB infection or active TB or NTMBI must immediately stop further administration of study drug and will be referred to an appropriate medical specialist for further evaluation.

Confirmed LTB or active TB or NTMBI must be reported to the Sponsor immediately as described above.

12.8.2 Pregnancy testing

Pregnancy testing will consist of serum testing at Screening Visit and urine testing at dosing visits and End-of-Study Visit as indicated in the schedule of study assessments (Section 5.2). The Screening Visit serum pregnancy testing results must be negative and should be confirmed by a negative urine pregnancy test prior to first dose of IMP. The urine pregnancy test will be performed locally. A negative urine pregnancy test result should be obtained prior to each dose of IMP. A positive urine pregnancy test must be confirmed using a serum pregnancy test. Pregnancy tests should be administered to all female subjects of childbearing potential, regardless of their use of birth control.

12.8.3 Vital signs

Vital signs will be measured at all visits as indicated in the schedule of study assessments (Section 5.2).

Vital signs to be assessed are as follows:

- Pulse rate
- Systolic/diastolic blood pressure
- Temperature (oral preferred, ear or axillary allowed)
- Respiratory rate

Subjects should be sitting for 5 minutes prior and during the collection of blood pressure, pulse rate, and respiration rate measurements. On dosing days, vital signs will be measured prior to IMP administration, every 15 minutes during the infusion, at the end of infusion, 2 hours after end of infusion, and 4 hours after end of infusion.

At nondosing visits, vital signs need only be taken once during the visit.

12.8.4 Body weight and height

Subject's body weight will be determined at Screening and at the End-of-Study Visit. Height will be measured at Screening only.

12.8.5 Physical examination

Physical examination will be performed at visits as specified in the schedule of study assessments (Section 5.2) and findings will be recorded in the eCRF. A complete physical examination will be performed at Screening and EOS/Early Withdrawal Visit. At all other visits (where physical examination is performed), an abbreviated physical examination will be conducted.

Clinically important abnormal changes in subsequent physical examinations will be recorded as AEs. Physical examinations must be documented in source documentation.

The following body systems will be examined as a part of the complete physical examination:

- General appearance
- Ear, nose, and throat
- Eyes
- Hair and skin
- Respiratory
- Cardiovascular
- Gastrointestinal
- Musculoskeletal
- Hepatic
- Neurological (including limb reflexes)
- Mental status
- **Abbreviated Physical Examination**
- The following body systems will be examined as a part of the abbreviated physical examination:
- General appearance
- Ear, nose, and throat
- Eyes
- Skin
- Respiratory
- Gastrointestinal
- Neurological (focused assessment of sensitivity and power)

- **Neurological examination for severe headache**

A neurological assessment will be performed only for subjects who experience severe headaches. This assessment will include: 1) General appearance, including posture, motor activity and meningeal signs and, if indicated, following assessments to be done; 2) Cranial nerves examination; 3) Motor system examination, including muscle tone and power and sensory system examination – light touch; 4) Reflexes, including deep tendon reflexes; 5) Coordination, gait (if possible) and; 6) Fundoscopy.

12.8.6 12-Lead ECG

A standard 12-lead ECG will be performed at visits as specified in the schedule of study assessments (Section 5.2). Care should be taken to assure proper lead placement and quality ECG recordings. Subjects should rest in a supine position in a controlled, calm environment for at least 15 minutes prior to the recording and should be motionless during the recording.

The ECG will be performed in triplicate prior to blood collection for assessment of laboratory parameters. Three ECGs should be recorded in a time frame of 5 minutes with at least 1 minute difference, 1-2 minutes between the ECGs.

The ECGs will be read at the clinical study site by an appropriately qualified physician. The PR, RR, QRS, QT, and corrected QT (QTc) intervals and heart rate will be recorded. All ECG readings from an individual subject should be read by the same reader, if possible. Findings will be recorded in the eCRF.

For the QTc, the following correction formula will be applied:

Fridericia's correction: $QTc = QT/RR^{0.33}$

13 STUDY MANAGEMENT AND ADMINISTRATION

13.1 Adherence to protocol

The investigator should not deviate from the protocol. However, the investigator should take any measure necessary in deviation from or not defined by the protocol in order to protect clinical study subjects from any immediate hazard to their health and safety. In this case, this action should be taken immediately, without prior notification of the regulatory authority, IRB/IEC, or sponsor.

After implementation of such measure, the investigator must notify the CPM of the sponsor within 24 hours and follow any local regulatory requirements.

13.2 Monitoring

UCB (or designee) will monitor the study to meet the sponsor's monitoring Standard Operating Procedures (SOPs), ICH-GCP guideline, and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate. Monitoring of the study may be delegated by UCB to a CRO or a contract monitor.

The investigator and his/her staff are expected to cooperate with UCB (or designee) and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information. The investigator(s)/institution(s) will permit direct access to source

data/documents for study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s).

The investigator will allow UCB (or designee) to periodically review all eCRFs and corresponding source documents (eg, hospital and laboratory records for each study participant). Monitoring visits will provide UCB (or designee) with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of eCRFs, ensure that all protocol requirements, applicable authorities' regulations, and investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

13.2.1 Definition of source data

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes). Photocopies of CRFs are not considered acceptable source documents.

Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, completed scales, or quality of life questionnaires, for example. Source documents should be kept in a secure, limited access area.

Source documents that are computer generated and stored electronically must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated by the investigator and become a permanent part of the subject's source documents. The investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

Electronic data records, such as Holter monitor records or electroencephalogram records, must be saved and stored as instructed by UCB (or designee).

13.2.2 Source data verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (eg, subject files, recordings from automated instruments, tracings [ECG], x-ray films, laboratory notes). All data reported on the eCRF should be supported by source documents, unless otherwise specified in Section 13.2.1.

13.3 Data handling

13.3.1 Case Report form completion

The study will be performed using electronic data capture (EDC). The investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRFs and in all required reports.

Any change or correction to the eCRF after saving must be accompanied by a reason for the change.

Corrections made after the investigator's review and approval (by means of a password/electronic signature) will be reapproved by the investigator.

The investigator should maintain a list of personnel authorized to enter data into the eCRF.

Detailed instructions will be provided in the eCRF Completion Guidelines.

13.3.2 Database entry and reconciliation

Case Report forms/external electronic data will be entered/loaded into a validated electronic database using a clinical data management system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. In the EDC system, the data are entered into the eCRFs once by the designated site personnel and are subsequently verified.

An electronic audit trail system will be maintained within the CDMS to track all data changes in the database once the data have been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

13.3.3 Subject Screening and Enrollment log/Subject Identification Code list

The subject's screening and enrollment will be recorded in the Subject Screening and Enrollment Log.

The investigator will keep a Subject Identification Code list. This list remains with the investigator and is used for unambiguous identification of each subject.

The subject's consent and enrollment in the study must be recorded in the subject's medical record. These data should identify the study and document the dates of the subject's participation.

13.4 Termination of the study

UCB reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, or unsatisfactory enrollment with respect to quality or quantity.

If the study is prematurely terminated or suspended, UCB (or its representative) will inform the investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The IRB/IEC should also be informed and provided with reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for the return of all unused IMP and other material in accordance with UCB procedures for the study.

13.5 Archiving and data retention

The investigator will maintain adequate records for the study, including eCRFs, medical records, laboratory results, Informed Consent documents, drug dispensing and disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

All essential documents are to be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an

agreement with UCB (CPMP/ICH/135/95, 2002 [Section 4.9.5]). The investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the sponsor's study master file.

13.6 Audit and inspection

The investigator will permit study-related audits mandated by UCB, after reasonable notice, and inspections by domestic or foreign regulatory authorities.

The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects enrolled have been protected, that enrolled subjects (ie, signing consent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of the IMP have been processed and reported in compliance with the planned arrangements, the protocol, investigational site, and IRB/IEC SOPs, ICH-GCP, and applicable regulatory requirements.

The investigator will provide direct access to all study documents, source records, and source data. If an inspection by a regulatory authority is announced, the investigator will immediately inform UCB (or designee).

13.7 Good Clinical Practice

Noncompliance with the protocol, ICH-GCP, or local regulatory requirements by the investigator, institution, institution staff, or designees of the sponsor will lead to prompt action by UCB to secure compliance. Continued noncompliance may result in the termination of the site's involvement in the study.

14 STATISTICS

A description of statistical methods follows and will be described in more detail in the Statistical Analysis Plan (SAP). Deviations from the SAP will be documented in the Clinical Study Report.

14.1 Definition of analysis sets

Enrolled Set (ES):

The ES will consist of all subjects who have given informed consent.

Safety Set (SS):

The SS will consist of all subjects who have received at least 1 infusion (full or partial infusion) of IMP and will be used for the demographics and analysis of safety data.

Full Analysis Set (FAS):

The FAS will consist of all subjects who have received at least 1 infusion (full infusion) of IMP and, in addition, have a Baseline and at least 1 post-Baseline measurement for platelet count.

The analysis of the PD (excluding total IgG, and IgG subclasses), efficacy, and immunologic variables will be performed on the FAS. Selected outputs may be repeated for the PD Per Protocol Set (PD-PPS). Further details will be provided in the SAP.

Per Protocol Set:

The PPS is a subset of the FAS, consisting of those subjects who had received all foreseen sc infusions, had a platelet count measurement during the Observation Period, and no important protocol deviations that may potentially affect the platelet count as confirmed during a pre-analysis review of the data prior to database lock. Protocol deviations may not necessarily lead to total exclusion of a subject from the PPS but may lead to exclusion of specific data.

Pharmacokinetic Per Protocol Set (PK-PPS):

The PK-PPS is a subset of the FAS, consisting of those subjects who had no important protocol deviations potentially affecting the plasma concentration of UCB7665, as confirmed during a pre-analysis review of the data prior to database lock. Protocol deviations may not necessarily lead to total exclusion of a subject from the PK-PPS but may lead to exclusion of specific data.

Pharmacodynamic Per Protocol Set (PD-PPS)

The PD-PPS is a subset of the FAS, consisting of those subjects who had no important protocol deviations potentially affecting the serum concentration of total IgG, as confirmed during a pre-analysis review of the data prior to database lock. Protocol deviations may not necessarily lead to total exclusion of a subject from the PD-PPS but may lead to exclusion of specific data.

The PD-PPS will be used for the analysis of the total IgG, and IgG subclasses.

14.2 General statistical considerations

All analyses will be performed using SAS® version 9.2 or later (SAS Institute, Cary, NC, USA). Continuous variables will be summarized by visit (where applicable) with the statistics including the number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized by visit (where applicable) with frequency counts and percentages. Analyses will be performed by dose arm, unless otherwise stated. In the event that the number of planned infusions in the dose arms are modified following review by the DMC, the data will be summarized based on the actual dose arms completing the study. For example, if the weekly 5x4mg/kg dose arm is modified such that some subjects receive only 4 infusions, then the data will be summarized separately for this new dose regimen.

Data listings containing all documented data and all calculated data will be generated.

Baseline will be the last non-missing data collected prior to the first dose of IMP, and measurement-specific Baseline values will be defined in the SAP.

14.3 Planned safety analyses

14.3.1 Analysis of the primary safety variable

All AEs will be coded using the Medical Dictionary for Regulatory Activities® (MedDRA®). The incidence of subjects with TEAEs will be determined and presented by dose arm and overall.

Only TEAEs will be included in the summary tables. As an additional analysis, the incidence of subjects with TEAEs will be determined and presented separately for the Dosing Period and the Observation Period by dose arm and overall.

Adverse events starting before time of IMP administration or after 8 weeks after the final dose will be listed only.

14.3.2 Other safety analyses

The absolute and relative frequencies for subjects with a given TEAE with respect to the preferred term according to the latest available version of the MedDRA, as well as the absolute frequencies of the individual TEAEs that have occurred, will be determined within each system organ class. Additional tables will summarize TEAEs by maximum intensity and causal relationship with UCB7665, as judged by the investigator. Adverse events will be categorized by severity according to the CTCAE version 4.03 grading. In case the CTCAE grading is not available, the intensity (mild/moderate/severe) will be utilized. For the purpose of the tabulations CTCAE grades will be aligned with the intensity classifications (mild/moderate/severe) to enable pooling of the AEs in the summaries. The TEAEs leading to discontinuation of IMP and treatment-emergent SAEs will also be summarized. The action taken, time of onset relative to dosing, and duration of each AE will be listed only.

For the continuous laboratory variables, the values and changes from Baseline will be summarized at each time point. For categorized values according to the reference range, shift tables from Baseline to each post-Baseline time point will be presented for selected variables to be defined in the SAP. Values outside the reference range will be flagged in the data listings. The number and percentage of subjects with markedly abnormal laboratory results (based on CTCAE grading) will be tabulated for each dose arm.

Normal versus abnormal findings with regard to the various ECG parameters and the overall ECG will be analyzed as required. The focus of the 12-lead ECG analysis will be the identification of outliers and of any trends for changes following administration of UCB7665 with respect to QT/QTc. Descriptive statistics will be presented for ECG value and changes from Baseline over time based on the mean of the triplicate assessments at each time point.

Descriptive statistics will be reported for all vital sign measurements (including systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate). Measured values and changes from Baseline will be summarized by time point.

Physical examination findings and the results of any pregnancy testing will be presented in listings only.

Safety analyses will be presented by dose arm.

14.4 Planned efficacy and other analyses

14.4.1 Efficacy analyses

The main efficacy variable is the maximum increase from Baseline in platelet count during the study. The maximum increase from Baseline and maximum platelet count during the study will be summarized by dose arm.

In addition, all measurements of platelet count will be summarized by dose arm and time point using descriptive statistics (including changes from Baseline).

For dose arms with ≥10 subjects, a 1-sided t-test will be applied to assess if the average maximum increase from Baseline is greater than zero. In case the assumptions for the-t-test are not fulfilled, an alternative nonparametric method may be considered. Further details will be

provided in the SAP. The Response, Complete Response, and platelet count ≥50x10^9/L will be summarized (number of subjects and percentages) and presented with 90% 2-sided confidence intervals for the rate of responders at each time point and overall (across all time points). Response and Complete Response are defined in Section 4.2.2. The analysis will be repeated for the Clinical Response variables defined in Section 4.2.2.

Time to Response, time to Complete Response, time to platelet count ≥50x10^9/L, duration of Response, duration of Complete Response, duration of platelet count ≥50x10^9/L, and Baseline-corrected AUEC for platelet count will be calculated and summarized by dose arm. The time to first response will be analyzed using a log-rank test and displayed using Kaplan-Meier curves. The time to Response, time to Complete Response, and respective durations will be summarized by dose arm.

The results from the ITP bleeding scale will be summarized at each time point and will include the grades for each of the 3 major domains: skin (S), visible mucosae (M), and organs (O). In addition the number and percentage of subjects with severe or clinically relevant bleeding and number and percentage of subjects with absence of bleeding will be summarized at each time point.

Results of the NFI-MS will be summarized at each time point, using summary scores where applicable. Changes from Baseline will be calculated and summarized.

Additional subgroup analyses may be performed as needed and further details will be provided in SAP regarding these analyses.

14.4.2 Pharmacokinetic analyses

Pharmacokinetic variables of UCB7665 (eg, like AUC, C_{max}) cannot be derived, since blood sampling will be performed at 1 time point per visit only. Thus, PK is restricted to concentration data.

Individual concentrations of UCB7665 data will be summarized using the number of available observations, mean, median, SD, minimum, maximum, geometric mean, and geometric coefficient of variation (assuming log normally distributed data). Values below the lower limit of quantification (LLOQ) will be reported with a clear sign indicating that they were below the LLOQ. Descriptive statistics of concentrations will be calculated if at least two thirds of the individual data points are quantifiable (≥LLOQ). Individual concentrations of UCB7665 will also be displayed graphically.

Population PK analyses and PK/PD analyses may be conducted for the PD variables of interest. All such PK and PK/PD analyses will be described in a separate Data Analysis Plan; however, results will not be reported in the Clinical Study Report.

14.4.3 Pharmacodynamic analyses

For all PD variables, descriptive statistics for the values and change from Baseline and/or percentage change from Baseline will be tabulated by time point.

The PD variables will include ITP-specific autoantibodies [redacted] total IgG, and IgG subclasses. In addition, for total IgG, the maximum decrease from Baseline and minimum value will be evaluated and summarized. Figures of mean values over time and changes from Baseline will be presented.

14.4.4 Immunologic variables

All immunologic variables including concentrations of immunoglobulins (IgA, IgE, and IgM), serum (C3 and C4) and plasma (C3a and C5a) complement levels, serum BAFF levels, and lymphocyte counts (B and T) will be summarized by dose arm over time (including changes from Baseline) using descriptive statistics. Figures of mean values over time and changes from Baseline may be presented.

The ADA status (negative/positive) will be summarized by dose arm at each visit and overall; figures will also be presented in conjunction with PK concentrations of UCB7665.

The results of any cytokine analyses (for subjects who experience infusion reactions) will be summarized if appropriate.

Further details will be provided in the SAP.

14.4.5 Other analyses

14.4.5.1 Subject disposition

The number of subjects who were screened, dosed and completed/prematurely discontinued the study, as well as the reason for discontinuation, will be presented using frequency counts and percentages.

14.4.5.2 Subject characteristics

Summaries of the following will be provided:

- Demographics (including gender, age, height, weight, body mass index)
- Medical history
- Past, prior, and concomitant medications

Concomitant medical procedures will be listed only.

14.4.5.3 Baseline disease characteristics

Summaries of the following will be provided:

- Baseline disease characteristics (including disease duration)
- Baseline values of the immunological parameters (IgG, IgM, IgA, IgE, lymphocytes [B and T])
- ITP-specific antibodies [redacted]
- Serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a)

14.4.5.4 Subject exit interview

The results of the exit interview will be reported by UCB and separate to the Clinical Study Report.

14.5 Handling of protocol deviations

Important protocol deviations are identified as part of the data cleaning process in the Data Cleaning Plan (DCP). Ongoing data cleaning meetings will be held throughout the duration of the study. Objectives of these meetings include to review and update (if necessary) the important

protocol deviations in the DCP and discuss exclusion of subjects from analysis populations. Furthermore, overall trends in protocol deviations will be discussed at the Data Evaluation Meeting. Through this ongoing data cleaning and evaluation process, all decisions regarding important protocol deviations and exclusions from analysis populations are made on an ongoing basis.

14.6 Handling of dropouts or missing data

All imputation of missing or partial dates for safety assessments, as well as handling missing efficacy data (where applicable), will be detailed in the SAP.

14.7 Planned interim analysis and data monitoring

A DMC will be convened to monitor emergent safety data during the study. The DMC will comprise at least 1 external expert, the UCB study physician, the UCB PS representative, and a biostatistician. Safety related decisions must be made with the agreement of at least the external expert, the UCB study physician, and the UCB PS representative. Decisions involving reductions in dose regimen must also have the agreement of the UCB statistician and UCB pharmacometrician.

For the sequential adaptive design in this study, at least 11 interim analyses will be performed. Safety data from the interim analyses will be reviewed by the DMC to monitor the safety, to adapt the dose regimen, and to decide when and if the UCB7665 7mg/kg weekly group (Dose Arm 2), UCB7665 10mg/kg weekly group (Dose Arm 3), UCB7665 15mg/kg group (Dose Arm 4) and UCB7665 20mg/kg group (Dose Arm 5) should be opened. Planned dosing may be discontinued for all subjects in a dose arm (see Section 6.5).

The first interim analysis will be conducted after 3 subjects (receiving 5x4mg/kg) have attended the second visit of the Observation Period (ie, 7 days after final dosing). Based on this analysis, the safety of UCB7665 will be assessed by the DMC. The DMC can either recommend to continue the study as planned, to reduce the number of sc infusions (eg, to 3), or to stop the study. If the number of infusions will be reduced, the subjects in the study already treated with the IMP will receive the reduced number of infusions. Subjects enrolled after the decision of the DMC will receive the reduced number of infusions. There will be no substitution of the subject with the original number of infusions; thus, the total number of subjects will not be increased.

If the study continues without modifications, the next interim analysis will take place after data from 3 additional subjects are available. Based on the available combined data of the first 6 subjects, the DMC will decide if the 3x7mg/kg dose arm can be initiated. If the new dose arm will be initiated and if the 5x4mg/kg will be continued, new subjects will be randomly assigned to 1 of the 2 dose arms in an allocation ratio of 1:1.

If the decision is to open the 3x7mg/kg dose arm, the third interim analysis will be performed after 3 subjects (receiving 3x7mg/kg) have attended the second visit of the Observation Period (ie, 7 days after final dosing). The safety of UCB7665 will be assessed by the DMC. In addition, the DMC might recommend reducing the number of sc infusions in the UCB7665 7mg/kg dose arm.

The fourth planned interim analysis and review of data by DMC will take place after safety data (7 days after final dose) is available for the first 6 subjects in Dose Arm 2.

All subsequent DMC meetings will be dependent on opening of Dose Arms 3, 4 and 5 and decisions of the previous DMC meetings. Review of data will occur after every 3 subjects. More details are included in the DMC charter.

During the first three interim analyses, recruitment in the Dose Arms 1 and 2 will not be stopped. If needed, subsequent DMC meetings may take place and the frequency will be detailed in the DMC charter.

The DMC will monitor data for all reported AEs, clinical findings, including vital signs (pulse rate, blood pressure, temperature, and respiratory rate) and safety laboratory values, and immunogenicity data. Pharmacokinetic data will not be required for DMC review as blood sampling will be performed at a single time point per visit only. Thus, PK data are restricted only to the concentration data and can therefore make no plausible contribution to the assessment of safety in this particular study.

Ad hoc DMC meetings can be held for other reasons if determined appropriate by the sponsor and/or external expert.

The deliberations and decisions of the DMC will be formally minuted/documented.

A detailed description of the DMC composition, processes and responsibilities, criteria to escalate to the next dose arm, and criteria to stop, or continue a dose arm will be provided in a separate DMC charter.

The analyses will be described in a separate interim SAP and will include all safety data specified in the DMC charter, which is available at the time. For the interim analyses the data, subject to analysis, should be as clean as possible; however, the database will not be locked and a snapshot will be taken.

14.8 Determination of sample size

The sample size of 15 subjects in Dose Arms 1 and 2, is mainly based on the efficacy objective of the study. In addition the 15 subjects in Dose Arms 1 and 2 ensure that sufficient data are available to form conclusions about the safety of administering UCB7665. Based on the safety data from dose arms 1 and 2, the sample size of 6 to 12 subjects in Dose Arms 3, 4 and 5 is judged to be sufficient in order to explore subjects' safety and IgG reductions under different dose regimens and is not based on a formal sample size calculation.

For Dose Arms 1 and 2, an approximate sample size calculation for the efficacy variable "maximum increase from Baseline in platelet count" shows that 15 subjects would be sufficient to show a change from Baseline with 1-sided testing at 5% and power of 80%. The anticipated change is based on an assumed Baseline average of $25x10^9$/L and a clinically meaningful maximum value of $100x10^9$/L. The calculation made use of platelet count data presented in a publication by Robak T (Robak et al, 2009), but it is approximate as maximum changes from Baseline for individual subjects were not available, necessitating the use of the maximum average platelet count instead. The SD is taken from visual inspection.

With 15 subjects, the responder endpoints will confirm a true 50% response rate, in excess of the maximum 15% anticipated with no treatment benefit, with power in excess of 80%.

15 ETHICS AND REGULATORY REQUIREMENTS

15.1 Informed consent

Subject's informed consent must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the subject in both oral and written form by the investigator (or designee). Each subject will have the opportunity to discuss the study and its alternatives with the investigator.

Prior to participation in the study, the written Informed Consent form should be signed and personally dated by the subject, or his/her legal representative, and by the person who conducted the informed consent discussion (investigator or designee). The subject or his/her legal representative must receive a copy of the signed and dated Informed Consent form. As part of the consent process, each subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.

If the Informed Consent form is amended during the study, the investigator (or the sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended Informed Consent form by the IRB/IEC and use of the amended form.

The subject may withdraw his/her consent to participate in the study at any time. A subject is considered as enrolled in the study when he/she has signed the Informed Consent form. An eCRF must not be started, nor may any study specific procedure be performed for a given subject, without having obtained his/her written consent to participate in the study.

Subjects have the right to withdraw their consent for the exploratory genomic substudy at any point without any impact on their care or participation in the main study. In this case, any data already generated on the samples will be retained and used, but no further analysis will occur.

15.2 Subject identification cards

Upon signing the Informed Consent and Assent form (as applicable), the subject or legal representative will be provided with a subject identification card in the language of the subject. The investigator will fill in the subject identifying information and medical emergency contact information. The investigator will instruct the subject to keep the card with him/her at all times.

15.3 Institutional Review Boards and Independent Ethics Committees

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, ICH-GCP, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The investigator/UCB will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the investigator/UCB will forward copies of the protocol, Informed Consent form, Investigator's Brochure, investigator's curriculum vitae (if applicable),

advertisement (if applicable), and all other subject-related documents to be used for the study to the IRB/IEC for its review and approval.

Before initiating a study, the investigator will have written and dated full approval from the responsible IRB/IEC for the protocol.

The investigator will also promptly report to the IRB/IEC all changes in the study, all unanticipated problems involving risks to human subjects or others, and any protocol deviations, to eliminate immediate hazards to subjects.

The investigator will not make any changes in the study or study conduct without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to the subjects. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the investigator to obtain an expedited review by the IRB/IEC as allowed.

As part of the IRB/IEC requirements for continuing review of approved studies, the investigator will be responsible for submitting periodic progress reports to the IRB/IEC (based on IRB/IEC requirements), at intervals appropriate to the degree of subject risk involved, but no less than once per year. The investigator should provide a final report to the IRB/IEC following study completion.

UCB (or its representative) will communicate safety information to the appropriate regulatory authorities and all active investigators in accordance with applicable regulatory requirements. The appropriate IRB/IEC will also be informed by the investigator or the sponsor, as specified by the applicable regulatory requirements in each concerned country. Where applicable, investigators are to provide the sponsor (or its representative) with evidence of such IRB/IEC notification.

15.4 Subject privacy

UCB staff (or designee) will affirm and uphold the subject's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the subject number assigned at Screening.

The investigator agrees that representatives of UCB, its designee, representatives of the relevant IRB/IEC, or representatives of regulatory authorities will be allowed to review that portion of the subject's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports for deaths occurring during the study).

Genetic analysis data will not be shared with the subjects and will be subject to the highest level of data protection, as per European regulations.

Samples may be shared with collaborators working within UCB and may be analyzed at a third party site, but only in relation to the aims of this exploratory analysis as detailed in this study protocol. Samples may be stored for up to 20 years and maybe used at any time up to that point. Samples will remain under the control of UCB at all times and may be destroyed at any point before the 20 year expiration date.

15.5 Protocol amendments

Protocol changes may affect the legal and ethical status of the study and may also affect the statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective.

Significant changes to the protocol will only be made as an amendment to the protocol and must be approved by UCB, the IRB/IEC, and the regulatory authorities (if required), prior to being implemented.

16 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

Finance, insurance, and publication rights are addressed in the investigator and/or CRO agreements, as applicable.

17 REFERENCES

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18.7 Protocol Amendment 1

Rationale for the amendment

The primary purpose of this substantial amendment it to include additional laboratory tests (serology test) at the Screening Visit in order to exclude subjects with chronic and ongoing infections with HIV, hepatitis B, and hepatitis C. Exclusion criteria related to medical history were updated to define precisely and increase clarity. Withdrawal criteria for PDILI and evaluation of PDILI were also updated to enable the effective management and assessment of any PDILI cases as outlined in the Food and Drug Administration (FDA) Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation (Jul 2009), UCB has developed pre-specified criteria for managing any PDILI events and discontinuing IMP. In this amendment, a more conservative approach compared to the previous version is included. However, there have been no changes in the potential risk of PDILI with UCB7665 since the previous version.

In addition, height was added in order to be able to calculate body mass index, the SAE reporting details were updated, and several additional exploratory biomarkers were added as immunological variables. Minor clarifications were added where necessary, and typographical errors or omissions were corrected.

Modifications and changes

Global changes

The following changes were made throughout the protocol:

- Addition of HIV, hepatitis B, and hepatitis C test at the screening tests.
- Addition of exploratory biomarker assessments.
- Definition of complement levels for C3, C3a, C4 and C5a.

Specific changes

Change #1.

STUDY CONTACT INFORMATION

Sponsor Study Physician

Name:	[redacted], MD
Address:	UCB BIOSCIENCES GmbH Alfred-Nobel-Straße 10 40789 Monheim Germany
Phone:	[redacted]
Fax:	[redacted]

Has been changed to:

Name:	[redacted], MD

Address:	UCB BIOSCIENCES GmbH Alfred-Nobel-Straße 10 40789 Monheim GERMANY
Phone:	[redacted] [redacted] (mobile)
Fax:	[redacted]

Change #2.

STUDY CONTACT INFORMATION

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** +32 2 386 24 21
Email	**Global:** DSICT@ucb.com (for interventional clinical studies)

Has been changed to:

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** +32 2 386 65 61
Email	**Global:** safetyreportingUCB7665@ucb.com (for interventional clinical studies)

Change #3.

Section 1 SUMMARY

Paragraph 7

The first 6 subjects will be enrolled in Dose Arm 1 only. While recruitment is ongoing, safety data for the first 3 subjects up to 7 days after the final dose will be reviewed by a Data Monitoring Committee (DMC). During a second DMC meeting, safety data for the first 6 subjects up to 7 days after the final dose will be reviewed. Following this review, the DMC will make a decision on whether to open Dose Arm 2 for enrollment. Once the DMC has approved initiation of Dose Arm 2, subsequent subjects will be randomized to 1 of the 2 dose arms using an interactive voice/web response system (IXRS). The aim is to have 15 subjects in each dose arm. The DMC may also decide to reduce the number of doses in each of the dose arms based on review of data during the study. Safety data will also be reviewed on an ongoing basis during the study so as to continuously evaluate the safety of subjects.

Has been changed to:

The first 6 subjects will be enrolled in Dose Arm 1 only. While recruitment is ongoing, safety data for the first 3 subjects up to 7 days after the final dose of the third subject will be reviewed by the Data Monitoring Committee (DMC). During a second DMC meeting, all available safety data up to cut off date defined as 7 days after the final dose of the sixth subject will be reviewed. Following this review, the DMC will make a decision on whether to open Dose Arm 2 for enrollment. Once the DMC has approved initiation of Dose Arm 2, subsequent subjects will be randomized to 1 of the 2 dose arms using an interactive voice/web response system (IXRS). Once 15 subjects are in the 4mg/kg group, the remaining subjects will not be randomized. They will be allocated to the 7mg/kg group. The aim is to have 15 subjects in each dose arm. The DMC may also decide to reduce the number of doses in each of the dose arms based on review of data during the study. Safety data will also be reviewed on an ongoing basis during the study so as to continuously evaluate the safety of subjects.

Change #4.

Section 1 SUMMARY

Paragraph 9

The secondary objective of the study is to assess the clinical efficacy of UCB7665 as measured by the change in platelet count and to assess the pharmacodynamic (PD) effect of UCB7665 as measured by the change in total IgG concentrations in blood. The exploratory objectives [redacted]; to evaluate the clinical efficacy as measured by the change in ITP bleeding score; to evaluate the effect of UCB7665 on the concentrations of total protein, albumin, α-globulin and β-globulin, IgG subclasses, IgM, IgA, and IgE, and serum complement levels; to evaluate the emergence of anti-drug antibodies (ADA), ie, anti-UCB7665 antibodies with respect to immunogenicity and pharmacokinetics (PK)/PD; to evaluate the relationship between changes in platelet count and total IgG, IgG subclasses, ITP-specific autoantibodies; and to assess the plasma concentrations of UCB7665 administered by sc infusion.

Has been changed to:

The secondary objective of the study is to assess the clinical efficacy of UCB7665 as measured by the change in platelet count and to assess the pharmacodynamic (PD) effect of UCB7665 as measured by the change in total IgG concentrations in serum. The exploratory objectives include the following: [redacted] to evaluate the clinical efficacy as measured by the change in ITP bleeding score; to evaluate the effect of UCB7665 on the concentrations of total protein, albumin, α-globulin and β-globulin, IgG subclasses, IgM, IgA, and IgE, and serum or plasma complement levels; to evaluate the emergence of anti-drug antibodies (ADA), ie, anti-UCB7665 antibodies with respect to immunogenicity and pharmacokinetics (PK)/PD; to evaluate the relationship between changes in platelet count and total IgG, IgG subclasses, ITP-specific autoantibodies; and to assess the plasma concentrations of UCB7665 administered by sc infusion.

Change #5.

Section 1 SUMMARY

Paragraph 11

Description of PDILI evaluation has been added.

Change #6.

Section 1 SUMMARY

Paragraph 12

….. The PD variables are maximum change in total IgG concentration during the study; IgG subclass concentrations; and ITP-specific autoantibody [redacted] concentrations in blood over time. Other immunological variables to be evaluated are total IgA, IgE, and IgM levels; serum complement levels (C3, C3a, C4, and C5a); ADA; and cytokines (for subjects experiencing infusion reactions).

Has been changed to:

….. The PD variables are minimum value and maximum decrease in total IgG concentration during the study; IgG subclass concentrations; and ITP-specific autoantibody [redacted] in serum over time. Other immunological variables to be evaluated are total IgA, IgE, and IgM levels; serum (C3 and C4) and plasma (C3a and C5a) complement levels; ADA status (negative/positive) and relative mass units; serum biomarkers [redacted] B cell activating factor (BAFF) levels and the results of the IgG depletion assay; and cytokines (for subjects experiencing infusion reactions). Additional exploratory biomarkers may be investigated if needed using the samples already available.

Change #7.

Section 3.2 Secondary objectives

Bullet 2

The secondary objectives of this study are:

- To assess the PD effect of UCB7665 as measured by the change in total IgG concentration in blood

Has been changed to:

The secondary objectives of this study are:

- To assess the PD effect of UCB7665 as measured by the change in total IgG concentration in serum

Change #8.

Section 3.3 Exploratory objectives

Bullet 1 and 3

The exploratory objectives of this study are:

- [redacted]
- To evaluate the effect of UCB7665 on the concentrations of total protein, albumin, α-globulin and β-globulin, IgG subclasses, IgM, IgA, and IgE, and serum complement levels

Has been changed to:

The exploratory objectives of this study are:

- [redacted]
- To evaluate the effect of UCB7665 on the concentrations of total protein, albumin, α-globulin and β-globulin, IgG subclasses, IgM, IgA, and IgE, and serum or plasma complement levels

Change #9.

Section 4.2 Efficacy variables

Bullet 15

- Value and change from Baseline in the ITP bleeding score over time

Has been changed to:

- ITP bleeding score over time

Change #10.

Section 4.3.2 Pharmacodynamic variables

The PD variables are:

- Maximum change from Baseline in total IgG concentration during the study
- Change from Baseline in ITP-specific autoantibody concentrations in blood over time: [redacted]
- Change from Baseline in IgG subclass concentrations over time
- Value and change from Baseline in IgG concentrations over time

Has been changed to:

- Minimum value and maximum decrease from Baseline in total IgG concentration during the study
- Value and change from Baseline in total IgG concentrations over time
- The value and change from Baseline in endogenous IgG concentrations will be measured by IgG depletion assay
- Change from Baseline in ITP-specific autoantibody in serum over time: [redacted]
- Change from Baseline in IgG subclass concentrations over time

Change #11.

Section 4.4 Other immunological variables

Other immunological variables are:

- Change from Baseline in immunoglobulin concentrations (total IgA, IgE, and IgM) over time
- Change from Baseline in serum complement levels (C3, C3a, C4, and C5a) over time
- Value and change from Baseline in ADA (anti-UCB7665 antibodies) over time
- Cytokines

Cytokine samples will be taken at Baseline for all subjects and at subsequent visits only if the subject experiences infusion reactions.

Has been changed to:

Other immunological variables are:

- Change from Baseline in serum immunoglobulin concentrations (total IgA, IgE, and IgM) over time
- Change from Baseline in serum (C3 and C4) and plasma (C3a and C5a) complement levels over time
- Change from Baseline in serum biomarkers [redacted] over time
- ADA (anti-UCB7665 antibodies) status (negative/positive) and change from Baseline in relative mass units over time
- Change from Baseline in cytokines over time (for subjects experiencing infusion reactions)
- Change from Baseline in serum BAFF levels over time

Cytokine samples will be taken at Baseline for all subjects and at subsequent visits only if the subject experiences infusion reactions.

Additional exploratory biomarkers may be investigated if needed using the samples already available.

Change #12.

Section 5.1 Study description

Paragraph 5

Dosing Period: The first 6 subjects in the study will receive UCB7665 4mg/kg. These subjects in the Dose Arm 1 will not be randomized. While recruitment is still ongoing, safety data for the first 3 subjects up to 7 days after the final dose will be reviewed by a DMC. During a second DMC meeting, safety data for the first 6 subjects up to 7 days after the final dose will be reviewed. During these reviews recruitment in the dose arm will not be stopped. Following this review, the DMC will make a decision on whether to open Dose Arm 2 for enrollment. Once the DMC has approved opening of Dose Arm 2 for enrollment, subjects will subsequently be randomized to one of the 2 dose arms using IXRS. If the new dose arm will be initiated and if the

UCB7665 4mg/kg arm will be continued, new subjects will be randomized to 1 of the 2 dose arms in an allocation ratio of 1:1 (randomization will stop once 15 subjects are treated with UCB7665 4mg/kg dose).

Has been changed to:

Dosing Period: The first 6 subjects in the study will receive UCB7665 4mg/kg. These subjects in the Dose Arm 1 will not be randomized. While recruitment is still ongoing, safety data for the first 3 subjects up to 7 days after the final dose of the third subject will be reviewed by the DMC. During a second DMC meeting, all available safety data up to cut off date defined as 7 days after the final dose of the sixth subject will be reviewed. During these reviews recruitment in the dose arm will not be stopped. Following this review, the DMC will make a decision on whether to open Dose Arm 2 for enrollment. Once the DMC has approved opening of Dose Arm 2 for enrollment, subjects will subsequently be randomized to 1 of the 2 dose arms using IXRS. If the new dose arm will be initiated and if the UCB7665 4mg/kg arm will be continued, new subjects will be randomized to 1 of the 2 dose arms in an allocation ratio of 1:1 (Once 15 subjects are in the 4mg/kg group, the remaining subjects will not be randomized. They will be allocated to the 7mg/kg group.).

Change #13.

Section 5.2 Schedule of study assessments

Assessments of height, serology test for HIV, hepatitis B, and hepatitis C and biomarkers have been added to the Table 5-1. Footnotes f, g, n have been updated.

Change #14.

Section 5.2 Schedule of study assessments

Assessments of height, serology test for HIV, hepatitis B, and hepatitis C and biomarkers have been added to the Table 5-2. Footnotes f, g, n have been updated.

Change #15.

Section 5.2 Schedule of study assessments

Assessments of biomarkers have been added to the Table 5-3. Footnote d has been updated.

Table 5-1: Schedule of assessments for the UCB7665 4mg/kg dose arm

Assessments		Screening Period	Dosing Period						Observation Period							
			Dose 1		Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a] BL Visit	3	4[a]	5[a]	6[a]	7[a]	8	9	10[b]	11	12[b]	13	14[b]	15 EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	22	29	32	36	43	50	57	64	71	85
	Week		1	1	2	3	4	5	5	6	7	8	9	10	11	13
	Visit Window			±1d	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Written informed consent		X														
Demographic data		X														
Verification of inclusion/exclusion criteria		X	X													
Platelets for inclusion/ withdrawal check (local laboratory)[f]			X		X	X	X	X								
Randomization[g]			X													
Withdrawal criteria[h]			X	X	X	X	X	X								
General medical/procedures history		X														
ITP history		X														
Prior and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 5-1: Schedule of assessments for the UCB7665 4mg/kg dose arm

Assessments		Screening Period	Dosing Period						Observation Period							
			Dose 1		Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a]	3	4[a]	5[a]	6[a]	7[a]	8	9	10[b]	11	12[b]	13	14[b]	15
			BL Visit													EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	22	29	32	36	43	50	57	64	71	85
	Week		1	1	2	3	4	5	5	6	7	8	9	10	11	13
	Visit Window			±1d	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Concomitant medical procedures			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight		X														X
Height		X														
Recording of AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[i]		X	X		X	X	X	X		X		X		X		X
12-lead ECG		X	X		X	X	X	X		X						X
Karnofsky Performance Status		X														
Laboratory parameters (hematology, chemistry, urinalysis)		X[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serology test for HIV, hepatitis B, and hepatitis C		X														

Table 5-1: Schedule of assessments for the UCB7665 4mg/kg dose arm

Assessments		Screening Period	Dosing Period						Observation Period							
			Dose 1		Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a] BL Visit	3	4[a]	5[a]	6[a]	7[a]	8	9	10[b]	11	12[b]	13	14[b]	15 EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	22	29	32	36	43	50	57	64	71	85
	Week		1	1	2	3	4	5	5	6	7	8	9	10	11	13
	Visit Window			±1d	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Blood sample for cytokines			X	X[k]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]
Serum pregnancy test		X														
Urine pregnancy test			X		X	X	X	X								X
Call to IXRS for treatment kit number			X		X	X	X	X								
Administration of IMP			X		X	X	X	X								
Blood sampling for plasma concentration of UCB7665			X	X	X	X	X	X	X	X						
Anti-UCB7665 antibodies/IgG depletion assay			X	X	X	X	X	X	X	X	X		X		X	X
Serum complements (C3 and C4) and plasma complements (C3a and C5a)			X			X			X				X			

Table 5-1: Schedule of assessments for the UCB7665 4mg/kg dose arm

Assessments		Screening Period	Dosing Period						Observation Period							
			Dose 1		Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a]	3	4[a]	5[a]	6[a]	7[a]	8	9	10[b]	11	12[b]	13	14[b]	15
			BL Visit													EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	22	29	32	36	43	50	57	64	71	85
	Week		1	1	2	3	4	5	5	6	7	8	9	10	11	13
	Visit Window			±1d	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Serum biomarkers [redacted]			X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum biomarkers [redacted]			X	X	X	X	X	X								
Serum BAFF levels			X		X	X	X	X			X				X	
Immunoglobulins (total IgG, IgG subclasses)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IgA, IgM, IgE[l]			X					X		X					X	
ITP-specific autoantibodies[m]			X							X						X
ITP bleeding scale		X	X		X	X	X	X		X		X		X		X
NFI-MS			X							X		X		X		X
Headache questionnaire[n]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject exit interview[o]																X

AE=adverse event; BAFF= B cell activating factor; BL=Baseline; CSF=cerebrospinal fluid; CT=computed tomography; d=day(s); DMC=Data Monitoring Committee; ECG=electrocardiogram; EOS=End of Study; EW=Early Withdrawal; [redacted]; HIV=human immunodeficiency virus; Ig=immunoglobulin; IMP=investigational medicinal product; ITP=immune thrombocytopenia; IXRS= interactive voice/web response system; LP=lumbar puncture; MRI=magnetic resonance imaging; NFI-MS=Neurological Fatigue Index for multiple sclerosis; [redacted]

[a] Frequency of assessments on dosing days is detailed in Table 5-3.

[b] Visits 10, 12, and 14 can be performed at home with a healthcare professional visiting the subject at his/her home.

[c] The End-of-Study Visit is 8 weeks following the final dose.

[d] A visit window of ±2 days is allowed for the dosing visits. The visit window of ±2 days is relative to the first dosing visit date. However, there should be a minimum interval of 5 days and maximum interval of 9 days as compared to the previous dose.

[e] The visit windows in the Observation Period are relative to the final dosing visit date.

[g] Prior to dosing at Visit 2, 2 platelet samples will be taken. One sample will be analyzed locally and the value will be used to check inclusion criteria. The other platelet sample will be sent to the central laboratory. At subsequent dosing visits, a platelet sample will be assessed locally prior to dosing to evaluate withdrawal criterion of platelet count >350x10^9/L.

[h] The first 6 subjects will be enrolled in the Dose Arm 1 group only. Safety data for these 6 subjects up to 7 days after the last dose will be reviewed by the DMC. Following this review the DMC will make a decision to open Dose Arm 2 for enrollment. If Dose Arm 2 is opened, subjects subsequently enrolled will be randomly assigned subsequently to 1 of the 2 dose arms using an IXRS until 15 subjects are in Dose Arm 1.

Error! Reference source not found. Subjects can withdraw at any time during the study, based on the criteria in Section 6.4.

Error! Reference source not found. A complete physical examination will be performed at Screening and EOS/EW Visit. At all other visits (where physical examination is performed), an abbreviated physical examination will be conducted.

[l] At the Screening Visit, 2 separate blood samples will be obtained on the same day for evaluation of platelet count.

[n] Blood sample for cytokines will be obtained only in case of infusion reactions.

Error! Reference source not found. In case the number of infusions to be administered are reduced after DMC review of safety data, then the scheduled Visit 7 assessment for IgA, IgM, and IgE will be performed earlier at the last dosing visit.

Error! Reference source not found. [redacted]

Error! Reference source not found. This assessment is applicable only to subjects experiencing severe headaches and will be performed daily until resolution (ie, if headache becomes moderate or mild, normal collection of AEs should apply); this assessment will be followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

Error! Reference source not found. A semi-structured interview guide will be used and the interview will be recorded. In case of early withdrawal from the study, the subject exit interview should be performed at End-of-Study Visit only.

Table 5-2: Schedule of assessments for the UCB7665 7mg/kg dose arm

Assessments		Screening Period	Dosing Period				Observation Period							
			Dose 1		Dose 2	Dose 3								
	Visit	**1**	**2[a]**	**3**	**4[a]**	**5[a]**	**6**	**7**	**8[b]**	**9**	**10[b]**	**11**	**12[b]**	**13**
			BL Visit											**EOS/ EW[c]**
	Day	**-28 to -1**	**1**	**4**	**8**	**15**	**18**	**22**	**29**	**36**	**43**	**50**	**57**	**71**
	Week		**1**	**1**	**2**	**3**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**11**
	Visit Window			**±1d**	**±2d[d]**	**±2d[d]**	**±1d**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**
Written informed consent		X												
Demographic data		X												
Verification of inclusion/exclusion criteria		X	X											
Platelets for inclusion/withdrawal check (local laboratory) [f]			X		X	X								
Randomization[g]			X											
Withdrawal criteria[h]			X	X	X	X								
General medical/procedures history		X												
ITP history		X												
Prior and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medical procedures			X	X	X	X	X	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight		X												X
Height		X												
Recording of AEs		X	X	X	X	X	X	X	X	X	X	X	X	X

Table 5-2: Schedule of assessments for the UCB7665 7mg/kg dose arm

Assessments		Screening Period	Dosing Period				Observation Period							
			Dose 1		Dose 2	Dose 3								
	Visit	**1**	**2**[a]	**3**	**4**[a]	**5**[a]	**6**	**7**	**8**[b]	**9**	**10**[b]	**11**	**12**[b]	**13**
			BL Visit											**EOS/ EW**[c]
	Day	**-28 to -1**	**1**	**4**	**8**	**15**	**18**	**22**	**29**	**36**	**43**	**50**	**57**	**71**
	Week		**1**	**1**	**2**	**3**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**11**
	Visit Window			**±1d**	**±2d**[d]	**±2d**[d]	**±1d**	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]
Physical examination[i]		X	X		X	X		X		X		X		X
12-lead ECG		X	X		X	X		X						X
Karnofsky Performance Status		X												
Laboratory parameters (hematology, chemistry, urinalysis)		X[j]	X	X	X	X	X	X	X	X	X	X	X	X
Serology test for HIV, hepatitis B, and hepatitis C		X												
Blood sample for cytokines			X	X[k]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]
Serum pregnancy test		X												
Urine pregnancy test			X		X	X								X
Call to IXRS for treatment kit number			X		X	X								
Administration of IMP			X		X	X								
Blood sampling for plasma concentration of UCB7665			X	X	X	X	X	X						
Anti-UCB7665 antibodies/IgG depletion assay			X	X	X	X	X	X	X		X		X	X

Table 5-2: Schedule of assessments for the UCB7665 7mg/kg dose arm

Assessments		Screening Period	Dosing Period				Observation Period							
			Dose 1		Dose 2	Dose 3								
	Visit	**1**	**2[a]**	**3**	**4[a]**	**5[a]**	**6**	**7**	**8[b]**	**9**	**10[b]**	**11**	**12[b]**	**13**
			BL Visit											**EOS/ EW[c]**
	Day	**-28 to -1**	**1**	**4**	**8**	**15**	**18**	**22**	**29**	**36**	**43**	**50**	**57**	**71**
	Week		**1**	**1**	**2**	**3**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**11**
	Visit Window			**±1d**	**±2d[d]**	**±2d[d]**	**±1d**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**
Serum complements (C3 and C4) and plasma complements (C3a and C5a)			X			X	X				X			
Serum biomarkers [redacted]			X	X	X	X	X	X	X	X	X	X	X	
Serum biomarkers [redacted]			X	X	X	X								
Serum BAFF levels			X		X	X			X				X	
Immunoglobulins (total IgG, IgG subclasses)		X	X	X	X	X	X	X	X	X	X	X	X	X
IgA, IgM, IgE[l]			X			X		X					X	
ITP-specific autoantibodies[m]			X					X						X
ITP bleeding scale		X	X		X	X		X		X		X		X
NFI-MS			X					X		X		X		X
Headache questionnaire[n]			X	X	X	X	X	X	X	X	X	X	X	X
Subject exit interview[o]														X

AE=adverse event; BAFF=B cell activating factor; BL=baseline; CSF=cerebrospinal fluid; CT=computed tomography; d=day(s); DMC=Data Monitoring Committee; ECG=electrocardiogram; EOS=End of Study; EW=Early Withdrawal; [redacted] HIV=human immunodeficiency virus; Ig=immunoglobulin; IMP=investigational medicinal product; ITP=immune thrombocytopenia; IXRS= interactive voice/web response system; LP=lumbar

puncture; MRI=magnetic resonance imaging; NFI-MS=Neurological Fatigue Index for multiple sclerosis; [redacted]

[a] Frequency of assessments on dosing days is detailed in Table 5–3.

[b] Visits 8, 10, and 12 can be performed at home with a healthcare professional visiting the subject at his/her home.

[c] The End-of-Study Visit is 8 weeks following the final dose.

[d] A visit window of ±2 days is allowed for the dosing visits. The visit window of ±2 days is relative to the first dosing visit date. However, there should be a minimum interval of 5 days and maximum interval of 9 days as compared to the previous dose.

[e] The visit windows in the Observation Period are relative to the final dosing visit date.

(local laboratory)Prior to dosing at Visit 2, 2 platelet samples will be taken. One sample will be analyzed locally and the value will be used to check inclusion criteria. The other platelet sample will be sent to the central laboratory. At subsequent dosing visits, a platelet sample will be assessed locally prior to dosing to evaluate withdrawal criterion of platelet count >350x10^9/L.

[h] The first 6 subjects will be enrolled in the Dose Arm 1 group. Safety data for these 6 subjects up to 7 days after the last dose will be reviewed by the DMC. Following this review the DMC will make a decision to open Dose Arm 2 for enrollment. If Dose Arm 2 is opened, subjects subsequently enrolled will be randomly assigned to one of the dose arms using an IXRS until 15 subjects are in Dose Arm 1.

[i] Subjects can withdraw at any time during the study, based on the criteria in Section 6.4.

[j] A complete physical examination will be performed at Screening and EOS/EW Visit. At all other visits (where physical examination is performed), an abbreviated physical examination will be conducted.

[l] At the Screening Visit, 2 separate blood samples will be obtained on the same day for evaluation of platelet count.

[n] Blood sample for cytokines will be obtained only in case of infusion reactions.

Error! Reference source not found. In case the number of infusions to be administered are reduced after DMC review of safety data, then the scheduled Visit 5 assessment for IgA, IgM, and IgE will be performed earlier at the last dosing visit.

Error! Reference source not found. [redacted]

Error! Reference source not found. This assessment is applicable only to subjects experiencing severe headaches and will be performed daily until resolution (ie, if headache becomes moderate or mild, normal collection of AEs should apply); this assessment will be followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

Error! Reference source not found. A semi-structured interview guide will be used and the interview will be recorded. In case of early withdrawal from the study, the subject exit interview should be performed at End-of-Study Visit only.

Table 5-3: Schedule of investigations on the dosing days

	Predose	End of infusion	2h after end of infusion	4h after end of infusion
Withdrawal criteria	X			
Platelet count (local laboratory) for inclusion check at Visit 2 and for withdrawal criterion at other dosing visits	X			
Prior and concomitant medications	X			
Concomitant medical procedures	X			
Vital signs[a]	X	X	X	X
Physical examination	X			
12-lead ECG	X			
Hematology	X			
Clinical chemistry	X			
Urinalysis	X			
Urine pregnancy test	X			
Immunoglobulins[b]	X			
ITP-specific autoantibodies[c]	X			
Blood sampling for UCB7665 plasma concentration	X			
Anti-UCB7665 antibodies/IgG depletion assay	X			
Serum (C3 and C4) and plasma complements (C3a and C5a)[d]	X			
Serum biomarkers [redacted]	X		X	X
Serum BAFF levels	X		X	X
Blood sampling for cytokines[e]	X			

Table 5-3: Schedule of investigations on the dosing days

	Predose	End of infusion	2h after end of infusion	4h after end of infusion
ITP bleeding scale	X			
AEs	X	X	X	X
NFI-MS[f]	X			

AE=adverse event; BAFF=B cell activating factor; ECG=electrocardiogram; h=hours; Ig=immunoglobulin; IMP=investigational medicinal product; ITP=immune thrombocytopenia; NFI-MS=Neurological Fatigue Index for multiple sclerosis; [redacted] PRO=Patient Reported Outcomes; [redacted]

[b] In addition to time points mentioned, vital signs will be evaluated every 15 minutes during infusion. Respiratory rate will be assessed only once predose.

[d] Total IgG and IgG subclasses.

[e] Evaluation of ITP-specific autoantibodies will be performed prior to dose 1 only.

[f] Serum and plasma complement levels will be assessed prior to dose 1 and dose 3 only.

Error! Reference source not found. Blood sample for Baseline cytokine values will be obtained at Visit 2 for all subjects at predose and at other visits in case of infusion reactions.

Error! Reference source not found. PRO endpoint (NFI-MS) will be assessed prior to dose 1 only.

Change #16.

Section 6.2.1 Exclusion criteria related to health status

Number 3 and 10

3. Subject has a Karnofsky Performance Status (Appendix 18.1) rating <60 at Screening Visit.

10. Subject has liver impairment, defined as:

- Subject has >2xULN alanine aminotransferase (ALT) or alkaline phosphatase (ALP), or >ULN bilirubin (≥1.5xULN bilirubin if known Gilbert's syndrome) at Screening Visit. If the subject has isolated >ULN and <1.5xULN bilirubin, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

For subjects with a Baseline result >ULN, a baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the medical history section of the electronic Case Report form (eCRF).

If subject has >ULN that does not meet the exclusion limit for ALT or ALP at screening, repeat, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the subject must be discussed with the Medical Monitor.

Serum ALT results up to 25% above the upper exclusion limit may be repeated once for confirmation. This includes rescreening (see Section 6.3).

Has been changed to:

3. Subject has a Karnofsky Performance Status (Appendix 18.1) rating <60% at Screening Visit.

10. Subject has liver impairment, defined as:

- Subject has >1.5xULN of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP), or >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If the subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

For subjects with a Baseline result >ULN for ALT, AST, ALP, or total bilirubin, a Baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the electronic Case Report form (eCRF).

If subject has >ULN for ALT, AST, or ALP that does not meet the exclusion limit at screening, repeat the tests, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the subject must be discussed with the Medical Monitor.

Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. This includes rescreening (see Section 6.3).

Change #17.

Section 6.2.2 Exclusion criteria related to medical history

14. Subject has evidence of a secondary cause of immune thrombocytopenic purpura from the past medical history (eg, bacterial or viral infection, past medical history of leukemia, lymphoma, combined variant immunodeficiency, systemic lupus erythematosus, thyroid disease) or to drug treatments (eg, heparin, quinine, antimicrobials, anticonvulsants) or subject has a multiple immune cytopenia, eg, Evan's syndrome.
15. Subject has a history of clinically relevant ongoing chronic infections including but not limited to human immunodeficiency virus (HIV), hepatitis B, hepatitis C, active or latent tuberculosis.
20. Subject has a history of known inflammatory bowel disease, diverticular disease, and gastric or esophageal ulceration.
21. Subject has experienced gastrointestinal bleed in the last 6 months prior to Screening Visit and/or has current gastritis or esophagitis.
23. Subject has a medical history of thrombosis.
24. Subject has a history of coagulopathy disorders.

Has been changed to:

14. Subject has evidence of a secondary cause of immune thrombocytopenic purpura from the past medical history (eg, bacterial or viral infection, past medical history of leukemia, lymphoma, common variable immunodeficiency, systemic lupus erythematosus, auto-immune thyroid disease) or to drug treatments (eg, heparin, quinine, antimicrobials, anticonvulsants) or subject has a multiple immune cytopenia, eg, Evan's syndrome.
15. Subject has a history of clinically relevant ongoing chronic infections including but not limited to human immunodeficiency virus (HIV), hepatitis B, hepatitis C, active or latent tuberculosis, or is tested positive for HIV, hepatitis B, or hepatitis C at the Screening Visit.
20. Subject has a history of known inflammatory bowel disease, diverticular disease, or has a history of confirmed, duodenal, gastric or esophageal ulceration in the past 6 months.
21. Subject has experienced a clinically symptomatic gastrointestinal bleed (positive hemoccult tests without any signs and symptoms of gastrointestinal bleedings will not be considered as "clinically symptomatic") in the last 6 months prior to Screening Visit and/or has current gastritis or esophagitis and/or has a known risk for clincial relevant gastrointestinal bleeding beyond ITP.
23. Subject has a medical history of thrombosis within the past 5 years or a history of thrombosis with unknown cause at any time or a known significant risk for thrombosis.
24. Subject has a history of coagulopathy disorders other than ITP.

Change #18.

Section 6.2.3 Exclusion criteria related to concomitant medications/procedures

Definition of generic name was added and wording of "wash-out" changed to "washout" in Table 6-1.

Table 6-1: Washout periods for immunosuppressants, biologics and other therapies

Generic name (most common commercial/trade names)	Washout period relative to Baseline Visit (regardless of route)
Immunosuppressants	
Cyclophosphamide	6 months
Pimecrolimus (Elidel®)	4 weeks
Vinca alkaloids (vincristine, vinblastine)	12 weeks
Biologics (mAbs and fusion proteins)	
Abatacept (CTLA 4-Ig) (Orencia®)	6 months
Belimumab (Benlysta™)	6 months
Golimumab (Simponi™)	6 months
Natalizumab (Tysabri®)	6 months
Ofatumumab (Arzerra)	6 months
Rituximab (Rituxan®) and ocrelizumab	6 months
TACI-Ig (Atacicept)	10 months
Veltuzumab	6 months
Other biologics	3 months
Others	
Intravenous immunoglobulin	4 weeks
IPP-201101 (Lupuzor™)	3 months
Plasma exchange (PLEX)	4 weeks
TPO-R agonists (eltrombopag, romiplostim)	4 weeks
Anti-D	4 weeks
Antiplatelets and Anticoagulants (Vitamin K antagonists)	
Warfarin	2 weeks
Fenprocoumon	2 weeks
Acenocoumarol	2 weeks
Heparin	1 week
Clopidogrel	1 week
Salicylates (Aspirin)	1 week
Dipyramidole	1 week

Table 6-1: Washout periods for immunosuppressants, biologics and other therapies

Generic name (most common commercial/trade names)	Washout period relative to Baseline Visit (regardless of route)
Prasugrel	1 week
Ticagrelor	1 week
Tirofiban	1 week
Abciximab	1 week

Change #19.

Section 6.4 Withdrawal criteria

Number 2, bullet 5

2. Subject develops an illness or has a change in health status that would interfere with his/her continued participation, including but not limited to:
   - Subject has a clinically severe (life threatening) bleeding event (Skin [S]>2 and/or Mucosae [M]>1 and /or Organ [O]>1).

Has been changed to:

2. Subject develops an illness or has a change in health status that would interfere with his/her continued participation, including but not limited to:
   - Subject has a life threatening bleeding event.

Change #20.

Section 6.4 Withdrawal criteria

Subjects with potential drug-induced liver injury (PDILI) MUST stop treatment with IMP. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be stopped.

The below PDILI criteria require immediate and permanent discontinuation of IMP:

- Subjects with any of the following:
  - ALT ≥8xULN
  - ALT ≥3xULN and co-existing total bilirubin ≥2xULN

The below PDILI criteria requires immediate discontinuation of IMP:

- Subjects with ALT ≥3xULN who exhibit a temporally associated fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever (without clear alternative cause), rash, or eosinophilia (ie, >5%) must be immediately discontinued from IMP.

If a nondrug related cause for the symptoms can be confirmed, these subjects may resume IMP administration after discussion with the Medical Monitor.

The PDILI criterion below allows for subjects to continue on IMP at the discretion of the investigator.

- ALT ≥3xULN (and ≥2x Baseline) and <8xULN, total bilirubin <2xULN, and no eosinophilia (ie, ≤5%), with no fever, rash, or symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain, or tenderness).

The investigator must consult UCB Medical Monitor within 24 hours if ALT ≥3xULN (with or without increase in bilirubin or with/without symptoms of liver dysfunction) and further dosing should be withheld until after discussion with UCB medical monitor.

Has been changed to:

Subjects with PDILI must be assessed to determine if IMP must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

The PDILI criteria below require **immediate and permanent** discontinuation of IMP:

- Subjects with either of the following:
  - ALT or AST ≥5xULN
  - ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN

The PDILI criterion below requires immediate discontinuation of IMP:

- Subjects with ALT or AST ≥3xULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, right upper quadrant pain or tenderness. Hypersensitivity symptoms include fever (without clear alternative cause), rash, or eosinophilia (ie, >5%).

If a nondrug-related cause for the symptoms can be confirmed, these subjects may resume IMP administration after discussion with responsible UCB physician, but only when the requirements for rechallenge with IMP as provided in Section 12.7.1.2.1 are followed.

The PDILI criterion below allows for subjects to continue on IMP at the discretion of the investigator.

- Subjects with ALT or AST ≥3xULN (and ≥2x Baseline) and <5xULN, total bilirubin <2xULN, and no eosinophilia (ie, ≤5%), with no fever, rash, or symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain, or tenderness).

Evaluation of PDILI must be initiated as described in Section 12.7.1. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

Change #21.

Section 7.8.1 Permitted immunosuppressant medications

Dose unit for Cyclosporin was updated.

Has been changed to:

Table 7–1: Permitted immunosuppressant medications

Permitted medications	Dose	Comment
Oral corticosteroids (prednisolone)	≤10mg/day	Stable dose for 2 weeks prior to Baseline
Methotrexate	≤30mg/week	Stable dose for 2 months prior to Baseline
Mycophenolate mofetil	≤3g/day	Stable dose for 2 months prior to Baseline
Cyclosporin	≤5mg/kg/day	Stable dose for 2 months prior to Baseline
Azathioprine	≤3mg/kg/day	Stable dose for 2 months prior to Baseline
Danazol	≤15mg/kg/day	Stable dose for 2 months prior to Baseline
Dapsone	100mg/day	Stable dose for 2 months prior to Baseline

Change #22.

Section 7.8.2 Prohibited concomitant treatments (medications and therapies)

Bullet 12

- Anticoagulants and antiplatelets (warfarin, heparin, clopidogrel, aspirin, salicylics, dipyramidole, prasugrel, ticregelor, ticofiban, abiximab)

Has been changed to:

- Anticoagulants and antiplatelets (warfarin, heparin, clopidogrel, aspirin, salicylics, dipyramidole, prasugrel, tricagrelor, tirofiban, abciximab)

Change #23.

Section 7.10 Randomization and numbering of subjects

Paragraph 2

The first 6 subjects (and those treated before DMC assessment after the 6 subjects) will not be randomized. Once the DMC has approved opening of Dose Arm 2 for enrollment, subsequent subjects will be randomized to 1 of the 2 dose arms in a 1:1 ratio.

Has been changed to:

The first 6 subjects (and those treated before DMC assessment after the 6 subjects) will not be randomized. Once the DMC has approved opening of Dose Arm 2 for enrollment, subsequent subjects will be randomized to 1 of the 2 dose arms in a 1:1 ratio. Once 15 subjects are in the 4mg/kg group, the remaining subjects will not be randomized. They will be allocated to the 7mg/kg group.

Change #24.

Section 7.10 Randomization and numbering of subjects

Paragraph 4

To randomize a subject, the investigator or designee will contact the IXRS and provide brief details about the subject to be randomized. The IXRS will automatically inform the investigator or designee of the subject's randomization number. The IXRS will allocate kit numbers to the subject based on the subject number during the course of the study.

Has been changed to:

To randomize a subject, the investigator or designee will contact the IXRS and provide brief details about the subject to be randomized. The IXRS will automatically inform the investigator or designee of the subject's kit number. The IXRS will allocate kit numbers to the subject based on the subject number or randomization during the course of the study.

Change #25.

Section 8.1.1 Visit 1 (Day -28 to -1) Screening Visit

Following assessments have been added.

- Height
- Serology test for HIV, hepatitis B, and hepatitis C

Change #26.

Section 8.2.1 Visit 2 (Week 1/Day 1) Baseline Visit

Paragraphs 1, 2, 3 and 4

Visit 2 can occur at any time after Visit 1, but no later than 28 days after Visit 1. Prior to randomization, 2 platelet samples will be taken. One sample will be analyzed locally and the value will be used to check inclusion criterion. The other platelet sample will be sent to the central laboratory.

Eligible subjects will be randomized at Visit 2 and first dose of IMP will be administered as per the subject's randomization, except that the first 6 subjects will be enrolled in Dose Arm 1.

Subjects randomized to Dose Arm 1 (UCB7665 4mg/kg sc) will receive a total of 5 doses of IMP at Visit 2 (Day 1, Week 1), Visit 4 (Week 2), Visit 5 (Week 3), Visit 6 (Week 4), and Visit 7 (Week 5).

Subjects randomized to Dose Arm 2 (UCB7665 7mg/kg sc) will receive a total of 3 doses of IMP at Visit 2 (Day 1, Week 1), Visit 4 (Week 2), and Visit 5 (Week 3).

Has been changed to:

Visit 2 can occur at any time after Visit 1, but no later than 28 days after Visit 1. Prior to dosing at Visit 2, 2 platelet samples will be taken. One sample will be analyzed locally and the value will be used to check inclusion criterion. The other platelet sample will be sent to the central laboratory.

Eligible subjects will be treated with IMP at Visit 2. The first 6 subjects will be enrolled in Dose Arm 1, subsequent subjects will be randomized to 1 of the 2 dose arms. Once 15 subjects are in Dose Arm 1, the remaining subjects will not be randomized. They will be allocated to Dose Arm 2.

Subjects allocated to Dose Arm 1 (UCB7665 4mg/kg sc) will receive a total of 5 doses of IMP at Visit 2 (Day 1, Week 1), Visit 4 (Week 2), Visit 5 (Week 3), Visit 6 (Week 4), and Visit 7 (Week 5).

Subjects allocated to Dose Arm 2 (UCB7665 7mg/kg sc) will receive a total of 3 doses of IMP at Visit 2 (Day 1, Week 1), Visit 4 (Week 2), and Visit 5 (Week 3).

Change #27.

Section 8.2.1 Visit 2 (Week 1/Day 1) Baseline Visit

Definition of complement levels were updated as:

- Serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a)

And following assessments have been added:

- Serum biomarkers [redacted] and serum BAFF levels. Blood samples are taken prior to dosing, 2 and 4 hours after end of infusion for serum biomarkers and BAFF

- Description for headache questionnaire was updated as:
- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to computed tomography (CT) scan, magnetic resonance imaging (MRI) and/or lumbar puncture (LP) for cerebrospinal fluid (CSF) collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

Change #28.

Section 8.2.2 Visit 3 (Week 1/Day 4)

Following assessments have been added:

- Serum biomarkers [redacted]

- Description for headache questionnaire was updated as:
- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

Change #29.

Section 8.2.3 Visit 4 (Week 2/Day 8)

Following assessments have been added.

- Call IXRS to obtain treatment kit number(s)
- Blood sample for the following laboratory parameters:

– Serum biomarkers [redacted] and serum BAFF levels. Blood samples are taken prior to dosing, 2 and 4 hours after end of infusion for serum biomarkers and BAFF

Description for headache questionnaire was updated as:

- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/ or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

Change #30.

Section 8.2.4 Visit 5 (Week 3/Day 15)

Definition of complement levels were updated as:

– Serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a)

Following assessments have been added.

- Call IXRS to obtain treatment kit number(s)
- Blood sample for the following laboratory parameters:
  – Serum biomarkers [redacted] and serum BAFF levels. Blood samples are taken prior to dosing, 2 and 4 hours after end of infusion for serum biomarkers and BAFF

Description for headache questionnaire was updated as:

- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/ or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

Change #31.

Section 8.2.5 Visit 6 (Week 4/Day 22) [UCB7665 4mg/kg only]

And following assessments have been added.

- Call IXRS to obtain treatment kit number(s)
- Blood sample for the following laboratory parameters:
  – Serum biomarkers [redacted] and serum BAFF levels. Blood samples are taken prior to dosing, 2 and 4 hours after end of infusion for serum biomarkers and BAFF
- Description for headache questionnaire was updated as:
- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if

indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

Change #32.

Section 8.2.6 Visit 7 (Week 5/Day 29) [UCB7665 4mg/kg only]

Following assessments have been added.

- Call IXRS to obtain treatment kit number(s)
- Blood sample for the following laboratory parameters:
  - Serum biomarkers [redacted] and serum BAFF levels. Blood samples are taken prior to dosing, 2 and 4 hours after end of infusion for serum biomarkers and BAFF

Description for Headache questionnaire was updated as:

- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

Change #33.

Section 8.3.1 Visit 8 (Week 5/Day 32) [UCB7665 4mg/kg]/ Visit 6 (Week 3/Day 18) [UCB7665 7mg/kg]

Definition of complement levels were updated as:

- Serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a)

And following assessments have been added.

- Serum biomarkers [redacted]

- Description for headache questionnaire was updated as:
- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to computed tomography (CT) scan, magnetic resonance imaging (MRI) and/or lumbar puncture (LP) for cerebrospinal fluid (CSF) collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

Change #34.

Section 8.3.2 Visit 9 (Week 6/Day 36) [UCB7665 4mg/kg]/ Visit 7 (Week 4/Day 22) [UCB7665 7mg/kg]

Following assessments have been added.

- Blood sample for the following laboratory parameters:
  - Serum biomarkers [redacted]

Description for headache questionnaire was updated as:

- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, otherdiagnostic procedures including but not limited to CT scan, MRI and/ or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

Change #35.

Section 8.3.3 Visit 10 (Week 7/Day 43) [UCB7665 4mg/kg]/ Visit 8 (Week 5/Day 29) [UCB7665 7mg/kg]

Following assessments have been added.

- Blood sample for the following laboratory parameters:
  - Serum biomarkers [redacted]
  - Serum BAFF levels

Description for headache questionnaire was updated as:

- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/ or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

Change #36.

Section 8.3.4 Visit 11 (Week 8/Day 50) [UCB7665 4mg/kg]/ Visit 9 (Week 6/Day 36) [UCB7665 7mg/kg]

Following assessments have been added.

- Blood sample for the following laboratory parameters:
  - Serum biomarkers [redacted]

Description for headache questionnaire was updated as:

- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/ or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

Change #37.

Section 8.3.5 Visit 12 (Week 9/Day 57) [UCB7665 4mg/kg]/ Visit 10 (Week 7/Day 43) [UCB7665 7mg/kg]

Definition of complement levels were updated as:

- Serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a)

Following assessments have been added.

- Blood sample for the following laboratory parameters:
  - Serum biomarkers [redacted]

Description for headache questionnaire was updated as:

- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/ or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

Change #38.

Section 8.3.6 Visit 13 (Week 10/Day 64) [UCB7665 4mg/kg]/ Visit 11 (Week 8/Day 50) [UCB7665 7mg/kg]

Following assessments have been added.

- Blood sample for the following laboratory parameters:
  - Serum biomarkers [redacted]

Description for headache questionnaire was updated as:

- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/ or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

Change #39.

Section 8.3.7 Visit 14 (Week 11/Day 71) [UCB7665 4mg/kg]/ Visit 12 (Week 9/Day 57) [UCB7665 7mg/kg]

Following assessments have been added.

- Blood sample for the following laboratory parameters:
  - Serum biomarkers [redacted]
  - Serum BAFF levels

Description for headache questionnaire was updated as:

- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/ or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

Change #40.

Section 8.3.8 End-of-Study Visit: Visit 15 (Week 13/Day 85) [UCB7665 4mg/kg]/ Visit 13 (Week 11/Day 71) [UCB7665 7mg/kg]

Description for headache questionnaire was updated as:

- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/ or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

Change #41.

Section 8.5 Unscheduled Visit

Description for headache questionnaire was updated as:

- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/ or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

Change #42.

Section 10.2 Pharmacodynamic variables

Bullet 3

- ITP-specific autoantibody concentration

[redacted]

Has been changed to:

- Serum ITP-specific autoantibody

[redacted]

Change #43.

Section 11 ASSESSMENT OF OTHER IMMUNOLOGICAL VARIABLES

For all immunological assessments, blood samples will be collected predose (at dosing visits) by qualified site personnel at the same time that samples are collected for standard clinical laboratory. The time and date of the blood draws will be recorded in the eCRF. The following immunological assessments will be performed according to the schedule of study assessments (Section 5.2).

- Serum immunoglobulin concentration over time
  - IgA
  - IgE
  - IgM
- Serum complement levels over time
  - C3
  - C3a
  - C4
  - C5a
- Plasma anti-UCB7665 antibodies/IgG depletion assay
- Cytokines

Cytokine samples will be taken at Baseline Visit for all subjects. At subsequent visits, cytokine samples will be taken only when the subject experiences infusion reactions.

Has been changed to:

For all immunological assessments, blood samples will be collected predose (at dosing visits) by qualified site personnel at the same time that samples are collected for standard clinical laboratory. The time and date of the blood draws will be recorded in the eCRF. The following immunological assessments will be performed according to the schedule of study assessments (Section 5.2).

- Serum immunoglobulin concentration over time
  - IgA
  - IgE
  - IgM
- Serum complement levels over time
  - C3
  - C4
- Plasma complement levels over time
  - C3a
  - C5a
- Serum biomarkers levels over time

[redacted]

[redacted]

- Serum BAFF levels
- Plasma anti-UCB7665 antibodies/IgG depletion assay
- Cytokines
- Cytokine samples will be taken at Baseline Visit for all subjects. At subsequent visits, cytokine samples will be taken only when the subject experiences infusion reactions.

Change #44.

Section 12.1.1 Definition of adverse event

Following wordings have been added to paragraph 4:

Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or more bleeding events should be reported as AEs.

Change #45.

Section 12.1.3 Description of adverse events

Information of AE evaluation was added:

For recording an AE, CTCAE will be used, and only if it is impossible to assess severity using CTCAE, then AE intensity will be assessed using a scale of mild, moderate, or severe.

Change #46.

Section 12.1.6 Pregnancy

Paragraph 1 and sections onward, changed the name of UCB safety reporting department and its abbreviation from UCB's Drug Safety (DS) into UCB's Patient Safety (PS).

If an investigator is notified that a subject has become pregnant after the first intake of any IMP, the investigator must immediately notify UCB's Drug Safety (DS) department by providing the completed Pregnancy Report and Outcome form (for contact details see Serious Adverse Event reporting information at the beginning of this protocol). The subject should be withdrawn from the study as soon as pregnancy is known (by positive pregnancy test), and the following should be completed:

Has been changed to:

If an investigator is notified that a subject has become pregnant after the first intake of any IMP, the investigator must immediately notify UCB's Patient Safety (PS) department by providing the completed Pregnancy Report and Outcome form (for contact details see Serious Adverse Event reporting information at the beginning of this protocol). The subject should be withdrawn from the study as soon as pregnancy is known (by positive pregnancy test), and the following should be completed:

Change #47.

Suspected transmission of an infectious agent via a medicinal product was added as Section 12.1.7 and subsequent section numbers were changed accordingly.

Change #48.

Section 12.1.9 Hypersensitivity and adverse reactions

Paragraph 2

In case of occurrence of a hypersensitivity reaction (not determined by the investigator to be a minor local reaction at the infusion site, such as minimal itching) and depending upon its severity, appropriate countermeasures will immediately be taken by the investigator. The cytokine samples must be taken for infusion reactions.

Has been changed to:

Section 12.1.10 Hypersensitivity and adverse reactions

In case of occurrence of a hypersensitivity reaction (except for local injection site reaction) and depending upon its severity, appropriate countermeasures will immediately be taken by the investigator. The cytokine samples must be taken for infusion reactions.

Change #49.

Section 12.1.10 Management of severe headache

Paragraph 2, second sentence

Further workup will be performed (if indicated) at the discretion of the investigator and may include a CT scan and a LP for CSF collection, considering the local guidelines for performing LP in patients with ITP.

Has been changed to:

Section 12.1.11 Management of severe headache

Further workup will be performed at the discretion of the investigator and may include eg. a CT scan, MRI and/or a LP for CSF collection, considering the local guidelines for performing LP in patients with ITP.

Change #50.

Section 12.3 Adverse events of special interest

Paragraph 3, first sentence

Potential Hy's law, defined as ≥3xULN ALT with co-existing ≥2xULN bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality, must always be reported to UCB as an AE of special interest and a serious unexpected AE (ie, without waiting for any additional etiologic investigations to have been concluded).

Has been changed to:

Potential Hy's law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality, must

always be reported to UCB as an AE of special interest (ie, without waiting for any additional etiologic investigations to have been concluded).

Change #51.

Section 12.7 Laboratory measurements

Paragraphs 1 and 2, first sentence

Blood and urine specimens for routine assay of hematology including coagulation parameters, clinical chemistry, and urinalysis testing as well as pregnancy testing will be performed according to the Schedule of assessments (Section 5.2) to monitor the safety of subjects.

Prior to randomization, 2 platelet samples will be taken.

Has been changed to:

Blood and urine specimens for routine assay of hematology including coagulation parameters, clinical chemistry, urinalysis testing, and pregnancy testing as well as serology testing will be performed according to the Schedule of assessments (Section 5.2) to monitor the safety of subjects.

Prior to dosing at Visit 2, 2 platelet samples will be taken.

Change #52.

Section 12.7 Laboratory measurements

Table 12-2 has been updated to include serological test

Table 12-2: Laboratory measurements

Hematology	Chemistry	Coagulation parameters	Urinalysis	Pregnancy test
Basophils[a]	Calcium	INR	pH	Urine[b] HCG
Eosinophils[a]	Phosphate	Prothrombin time	Protein	Serum[c] HCG
Neutrophils[a]	Chloride	aPTT	Creatinine	
Lymphocytes[a]	Magnesium	Fibrinogen	Glucose	**Others**
Monocytes[a]	Potassium		Ketones	HbA1c
Hematocrit	Sodium		Urobilinogen	HIV
Hemoglobin	BUN		Bilirubin	Hepatitis B (HBsAg, anti-HBs, anti-HBc)
Platelet count	AST		Blood	Hepatitis C (anti-HCV)
RBC count	ALT		Nitrite	
WBC count	GGT		Albumin	
B- and T-Lymphocyte count	Total bilirubin		Leucocytes	
	Direct bilirubin (if indicated)			
	LDH			
	Total cholesterol			
	Triglycerides			
	ALP			
	Total protein			
	Albumin			
	α1-globulin, α2-globulin, and β-globulin			
	Creatinine			
	hs-CRP			
	Amylase			

ALP=alkaline phosphatase; ALT=alanine aminotransferase; anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; anti-HCV=hepatitis C virus antibody; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen;GGT=gamma-glutamyltransferase; HbA1c=glycosylated hemoglobin; HBsAg=hepatitis B surface antigen; HCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; hs-CRP=high-sensitivity C-reactive protein; INR=International Normalized Ratio; LDH=lactate dehydrogenase; RBC=red blood cell; WBC=white blood cell

[a] Absolute as well as percentages for the differential leucocyte counts will be performed.

[b] Urine pregnancy test will be performed predose on dosing days and at End-of-Study Visit.

[c] Serum pregnancy test is done at Visit 1 (Screening) and to confirm results of positive urine test if applicable.

Change #53.

Section 12.7.1 Section for Evaluation of PDILI was added.

Change #54.

Section 12.8.3 Body weight

Subject's body weight will be determined at Screening and at the End-of-Study Visit.

Has been changed to:

Section 12.8.3 Body weight and height

Subject's body weight will be determined at Screening and at the End-of-Study Visit. Height will be measured at Screening only.

Change #55.

Section 14.1 Definition of analysis sets

Safety Set (SS):

The SS will consist of all randomized subjects who have received at least 1 infusion (full or partial infusion) of IMP and will be used for the demographics and analysis of safety data.

Has been changed to:

Safety Set (SS):

The SS will consist of all subjects who have received at least 1 infusion (full or partial infusion) of IMP and will be used for the demographics and analysis of safety data.

Change #56.

Section 14.2 General statistical considerations

Paragraph 1, third sentence

Analyses will be performed by dose arm and overall, unless otherwise stated. In the event that the number of infusions in the planned dose arms (3x7mg/kg and 5x4mg/kg) are modified following review by the DMC, the data will be summarized based on the actual dose arms completing the study.

Has been changed to:

Analyses will be performed by dose arm, unless otherwise stated. In the event that the number of infusions in the planned dose arms (3x7mg/kg and 5x4mg/kg) are modified following review by the DMC, the data will be summarized based on the actual dose arms completing the study.

Change #57.

Section 14.3.2 Other safety analyses

Paragraph 1, third sentence

Adverse events will be categorized by intensity (mild/moderate/severe) and severity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 grading.

Has been changed to:

Adverse events will be categorized by severity according to the CTCAE version 4.03 grading. In case the CTCAE grading is not available, the intensity (mild/moderate/severe) will be utilized.

Change #58.

Section 14.3.2 Other safety analyses

Paragraph 2, second sentence

For categorized values according to the reference range, shift tables from Baseline to each post Baseline time point will be presented.

Has been changed to:

For categorized values according to the reference range, shift tables from Baseline to each post Baseline time point will be presented for selected variables to be defined in the SAP.

Change #59.

Section 14.3.2 Other safety analyses

Paragraph 3, last sentence

Descriptive statistics will be presented for ECG value and changes from Baseline over time.

Has been changed to:

Descriptive statistics will be presented for ECG value and changes from Baseline over time based on the mean of the triplicate assessments at each time point.

Change #60.

Section 14.3.2 Other safety analyses

Paragraph 4, last sentence

Measured values and changes from Baseline will be summarized for all subjects by time point.

Has been changed to:

Measured values and changes from Baseline will be summarized by time point.

Change #61.

Section 14.3.2 Other safety analyses

Paragraph 6

Safety analyses will be presented by dose arms and overall.

Has been changed to:

Safety analyses will be presented by dose arm.

Change #62.

Section 14.4.1 Efficacy analyses

Paragraph 6

The results from the ITP bleeding score will be summarized at each time point and will include the scores for each of the three major domains: skin (S), visible mucosae (M), and organs (O) and the overall gradation of severity (SMOG).

Has been changed to:

The results from the ITP bleeding scale will be summarized at each time point and will include the grades for each of the 3 major domains: skin (S), visible mucosae (M), and organs (O).

Change #63.

Section 14.4.2 Pharmacokinetic analyses

Paragraph 2, third sentence

Descriptive statistics of concentrations will be calculated if at least one third of the individual data points are quantifiable (≥LLOQ).

Has been changed to:

Descriptive statistics of concentrations will be calculated if at least two thirds of the individual data points are quantifiable (≥LLOQ).

Change #64.

Section 14.4.3 Pharmacodynamic analyses

Paragraph 2

The PD variables will include ITP-specific autoantibody concentrations [redacted], total IgG, and IgG subclasses. In addition, for total IgG, the maximum change from Baseline will be evaluated and summarized. Figures of mean values over time and changes from Baseline will be presented.

Has been changed to:

The PD variables will include ITP-specific autoantibodies [redacted] total IgG, and IgG subclasses. In addition, for total IgG, the maximum decrease from Baseline and minimum value will be evaluated and summarized. Figures of mean values over time and changes from Baseline will be presented.

Change #65.

Section 14.4.4 Immunologic variables

Paragraphs 1 and 2

All immunologic variables including concentrations of immunoglobulins (IgA, IgE, and IgM) and serum complement parameters (C3, C3a, C4, and C5a) will be summarized by dose arm over time (including changes from Baseline) using descriptive statistics. Figures of mean values over time and changes from Baseline will be presented.

The results and changes from Baseline for the measurement of ADA will be summarized by dose arm; figures will also be presented.

Has been changed to:

All immunologic variables including concentrations of immunoglobulins (IgA, IgE, and IgM), serum (C3 and C4) and plasma (C3a and C5a) complement levels, serum biomarkers [redacted], serum BAFF levels and the results of the IgG depletion assay will be summarized by dose arm over time (including changes from Baseline) using descriptive statistics. Figures of mean values over time and changes from Baseline may be presented.

The ADA status (negative/positive) and changes in relative mass units from Baseline will be summarized by dose arm; figures will also be presented.

Change #66.

Section 14.4.5.1 Subject disposition

The number of subjects who were screened, enrolled into the study, and completed/prematurely discontinued the study, as well as the reason for discontinuation, will be presented using frequency counts and percentages.

Has been changed to:

The number of subjects who were screened, dosed and completed/prematurely discontinued the study, as well as the reason for discontinuation, will be presented using frequency counts and percentages.

Change #67.

Section 14.4.5.3 Baseline disease characteristics

Definition of complement levels were updated as:

- Serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a).

Change #68.

Section 14.7 Planned interim analysis and data monitoring

Paragraph 1

A DMC will be convened to monitor emergent safety and immunogenicity data during the study. The DMC will comprise at least 1 external expert, the UCB study physician, the UCB DS representative, and a biostatistician. Safety related decisions must be made with the agreement of at least the external expert, the UCB study physician, and the UCB DS representative. Decisions involving reductions in dose regimen must also have the agreement of the UCB statistician and UCB pharmacometrician.

Has been changed to:

A DMC will be convened to monitor emergent safety data during the study. The DMC will comprise at least 1 external expert, the UCB study physician, the UCB PS representative, and a biostatistician. Safety related decisions must be made with the agreement of at least the external expert, the UCB study physician, and the UCB PS representative. Decisions involving reductions in dose regimen must also have the agreement of the UCB statistician and UCB pharmacometrician.

Change #69.

Section 14.7 Planned interim analysis and data monitoring

Paragraph 4, last sentence

If the new dose arm will be initiated and if the 5x4mg/kg will be continued, new subjects will be randomized to 1 of the 2 dose arms in an allocation ratio of 1:1 (randomization will stop, once 15 subjects are treated with UCB7665 4mg/kg dose).

Has been changed to:

If the new dose arm will be initiated and if the 5x4mg/kg will be continued, new subjects will be randomized to 1 of the 2 dose arms in an allocation ratio of 1:1 (Once 15 subjects are in the 4mg/kg group, the remaining subjects will not be randomized. They will be allocated to the 7mg/kg group).

Change #70.

Section 14.7 Planned interim analysis and data monitoring

Paragraph 9, second sentence

If needed, subsequent DMC meetings will take place and the frequency will be detailed in the DMC charter.

Has been changed to:

If needed, subsequent DMC meetings may take place and the frequency will be detailed in the DMC charter.

Change #71.

Section 17 REFERENCES

New reference added

Food and Drug Administration. Guidance for Industry. Drug-induced liver injury: premarketing clinical evaluation. US Dept of Health and Human Services, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, 07/2009.

Change #72.

[redacted]

18.8 Protocol Amendment 2 (not implemented)

Rationale for the amendment

The primary purpose of this substantial amendment is to include an additional cohort to explore the PD effect of UCB7665 administered as an sc infusion in subjects with ITP following a more frequent dosing regimen (twice weekly).

During this amendment, additional exploratory genomic (DNA and RNA) analyses have been added as an optional substudy to evaluate the genomic components of ITP to understand the molecular etiology, progression, and treatment of the disease.

UCB considers that the required period for contraceptive use and pregnancy testing can be reduced from 3 months to 2 months after the final dose in female subjects due to nonlinear kinetics of UCB7665. Following single dose administration at the highest dose tested (7mg/kg) no drug was detectable in plasma after 5 days (target mediated disposition). Based on short systemic exposure of UCB7665, genotoxicity being not a class effect of monoclonal antibodies, and extending contraceptive and pregnancy testing by at least 30 days beyond the end of relevant systemic exposure, UCB considers that reducing the required period for contraceptive use and pregnancy testing from 3 months to 2 months after the final dose is still adequate to safeguard the subjects against possible effects of UCB7665 on human pregnancy.

Minor clarifications were added as necessary, and typographical errors or omissions were corrected.

Modifications and changes

Global changes

The following changes were made throughout the protocol:

- Addition of a new dose arm 4mg/kg administered twice per week

- Additional exploratory genomic analyses added as an optional substudy

Specific changes

Change #1

STUDY CONTACT INFORMATION

Sponsor Study Physician

Name:	[redacted], MD
Address:	UCB BIOSCIENCES GmbH Alfred-Nobel-Straße 10 40789 Monheim GERMANY
Phone:	[redacted] [redacted] (mobile)
Fax:	[redacted]

Has been changed to:

Name:	[redacted], MD
Address:	UCB BIOSCIENCES Inc. 8010 Arco Corporation Drive, Suite 175 Raleigh NC 27617, USA
Phone:	[redacted]
Fax:	[redacted]

Change #2

STUDY CONTACT INFORMATION

Clinical Project Manager

Name:	[redacted]
Address:	UCB Biopharma SPRL Allée de la Recherche 60 B-1070 Brussels BELGIUM
Phone:	[redacted]
Fax:	[redacted]

Has been changed to:

Name:	[redacted]
Address:	UCB BioSciences GmbH Alfred-Nobel-Strasse 10 40789 Monheim GERMANY
Phone:	[redacted]
Fax:	[redacted]

Change #2

LIST OF ABBREVIATIONS

ICH	International Conference on Harmonisation

Has been changed to:

ICH	International Council for Harmonisation

Change #3

LIST OF ABBREVIATIONS

The following additions were made to the list of abbreviations:

AUEC	area under the effect curve
DNA	deoxyribonucleic acid
EOS	End of Study
IGRA	interferon-gamma release assay
LTB	latent tuberculosis
mRNA	messenger ribonucleic acid

miRNA	micro ribonucleic acid
PD-PPS	Pharmacodynamic Per Protocol Set
RNA	ribonucleic acid

Change #4

Section 1 SUMMARY

Paragraph #3:

TP0001 is a Phase 2, multicenter, open-label, multiple-dose, 2-dose-arm study to evaluate the safety, tolerability, and efficacy of UCB7665 administered as subcutaneous (sc) doses of 4mg/kg or 7mg/kg, in subjects ≥18 years of age with persistent (>3 months up to 12 months after diagnosis) or chronic (more than 12 months after diagnosis) primary ITP.

Has been changed to:

TP0001 is a Phase 2, multicenter, open-label, multiple-dose, multiple-arm study to evaluate the safety, tolerability, and efficacy of UCB7665 administered as subcutaneous (sc) doses of 4mg/kg or 7mg/kg, in subjects ≥18 years of age with persistent (>3 months up to 12 months after diagnosis) or chronic (more than 12 months after diagnosis) primary ITP.

Change #5

Section 1 SUMMARY

Paragraph #4:

The study is planned to be conducted at approximately 25 sites in Europe and Australia. A total of 30 subjects are planned to enter the Dosing Period in the study. The maximum study duration for study participation for an individual subject is approximately 16 weeks.

Has been changed to:

The study is planned to be conducted at approximately 30 sites in Europe and Australia. A total of 36 subjects are planned to enter the Dosing Period in the study. The maximum study duration for study participation for an individual subject is approximately 16 weeks.

Change #6

Section 1 SUMMARY

Paragraph #5:

The study will evaluate 2 dose arms of UCB7665. Subjects in Dose Arm 1 will receive 5 doses of UCB7665 4mg/kg sc at 1 week intervals and subjects in Dose Arm 2 will receive 3 doses of UCB7665 7mg/kg sc at 1 week intervals.

Has been changed to:

The study is intended to evaluate 3 dose arms of UCB7665. Subjects in Dose Arm 1 will receive 5 doses of UCB7665 4mg/kg sc at 1 week intervals, subjects in Dose Arm 2 will receive 3 doses of UCB7665 7mg/kg sc at 1 week intervals, and subjects in Dose Arm 3 will receive 5 doses of UCB7665 4mg/kg sc at 3 to 4 day intervals (ie, twice per week over approximately 2 weeks).

Change #7

Section 1 SUMMARY

Paragraph #6:

The study consists of a Screening Period (up to 4 weeks), Dosing Period of 2 to 4 weeks, and an Observation Period of 8 weeks. The Screening Visit corresponds to Visit 1 of the study. The Dosing Period will commence at Visit 2 (Baseline Visit), with dosing visits scheduled at weekly intervals. The Observation Period will start after the final dose administration with a visit scheduled 3 days after the final dose and weekly thereafter (ie, weekly after final dose) for a period of 8 weeks. The End-of-Study Visit will be performed at the end of the Observation Period, ie, 8 weeks after the final dose of investigational medicinal product (IMP).

Has been changed to:

The study consists of a Screening Period (up to 4 weeks), Dosing Period of 2 to 4 weeks, and an Observation Period of 8 weeks. The Screening Visit corresponds to Visit 1 of the study. The Dosing Period will commence at Visit 2 (Baseline Visit), with dosing visits scheduled at weekly or twice weekly intervals. The Observation Period will start after the final dose administration with a visit scheduled 3 days after the final dose and weekly thereafter (ie, weekly after final dose) for a period of 8 weeks. The End-of-Study Visit will be performed at the end of the Observation Period, ie, 8 weeks after the final dose of investigational medicinal product (IMP).

Change #8

Section 1 SUMMARY

Paragraph #7:

The first 6 subjects will be enrolled in Dose Arm 1 only. While recruitment is ongoing, safety data for the first 3 subjects up to 7 days after the final dose will be reviewed by a Data Monitoring Committee (DMC). During a second DMC meeting, safety data for the first 6 subjects up to 7 days after the final dose will be reviewed. Following this review, the DMC will make a decision on whether to open Dose Arm 2 for enrollment. Once the DMC has approved initiation of Dose Arm 2, subsequent subjects will be randomized to 1 of the 2 dose arms using an interactive voice/web response system (IXRS). The aim is to have 15 subjects in each dose arm. The DMC may also decide to reduce the number of doses in each of the dose arms based on review of data during the study. Safety data will also be reviewed on an ongoing basis during the study so as to continuously evaluate the safety of subjects.

Has been changed to:

The first 6 subjects will be enrolled in Dose Arm 1 only. While recruitment is ongoing, safety data for the first 3 subjects up to 7 days after the final dose of the third subject will be reviewed by the Data Monitoring Committee (DMC). During a second DMC meeting, all available safety data up to cut off date defined as 7 days after the final dose of the sixth subject will be reviewed. Following this review, the DMC will make a decision on whether to open Dose Arm 2 for enrollment. Once the DMC has approved initiation of Dose Arm 2, the subsequent subjects will be randomly assigned in 1:1 ratio to either Dose Arm 1 or Dose Arm 2 using an interactive voice/web response system (IXRS). Once 15 subjects are enrolled in Dose Arm 1 and safety data review of at least 3 subjects in Dose Arm 2 is done, the subsequent subjects will be randomly

assigned in 1:1 ratio to either Dose Arm 2 or Dose Arm 3 using an IXRS. Once 15 subjects are enrolled in the Dose Arm 2 or 6 subjects are enrolled in Dose Arm 3, the respective dose arm will be closed. The aim is to have 15 subjects in Dose Arms 1 and 2 and 6 subjects in Dose Arm 3. The DMC may also decide to reduce the number of doses in each of the dose arms based on review of data during the study. Safety data will also be reviewed on an ongoing basis during the study so as to continuously evaluate the safety of subjects.

Change #9

Section 1 SUMMARY

Paragraph #13:

The following efficacy variables will be assessed: Response (platelet count $\geq 30x10^9$/L and at least 2-fold increase of the Baseline count) during the study and by visit; Complete Response (platelet count $\geq 100x10^9$/L) during the study and by visit; platelet count $\geq 50x10^9$/L during the study and by visit; the maximum value and maximum increase from Baseline in platelet count during the study; value and change from Baseline in platelet count over time; time to Response (time from starting treatment to achievement of Response); time to Complete Response (time from starting treatment to achievement of Complete Response); time to achieving platelet count $\geq 50x10^9$/L; duration of Response (measured from achievement of Response to loss of Response [defined as platelet count below $30x10^9$/L or less than 2-fold increase of Baseline platelet count]); duration of Complete Response (measured from achievement of Complete Response to loss of Complete Response [defined as platelet count below $100x10^9$/L]); duration of platelet count $\geq 50x10^9$/L (measured from achievement of platelet count $\geq 50x10^9$/L to reduction of platelet count below $50x10^9$/L); ITP bleeding score over time; and Patient Reported Outcome (PRO), ie, Neurological Fatigue Index for Multiple Sclerosis (NFI-MS) summary score over time. Plasma concentration of UCB7665 over time will be assessed as the PK variable. The PD variables are minimum value and maximum decrease in total IgG concentration during the study; IgG subclass concentrations; and ITP-specific autoantibody [redacted] in serum over time. Other immunological variables to be evaluated are total IgA, IgE, and IgM levels; serum (C3 and C4) and plasma (C3a and C5a) complement levels; ADA status (negative/positive) and relative mass units; serum biomarkers [redacted] B cell activating factor (BAFF) levels and the results of the IgG depletion assay; and cytokines (for subjects experiencing infusion reactions). Additional exploratory biomarkers may be investigated if needed using the samples already available.

Has been changed to:

The following efficacy variables will be assessed: Response (platelet count $\geq 30x10^9$/L and at least 2-fold increase of the Baseline count) during the study and by visit; Complete Response (platelet count $\geq 100x10^9$/L) during the study and by visit; platelet count $\geq 50x10^9$/L during the study and by visit; the maximum value and maximum increase from Baseline in platelet count during the study; value and change from Baseline in platelet count over time; Baseline-corrected area under the effect curve (AUEC) for platelet count; time to Response (time from starting treatment to achievement of Response); time to Complete Response (time from starting treatment to achievement of Complete Response); time to achieving platelet count $\geq 50x10^9$/L; duration of Response (measured from achievement of Response to loss of Response [defined as platelet

count below $30x10^9$/L or less than 2-fold increase of Baseline platelet count]); duration of Complete Response (measured from achievement of Complete Response to loss of Complete Response [defined as platelet count below $100x10^9$/L]); duration of platelet count ≥$50x10^9$/L (measured from achievement of platelet count ≥$50x10^9$/L to reduction of platelet count below $50x10^9$/L); Clinical Response (defined as platelet count ≥$30x10^9$/L <$100x10^9$/L with at least 2-fold increase from Baseline value and absence of bleeding); time to Clinical Response (time from starting treatment to achievement of Clinical Response); duration of Clinical Response (measured from achievement of Clinical Response to loss of Clinical Response [loss of Clinical Response defined as platelet count <$30x10^9$/L or less than 2-fold increase from Baseline platelet count or presence of bleeding]); Complete Clinical Response (defined as platelet count ≥$100x10^9$/L and absence of bleeding); time to Complete Clinical Response (time from starting treatment to achievement of Complete Clinical Response); duration of Complete Clinical Response (measured from achievement of Complete Clinical Response to loss of Complete Clinical Response [loss of Complete Clinical Response defined as platelet count <$100x10^9$/L or presence of bleeding]); no Clinical Response (defined as platelet count <$30x10^9$/L and less than 2-fold increase from Baseline or presence of bleeding); ITP bleeding score over time; and Patient Reported Outcome (PRO), ie, Neurological Fatigue Index for Multiple Sclerosis (NFI-MS) summary score over time. Plasma concentration of UCB7665 over time will be assessed as the PK variable. The PD variables are minimum value and maximum decrease in total IgG concentration during the study; IgG subclass concentrations; and ITP-specific autoantibody [redacted] in serum over time. Other immunological variables to be evaluated are total IgA, IgE, and IgM levels; serum (C3 and C4) and plasma (C3a and C5a) complement levels; ADA status (negative/positive) and relative mass units; serum biomarkers [redacted] B cell activating factor (BAFF) levels and the results of the IgG depletion assay; B and T lymphocytes; and cytokines (for subjects experiencing infusion reactions). Additional exploratory biomarkers may be investigated if needed using the samples already available.

Change #10

Section 1 SUMMARY

Paragraph #14:

Exploratory genomic analyses substudy details are added as follows:

During this study, subjects will also have the option of providing additional informed consent for exploratory deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) (ie, messenger RNA [mRNA] and micro RNA [miRNA]) analyses. Participation in this additional portion of the study is optional and does not preclude subject's eligibility for participation in the main study. The additional genomic samples must not be collected if the subject has not consented to participate in this exploratory genomic substudy.

Change #11

Section 1 INTRODUCTION

Paragraph #13:

Exploratory genomic analyses substudy details are added as follows:

Subjects will also have the option of providing additional informed consent for exploratory DNA and RNA (mRNA and miRNA) analyses as described in Section 5.1.1.

Change #12

Section 3.3 Exploratory objectives

NEW bullet:

- To evaluate the genomic components of ITP to understand the molecular etiology, progression, and treatment of the disease, applicable only for subjects consenting to participate in the optional genomic analyses substudy.

Change #13

Section 4.2 Efficacy variables

Additional efficacy variable listed as follows:

- Baseline-corrected AUEC for platelet count
- Clinical Response: platelet count $\geq 30x10^9$/L and $<100x10^9$/L with at least 2-fold increase from Baseline value and absence of bleeding
- Time to Clinical Response: time from starting treatment to achievement of Clinical Response
- Duration of Clinical Response: measured from achievement of Clinical Response to loss of Clinical Response (loss of Clinical Response defined as platelet count $<30x10^9$/L or less than 2-fold increase from Baseline platelet count or presence of bleeding)
- Complete Clinical Response: platelet count $\geq 100x10^9$/L and absence of bleeding
- Time to Complete Clinical Response: time from starting treatment to achievement of Complete Clinical Response
- Duration of Complete Clinical Response: measured from achievement of Complete Clinical Response to loss of Complete Clinical Response (loss of Complete Clinical Response defined as platelet count $<100x10^9$/L or presence of bleeding)
- No Clinical Response: platelet count $<30x10^9$/L and less than 2-fold increase from Baseline or presence of bleeding

Change #14

Section 4.4 Other immunological variables

Additional immunological variable listed as follows:

- Lymphocyte counts (B and T)

Change #15

- Section 5.1 Study description
- Paragraphs #1 and #2:

This is a Phase 2, multicenter, open-label, multiple-dose, 2-dose-arm study to evaluate the safety, tolerability, and efficacy of UCB7665 in subjects with primary persistent or chronic ITP.

Dose Arm 1: UCB7665 4mg/kg sc (5 doses at an interval of 1 week)

Dose Arm 2: UCB7665 7mg/kg sc (3 doses at an interval of 1 week)

The maximum duration of the study per subject is approximately 16 weeks, consisting of a Screening Period (1 to 28 days), a Dosing Period of 2 or 4 weeks, and an Observation Period of 8 weeks.

Has been changed to:

This is a Phase 2, multicenter, open-label, multiple-dose, multiple-arm study to evaluate the safety, tolerability, and efficacy of UCB7665 in subjects with primary persistent or chronic ITP.

Dose Arm 1 (15 subjects): UCB7665 4mg/kg sc (5 doses at an interval of 1 week)

Dose Arm 2 (15 subjects): UCB7665 7mg/kg sc (3 doses at an interval of 1 week)

Dose Arm 3 (6 subjects): UCB7665 4mg/kg sc (5 doses at intervals of 3 to 4 days)

The maximum duration of the study per subject is approximately 16 weeks, consisting of a Screening Period (1 to 28 days), a Dosing Period of 2 to 4 weeks, and an Observation Period of 8 weeks.

Change #16

Section 5.1 Study description

Paragraph #4:

Dosing Period: The first 6 subjects in the study will receive UCB7665 4mg/kg. These subjects in the Dose Arm 1 will not be randomized. While recruitment is still ongoing, safety data for the first 3 subjects up to 7 days after the final dose of the third subject will be reviewed by the DMC. During a second DMC meeting, all available safety data up to cut off date defined as 7 days after the final dose of the sixth subject will be reviewed. During these reviews recruitment in the dose arm will not be stopped. Following this review, the DMC will make a decision on whether to open Dose Arm 2 for enrollment. Once the DMC has approved opening of Dose Arm 2 for enrollment, subjects will subsequently be randomized to 1 of the 2 dose arms using IXRS. If the new dose arm will be initiated and if the UCB7665 4mg/kg arm will be continued, new subjects will be randomized to 1 of the 2 dose arms in an allocation ratio of 1:1 (Once 15 subjects are in the 4mg/kg group, the remaining subjects will not be randomized. They will be allocated to the 7mg/kg group.).

Has been changed to:

Dosing Period: The first 6 subjects in the study will receive UCB7665 4mg/kg. These subjects in the Dose Arm 1 will not be randomized. While recruitment is still ongoing, safety data for the first 3 subjects up to 7 days after the final dose of the third subject in Dose Arm 1 will be

reviewed by the DMC. During a second DMC meeting, all available safety data up to cut off date defined as 7 days after the final dose of the sixth subject in Dose Arm 1 will be reviewed. During these reviews recruitment in the dose arm will not be stopped. Following this review, the DMC will make a decision on whether to open Dose Arm 2 for enrollment. Once DMC has approved initiation of Dose Arm 2, the subsequent subjects will be randomly assigned in 1:1 ratio to either Dose Arm 1 or Dose Arm 2 using an IXRS. Once 15 subjects are enrolled in the Dose Arm 1 and safety data review of at least 3 subjects in Dose Arm 2 is done, the subjects will subsequently be randomly assigned in 1:1 ratio to either Dose Arm 2 or Dose Arm 3 using IXRS. Once 15 subjects are in the Dose Arm 2 or 6 subjects are enrolled in Dose Arm 3, the respective dose arm will be closed.

Change #17

- Section 5.1 Study description

Paragraph #5:

At least 4 interim analyses will be performed. Based on the interim analysis, the DMC will assess the safety of UCB7665, determine whether to initiate the UCB7665 7mg/kg dose arm and may decide to adapt the dose regimen. Planned dosing may be discontinued for all subjects on a dose arm (see Section 6.5). Refer to Section 14.7 for details.

Has been changed to:

At least 4 interim analyses will be performed. Based on the interim analyses, the DMC will assess the safety of UCB7665, determine whether to initiate Dose Arm 2, and may decide to adapt the dose regimen. Planned dosing may be discontinued for all subjects in a dose arm (see Section 6.5). Refer to Section 14.7 for details.

Change #18

- Section 5.1 Study description

Paragraph #6:

In case the DMC recommends reducing the number of doses (infusions) for either the UCB7665 4mg/kg dose or UCB7665 7mg/kg dose based on review of safety data, then the additional dose arms receiving a reduced number of doses will be considered as additional new dose arms for the study.

Has been changed to:

In case the DMC recommends reducing the number of doses (infusions) for any of the predefined dose arms based on review of safety data, then the additional dose arms receiving a reduced number of doses will be considered as additional new dose arms for the study.

Change #19

- NEW Section 5.1.1 Exploratory genomic analyses

During this study, subjects will also have the option of providing additional informed consent for exploratory DNA and RNA analyses. Participation in this additional portion of the study is optional and does not preclude subject's eligibility for participation in the main study. The

additional genomic samples must not be collected if the subject has not consented to participate in this exploratory genomic substudy.

Once subject provides consent, through a separate informed consent form, blood samples will be drawn as follows:

For DNA: Blood samples will be collected at Baseline (Visit 2) for all dose arms. Subsequent blood sample will be collected prior to the last dose (ie, Visit 7 for Dose Arm 1, Visit 5 for Dose Arm 2, and Visit 6 for Dose Arm 3).

For RNA: Blood samples will be collected at following time points for different dose arms:

- Dose Arm 1: Baseline (Visit 2), 3 days after dose 1 (Visit 3), prior to the last dose (Visit 7), and End of Study Visit (Visit 15).
- Dose Arm 2: Baseline (Visit 2), 3 days after dose 1 (Visit 3), prior to the last dose (Visit 5), and End of Study Visit (Visit 13).
- Dose Arm 3: Baseline (Visit 2), prior to second dose (Visit 3), prior to the last dose (Visit 6), and End of Study Visit (Visit 14).

For each DNA blood sample a volume of 6mL whole blood is needed and for each RNA sample a volume of 2.5mL whole blood is needed.

Failure to provide consent to participate in this substudy will not impact subject's eligibility to participate in the main study.

Any exploratory biomarker or genomic analysis will only ever be related to the exploration of the underlying causes of ITP in patients, related biology, and drug response. Justification for additional genomic analyses is detailed in Section 5.4.6.

Details on the collection, storage, preparation, and shipping of samples will be presented in the Laboratory Manual provided separately.

Any results from this analysis will be reported separately and will not form a part of the main clinical study report.

Change #20

Section 5.1.3 Planned number of subjects and sites

A total of 30 subjects are planned to enter the Dosing Period in the study. This number should allow for an appropriate assessment of the safety and give information on efficacy of the treatment for planning of potential future studies. To achieve the required number of eligible subjects to enter the Dosing Period, it is anticipated that 40 subjects will need to be screened. These subjects will be enrolled at approximately 25 sites. First subject first visit is planned for Q1 2016, last subject last visit for Q3 2017.

Has been changed to:

A total of up to 36 subjects are planned to enter the Dosing Periods in the study (15 subjects in each of Dose Arms 1 and 2, and 6 subjects in Dose Arm 3). To achieve the required number of eligible subjects to enter the Dosing Period, it is anticipated that approximately 54 subjects will need to be screened. These subjects will be enrolled at approximately 30 sites. First subject first visit is planned for Q1 2016, last subject last visit for Q4 2017.

Change #21

Section 5.2 Schedule of study assessments

Table 5–1 presents the tabular scheme of study assessments for UCB7665 4mg/kg dose arm and Table 5–2 presents the tabular scheme of study assessments for UCB7665 7mg/kg dose arm. Table 5–3 presents the assessments to be performed on dosing days.

Has been changed to:

Table 5-1 presents the tabular scheme of study assessments for the weekly UCB7665 4mg/kg dose arm (Dose Arm 1), Table 5-2 presents the tabular scheme of study assessments for the weekly UCB7665 7mg/kg dose arm (Dose Arm 2), and Table 5-3 presents the tabular scheme of study assessments for the twice weekly UCB7665 4mg/kg dose arm (Dose Arm 3). Table 5-4 presents the assessments to be performed on dosing days.

Change #22

Section 5.2 Schedule of study assessments

Table 5–1: Schedule of assessments for the UCB7665 4mg/kg dose arm

Assessments		Screening Period	Dosing Period						Observation Period							
			Dose 1		Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a] BL Visit	3	4[a]	5[a]	6[a]	7[a]	8	9	10[b]	11	12[b]	13	14[b]	15 EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	22	29	32	36	43	50	57	64	71	85
	Week		1	1	2	3	4	5	5	6	7	8	9	10	11	13
	Visit Window			±1d	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Written informed consent		X														
Demographic data		X														
Verification of inclusion/exclusion criteria		X	X													
Platelets for inclusion/ withdrawal check (local laboratory)[f]			X		X	X	X	X								
Randomization[g]			X													
Withdrawal criteria[h]			X	X	X	X	X	X								
General medical/procedures history		X														
ITP history		X														

Table 5–1: Schedule of assessments for the UCB7665 4mg/kg dose arm

Assessments		Screening Period	Dosing Period						Observation Period							
			Dose 1		Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a]	3	4[a]	5[a]	6[a]	7[a]	8	9	10[b]	11	12[b]	13	14[b]	15
			BL Visit													EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	22	29	32	36	43	50	57	64	71	85
	Week		1	1	2	3	4	5	5	6	7	8	9	10	11	13
	Visit Window			±1d	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Prior and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medical procedures			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight		X														X
Height		X														
Recording of AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[i]		X	X		X	X	X	X		X		X		X		X
12-lead ECG		X	X		X	X	X	X		X						X
Karnofsky Performance Status		X														
Laboratory parameters (hematology, chemistry, urinalysis)		X[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 5–1: Schedule of assessments for the UCB7665 4mg/kg dose arm

Assessments		Screening Period	Dosing Period						Observation Period							
			Dose 1		Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a]	3	4[a]	5[a]	6[a]	7[a]	8	9	10[b]	11	12[b]	13	14[b]	15
			BL Visit													EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	22	29	32	36	43	50	57	64	71	85
	Week		1	1	2	3	4	5	5	6	7	8	9	10	11	13
	Visit Window			±1d	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Serology test for HIV, hepatitis B, and hepatitis C		X														
Blood sample for cytokines			X	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]
Serum pregnancy test		X														
Urine pregnancy test			X		X	X	X	X								X
Call to IXRS for treatment kit number			X		X	X	X	X								
Administration of IMP			X		X	X	X	X								
Blood sampling for plasma concentration of UCB7665			X	X	X	X	X	X	X	X						
Anti-UCB7665 antibodies/IgG depletion assay			X	X	X	X	X	X	X	X	X		X		X	X

Table 5–1: Schedule of assessments for the UCB7665 4mg/kg dose arm

Assessments		Screening Period	Dosing Period						Observation Period							
			Dose 1		Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a]	3	4[a]	5[a]	6[a]	7[a]	8	9	10[b]	11	12[b]	13	14[b]	15
			BL Visit													EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	22	29	32	36	43	50	57	64	71	85
	Week		1	1	2	3	4	5	5	6	7	8	9	10	11	13
	Visit Window			±1d	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Serum complements (C3 and C4) and plasma complements (C3a and C5a)			X			X			X				X			
Serum biomarkers [redacted]			X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum biomarkers [redacted]			X	X	X	X	X	X								
Serum BAFF levels			X		X	X	X	X			X				X	
Immunoglobulins (total IgG, IgG subclasses)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IgA, IgM, IgE[l]			X					X		X					X	
ITP-specific autoantibodies[m]			X							X						X
ITP bleeding scale		X	X		X	X	X	X		X		X		X		X
NFI-MS			X							X		X		X		X

Table 5–1: Schedule of assessments for the UCB7665 4mg/kg dose arm

Assessments		Screening Period	Dosing Period						Observation Period							
			Dose 1		Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a]	3	4[a]	5[a]	6[a]	7[a]	8	9	10[b]	11	12[b]	13	14[b]	15
			BL Visit													EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	22	29	32	36	43	50	57	64	71	85
	Week		1	1	2	3	4	5	5	6	7	8	9	10	11	13
	Visit Window			±1d	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Headache questionnaire[n]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject exit interview[o]																X

AE=adverse event; BAFF=B cell activating factor; BL=Baseline; CSF=cerebrospinal fluid; CT=computed tomography; d=day(s); DMC=Data Monitoring Committee; ECG=electrocardiogram; EOS=End of Study; EW=Early Withdrawal; [redacted] HIV=human immunodeficiency virus; Ig=immunoglobulin; IMP=investigational medicinal product; ITP=immune thrombocytopenia; IXRS= interactive voice/web response system; LP=lumbar puncture; MRI=magnetic resonance imaging; NFI-MS=Neurological Fatigue Index for multiple sclerosis; [redacted]

[a] Frequency of assessments on dosing days is detailed in Table 5-3.
[b] Visits 10, 12, and 14 can be performed at home with a healthcare professional visiting the subject at his/her home.
[c] The End-of-Study Visit is 8 weeks following the final dose.
[d] A visit window of ±2 days is allowed for the dosing visits. The visit window of ±2 days is relative to the first dosing visit date. However, there should be a minimum interval of 5 days and maximum interval of 9 days as compared to the previous dose.
[e] The visit windows in the Observation Period are relative to the final dosing visit date.
[f] Prior to dosing at Visit 2, 2 platelet samples will be taken. One sample will be analyzed locally and the value will be used to check inclusion criteria. The other platelet sample will be sent to the central laboratory. At subsequent dosing visits, a platelet sample will be assessed locally prior to dosing to evaluate withdrawal criterion of platelet count >350x10^9/L.
[g] The first 6 subjects will be enrolled in the Dose Arm 1 group only. Safety data for these 6 subjects up to 7 days after the last dose will be reviewed by the DMC. Following this review the DMC will make a decision to open Dose Arm 2 for enrollment. If Dose Arm 2 is opened, subjects subsequently enrolled will be randomly assigned subsequently to 1 of the 2 dose arms using an IXRS until 15 subjects are in Dose Arm 1.
[h] Subjects can withdraw at any time during the study, based on the criteria in Section 6.4.
[i] A complete physical examination will be performed at Screening and EOS/EW Visit. At all other visits (where physical examination is performed), an abbreviated physical examination will be conducted.

[j] At the Screening Visit, 2 separate blood samples will be obtained on the same day for evaluation of platelet count.
[k] Blood sample for cytokines will be obtained only in case of infusion reactions.
[l] In case the number of infusions to be administered are reduced after DMC review of safety data, then the scheduled Visit 7 assessment for IgA, IgM, and IgE will be performed earlier at the last dosing visit.
[m] [redacted]
[n] This assessment is applicable only to subjects experiencing severe headaches and will be performed daily until resolution (ie, if headache becomes moderate or mild, normal collection of AEs should apply); this assessment will be followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.
[o] A semi-structured interview guide will be used and the interview will be recorded. In case of early withdrawal from the study, the subject exit interview should be performed at End-of-Study Visit only.

Has been changed to:

Table 5–1: Schedule of assessments for the UCB7665 4mg/kg weekly dose arm (Dose Arm 1)

Assessments		**Screening Period**	**Dosing Period**						**Observation Period**							
			Dose 1		**Dose 2**	**Dose 3**	**Dose 4**	**Dose 5**								
	Visit	**1**	**2**[a]	**3**	**4**[a]	**5**[a]	**6**[a]	**7**[a]	**8**	**9**	**10**[b]	**11**	**12**[b]	**13**	**14**[b]	**15**
			BL Visit													**EOS/ EW**[c]
	Day	**-28 to -1**	**1**	**4**	**8**	**15**	**22**	**29**	**32**	**36**	**43**	**50**	**57**	**64**	**71**	**85**
	Week		**1**	**1**	**2**	**3**	**4**	**5**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**13**
	Visit Window			**±1d**	**±2d**[d]	**±2d**[d]	**±2d**[d]	**±2d**[d]	**±1d**	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]
Written informed consent[f]		X														
Demographic data		X														
Verification of inclusion/exclusion criteria		X	X													
Platelets for inclusion/ withdrawal check (local laboratory)[g]			X		X	X	X	X								

Table 5–1: Schedule of assessments for the UCB7665 4mg/kg weekly dose arm (Dose Arm 1)

Assessments		Screening Period	Dosing Period						Observation Period							
			Dose 1		Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a]	3	4[a]	5[a]	6[a]	7[a]	8	9	10[b]	11	12[b]	13	14[b]	15
			BL Visit													EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	22	29	32	36	43	50	57	64	71	85
	Week		1	1	2	3	4	5	5	6	7	8	9	10	11	13
	Visit Window			±1d	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Randomization[h]			X													
Withdrawal criteria[i]			X	X	X	X	X	X								
General medical/procedures history		X														
ITP history		X														
Prior and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medical procedures			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight		X														X
Height		X														
Recording of AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[j]		X	X		X	X	X	X		X		X		X		X
12-lead ECG[k]		X	X		X	X	X	X		X						X

Table 5–1: Schedule of assessments for the UCB7665 4mg/kg weekly dose arm (Dose Arm 1)

Assessments		Screening Period	Dosing Period						Observation Period							
			Dose 1		Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	**1**	**2**[a]	**3**	**4**[a]	**5**[a]	**6**[a]	**7**[a]	**8**	**9**	**10**[b]	**11**	**12**[b]	**13**	**14**[b]	**15**
			BL Visit													**EOS/ EW**[c]
	Day	**-28 to -1**	**1**	**4**	**8**	**15**	**22**	**29**	**32**	**36**	**43**	**50**	**57**	**64**	**71**	**85**
	Week		**1**	**1**	**2**	**3**	**4**	**5**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**13**
	Visit Window			**±1d**	**±2d**[d]	**±2d**[d]	**±2d**[d]	**±2d**[d]	**±1d**	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]
Karnofsky Performance Status		X														
Laboratory parameters (hematology, chemistry, urinalysis)		X[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serology test for HIV, hepatitis B, and hepatitis C		X														
Blood sample for cytokines			X	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]
Whole blood sample for DNA (optional)			X					X								
Whole blood sample for RNA (optional)			X	X				X								X
Serum pregnancy test		X														
Urine pregnancy test			X		X	X	X	X								X
Call to IXRS for treatment kit number			X		X	X	X	X								

Table 5–1: Schedule of assessments for the UCB7665 4mg/kg weekly dose arm (Dose Arm 1)

Assessments		Screening Period	Dosing Period						Observation Period							
			Dose 1		Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a] BL Visit	3	4[a]	5[a]	6[a]	7[a]	8	9	10[b]	11	12[b]	13	14[b]	15 EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	22	29	32	36	43	50	57	64	71	85
	Week		1	1	2	3	4	5	5	6	7	8	9	10	11	13
	Visit Window			±1d	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Administration of IMP			X		X	X	X	X								
Blood sampling for plasma concentration of UCB7665			X	X	X	X	X	X	X	X						
Anti-UCB7665 antibodies/IgG depletion assay			X	X	X	X	X	X	X	X	X		X		X	X
Serum complements (C3 and C4) and plasma complements (C3a and C5a)			X			X			X				X			
Serum biomarkers [redacted]			X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum biomarkers [redacted]			X	X	X	X	X	X								
Serum BAFF levels			X		X	X	X	X			X				X	

Table 5–1: Schedule of assessments for the UCB7665 4mg/kg weekly dose arm (Dose Arm 1)

Assessments		Screening Period	Dosing Period						Observation Period							
			Dose 1		Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a]	3	4[a]	5[a]	6[a]	7[a]	8	9	10[b]	11	12[b]	13	14[b]	15
			BL Visit													EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	22	29	32	36	43	50	57	64	71	85
	Week		1	1	2	3	4	5	5	6	7	8	9	10	11	13
	Visit Window			±1d	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Immunoglobulins (total IgG, IgG subclasses)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IgA, IgM, IgE[n]			X					X		X					X	
ITP-specific autoantibodies[o]			X							X						X
ITP bleeding scale		X	X		X	X	X	X		X		X		X		X
NFI-MS			X							X		X		X		X
Headache questionnaire[p]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject exit interview[q]																X

AE=adverse event; BAFF=B cell activating factor; BL=Baseline; CSF=cerebrospinal fluid; CT=computed tomography; d=day(s); DMC=Data Monitoring; DNA=deoxyribonucleic acid; Committee; ECG=electrocardiogram; EOS=End of Study; EW=Early Withdrawal; [redacted] HIV=human immunodeficiency virus; Ig=immunoglobulin; IMP=investigational medicinal product; ITP=immune thrombocytopenia; IXRS= interactive voice/web response system; LP=lumbar puncture; RNA=ribonucleic acid; MRI=magnetic resonance imaging; NFI-MS=Neurological Fatigue Index for multiple sclerosis; [redacted]

[a] Frequency of assessments on dosing days is detailed in Table 5-4.
[b] Visits 10, 12, and 14 can be performed at home with a healthcare professional visiting the subject at his/her home.
[c] The End-of-Study Visit is 8 weeks following the final dose.
[d] A visit window of ±2 days is allowed for the dosing visits. The visit window of ±2 days is relative to the first dosing visit date. However, there should be a minimum interval of 5 days and maximum interval of 9 days as compared to the previous dose.

[e] The visit windows in the Observation Period are relative to the final dosing visit date.
[f] Additional informed consent is needed for participation in the exploratory genomic substudy. All samples will be collected prior to dosing with IMP.
[g] Prior to dosing at Visit 2, 2 platelet samples will be taken. One sample will be analyzed locally and the value will be used to check inclusion criteria. The other platelet sample will be sent to the central laboratory. At subsequent dosing visits, a platelet sample will be assessed locally prior to dosing to evaluate withdrawal criterion of platelet count >350x10^9/L.
[h] The first 6 subjects will be enrolled in the Dose Arm 1 group only. Safety data for these 6 subjects up to 7 days after the last dose will be reviewed by the DMC. Following this review the DMC will make a decision to open Dose Arm 2 for enrollment. If Dose Arm 2 is opened, the subsequent subjects will be randomly assigned in 1:1 ratio to either Dose Arm 1 or Dose Arm 2 using an IXRS. Once 15 subjects are enrolled in Dose Arm 1 and safety data review of at least 3 subjects in Dose Arm 2 is done, the subsequent subjects will be randomly assigned in 1:1 ratio to either Dose Arm 2 or Dose Arm 3 using an IXRS. Once 15 subjects are in Dose Arm 2 or 6 subjects are enrolled in Dose Arm 3, the respective dose arm will be closed.
[i] Subjects can withdraw at any time during the study, based on the criteria in Section 6.4.
[j] A complete physical examination will be performed at Screening and EOS/EW Visit. At all other visits (where physical examination is performed), an abbreviated physical examination will be conducted.
[k] The ECG should be performed in triplicate prior to blood collection for assessment of laboratory parameters. Three ECGs should be recorded in a time frame of 5 minutes with at least 1 minute difference, 1-2 minutes between the ECGs.
[l] At the Screening Visit, 2 separate blood samples will be obtained on the same day for evaluation of platelet count.
[m] Blood sample for cytokines will be obtained only in case of infusion reactions.
[n] In case the number of infusions to be administered are reduced after DMC review of safety data, then the scheduled Visit 7 assessment for IgA, IgM, and IgE will be performed earlier at the last dosing visit.
[o] [redacted]
[p] This assessment is applicable only to subjects experiencing severe headaches and will be performed daily until resolution (ie, if headache becomes moderate or mild, normal collection of AEs should apply); this assessment will be followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.
[q] A semi-structured interview guide will be used and the interview will be recorded. In case of early withdrawal from the study, the subject exit interview should be performed at End-of-Study Visit only.

Change #23

Section 5.2 Schedule of study assessments

Table 5–2: Schedule of assessments for the UCB7665 7mg/kg dose arm

Assessments		Screening Period	Dosing Period				Observation Period							
			Dose 1		Dose 2	Dose 3								
	Visit	**1**	**2[a]**	**3**	**4[a]**	**5[a]**	**6**	**7**	**8[b]**	**9**	**10[b]**	**11**	**12[b]**	**13**
			BL Visit											**EOS/ EW[c]**
	Day	**-28 to -1**	**1**	**4**	**8**	**15**	**18**	**22**	**29**	**36**	**43**	**50**	**57**	**71**
	Week		**1**	**1**	**2**	**3**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**11**
	Visit Window			**±1d**	**±2d[d]**	**±2d[d]**	**±1d**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**
Written informed consent		X												
Demographic data		X												
Verification of inclusion/exclusion criteria		X	X											
Platelets for inclusion/withdrawal check (local laboratory) [f]			X		X	X								
Randomization[g]			X											
Withdrawal criteria[h]			X	X	X	X								
General medical/procedures history		X												
ITP history		X												
Prior and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medical procedures			X	X	X	X	X	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X

Table 5–2: Schedule of assessments for the UCB7665 7mg/kg dose arm

Assessments		Screening Period	Dosing Period				Observation Period							
			Dose 1		Dose 2	Dose 3								
	Visit	**1**	**2[a]**	**3**	**4[a]**	**5[a]**	**6**	**7**	**8[b]**	**9**	**10[b]**	**11**	**12[b]**	**13**
			BL Visit											**EOS/ EW[c]**
	Day	**-28 to -1**	**1**	**4**	**8**	**15**	**18**	**22**	**29**	**36**	**43**	**50**	**57**	**71**
	Week		**1**	**1**	**2**	**3**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**11**
	Visit Window			**±1d**	**±2d[d]**	**±2d[d]**	**±1d**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**
Body weight		X												X
Height		X												
Recording of AEs		X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[i]		X	X		X	X		X		X		X		X
12-lead ECG		X	X		X	X		X						X
Karnofsky Performance Status		X												
Laboratory parameters (hematology, chemistry, urinalysis)		X[j]	X	X	X	X	X	X	X	X	X	X	X	X
Serology test for HIV, hepatitis B, and hepatitis C		X												
Blood sample for cytokines			X	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]
Serum pregnancy test		X												
Urine pregnancy test			X		X	X								X
Call to IXRS for treatment kit number			X		X	X								
Administration of IMP			X		X	X								

Table 5–2: Schedule of assessments for the UCB7665 7mg/kg dose arm

Assessments		Screening Period	Dosing Period				Observation Period							
			Dose 1		Dose 2	Dose 3								
	Visit	**1**	**2[a]**	**3**	**4[a]**	**5[a]**	**6**	**7**	**8[b]**	**9**	**10[b]**	**11**	**12[b]**	**13**
			BL Visit											**EOS/ EW[c]**
	Day	**-28 to -1**	**1**	**4**	**8**	**15**	**18**	**22**	**29**	**36**	**43**	**50**	**57**	**71**
	Week		**1**	**1**	**2**	**3**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**11**
	Visit Window			**±1d**	**±2d[d]**	**±2d[d]**	**±1d**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**
Blood sampling for plasma concentration of UCB7665			X	X	X	X	X	X						
Anti-UCB7665 antibodies/IgG depletion assay			X	X	X	X	X	X	X		X		X	X
Serum complements (C3 and C4) and plasma complements (C3a and C5a)			X			X	X				X			
Serum biomarkers [redacted]			X	X	X	X	X	X	X	X	X	X	X	
Serum biomarkers [redacted]			X	X	X	X								
Serum BAFF levels			X		X	X			X				X	
Immunoglobulins (total IgG, IgG subclasses)		X	X	X	X	X	X	X	X	X	X	X	X	X
IgA, IgM, IgE[l]			X			X		X					X	
ITP-specific autoantibodies[m]			X					X						X
ITP bleeding scale		X	X		X	X		X		X		X		X
NFI-MS			X					X		X		X		X

Table 5–2: Schedule of assessments for the UCB7665 7mg/kg dose arm

Assessments		Screening Period	Dosing Period				Observation Period							
			Dose 1		Dose 2	Dose 3								
	Visit	1	2[a]	3	4[a]	5[a]	6	7	8[b]	9	10[b]	11	12[b]	13
			BL Visit											EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	18	22	29	36	43	50	57	71
	Week		1	1	2	3	3	4	5	6	7	8	9	11
	Visit Window			±1d	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Headache questionnaire[n]			X	X	X	X	X	X	X	X	X	X	X	X
Subject exit interview[o]														X

AE=adverse event; BAFF=B cell activating factor; BL=baseline; CSF=cerebrospinal fluid CT=computed tomography; d=day(s); DMC=Data Monitoring Committee; ECG=electrocardiogram; EOS=End of Study; EW=Early Withdrawal; [redacted] HIV=human immunodeficiency virus; Ig=immunoglobulin; IMP=investigational medicinal product; ITP=immune thrombocytopenia; IXRS= interactive voice/web response system; LP=lumbar puncture; MRI=magnetic resonance imaging; NFI-MS=Neurological Fatigue Index for multiple sclerosis; [redacted]

[a] Frequency of assessments on dosing days is detailed in Table 5-3.
[b] Visits 8, 10, and 12 can be performed at home with a healthcare professional visiting the subject at his/her home.
[c] The End-of-Study Visit is 8 weeks following the final dose.
[d] A visit window of ±2 days is allowed for the dosing visits. The visit window of ±2 days is relative to the first dosing visit date. However, there should be a minimum interval of 5 days and maximum interval of 9 days as compared to the previous dose.
[e] The visit windows in the Observation Period are relative to the final dosing visit date.
[f] Prior to dosing at Visit 2, 2 platelet samples will be taken. One sample will be analyzed locally and the value will be used to check inclusion criteria. The other platelet sample will be sent to the central laboratory. At subsequent dosing visits, a platelet sample will be assessed locally prior to dosing to evaluate withdrawal criterion of platelet count >350x10^9/L.
[g] The first 6 subjects will be enrolled in the Dose Arm 1 group. Safety data for these 6 subjects up to 7 days after the last dose will be reviewed by the DMC. Following this review the DMC will make a decision to open Dose Arm 2 for enrollment. If Dose Arm 2 is opened, subjects subsequently enrolled will be randomly assigned to one of the dose arms using an IXRS until 15 subjects are in Dose Arm 1.
[h] Subjects can withdraw at any time during the study, based on the criteria in Section 6.4.
[i] A complete physical examination will be performed at Screening and EOS/EW Visit. At all other visits (where physical examination is performed), an abbreviated physical examination will be conducted.
[j] At the Screening Visit, 2 separate blood samples will be obtained on the same day for evaluation of platelet count.

[k] Blood sample for cytokines will be obtained only in case of infusion reactions.
[l] In case the number of infusions to be administered are reduced after DMC review of safety data, then the scheduled Visit 5 assessment for IgA, IgM, and IgE will be performed earlier at the last dosing visit.
[m] [redacted]
[n] This assessment is applicable only to subjects experiencing severe headaches and will be performed daily until resolution (ie, if headache becomes moderate or mild, normal collection of AEs should apply); this assessment will be followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.
[o] A semi-structured interview guide will be used and the interview will be recorded. In case of early withdrawal from the study, the subject exit interview should be performed at End-of-Study Visit only.

Has been changed to:

Table 5–2: Schedule of assessments for the UCB7665 7mg/kg weekly dose arm (Dose Arm 2)

Assessments		**Screening Period**	**Dosing Period**				**Observation Period**							
			Dose 1		**Dose 2**	**Dose 3**								
	Visit	**1**	**2[a]**	**3**	**4[a]**	**5[a]**	**6**	**7**	**8[b]**	**9**	**10[b]**	**11**	**12[b]**	**13**
			BL Visit											**EOS/ EW[c]**
	Day	**-28 to -1**	**1**	**4**	**8**	**15**	**18**	**22**	**29**	**36**	**43**	**50**	**57**	**71**
	Week		**1**	**1**	**2**	**3**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**11**
	Visit Window			**±1d**	**±2d[d]**	**±2d[d]**	**±1d**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**
Written informed consent[f]		X												
Demographic data		X												
Verification of inclusion/exclusion criteria		X	X											
Platelets for inclusion/withdrawal check (local laboratory) [g]			X		X	X								
Randomization[h]			X											

Table 5–2: Schedule of assessments for the UCB7665 7mg/kg weekly dose arm (Dose Arm 2)

Assessments		Screening Period	Dosing Period				Observation Period							
			Dose 1		Dose 2	Dose 3								
	Visit	**1**	**2**[a]	**3**	**4**[a]	**5**[a]	**6**	**7**	**8**[b]	**9**	**10**[b]	**11**	**12**[b]	**13**
			BL Visit											**EOS/ EW**[c]
	Day	**-28 to -1**	**1**	**4**	**8**	**15**	**18**	**22**	**29**	**36**	**43**	**50**	**57**	**71**
	Week		**1**	**1**	**2**	**3**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**11**
	Visit Window			**±1d**	**±2d**[d]	**±2d**[d]	**±1d**	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]
Withdrawal criteria[i]			X	X	X	X								
General medical/procedures history		X												
ITP history		X												
Prior and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medical procedures			X	X	X	X	X	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight		X												X
Height		X												
Recording of AEs		X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[j]		X	X		X	X		X		X		X		X
12-lead ECG[k]		X	X		X	X		X						X
Karnofsky Performance Status		X												
Laboratory parameters (hematology, chemistry, urinalysis)		X[l]	X	X	X	X	X	X	X	X	X	X	X	X
Serology test for HIV, hepatitis B, and hepatitis C		X												

Table 5–2: Schedule of assessments for the UCB7665 7mg/kg weekly dose arm (Dose Arm 2)

Assessments		Screening Period	Dosing Period				Observation Period							
			Dose 1		Dose 2	Dose 3								
	Visit	**1**	**2[a]**	**3**	**4[a]**	**5[a]**	**6**	**7**	**8[b]**	**9**	**10[b]**	**11**	**12[b]**	**13**
			BL Visit											**EOS/ EW[c]**
	Day	**-28 to -1**	**1**	**4**	**8**	**15**	**18**	**22**	**29**	**36**	**43**	**50**	**57**	**71**
	Week		**1**	**1**	**2**	**3**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**11**
	Visit Window			**±1d**	**±2d[d]**	**±2d[d]**	**±1d**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**
Blood sample for cytokines			X	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]
Whole blood sample for DNA (optional)			X			X								
Whole blood sample for RNA (optional)			X	X		X								X
Serum pregnancy test		X												
Urine pregnancy test			X		X	X								X
Call to IXRS for treatment kit number			X		X	X								
Administration of IMP			X		X	X								
Blood sampling for plasma concentration of UCB7665			X	X	X	X	X	X						
Anti-UCB7665 antibodies/IgG depletion assay			X	X	X	X	X	X	X		X		X	X
Serum complements (C3 and C4) and plasma complements (C3a and C5a)			X			X	X				X			
Serum biomarkers [redacted]			X	X	X	X	X	X	X	X	X	X	X	

Table 5–2: Schedule of assessments for the UCB7665 7mg/kg weekly dose arm (Dose Arm 2)

Assessments		Screening Period	Dosing Period				Observation Period							
			Dose 1		Dose 2	Dose 3								
	Visit	1	2[a] BL Visit	3	4[a]	5[a]	6	7	8[b]	9	10[b]	11	12[b]	13 EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	18	22	29	36	43	50	57	71
	Week		1	1	2	3	3	4	5	6	7	8	9	11
	Visit Window			±1d	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Serum biomarkers [redacted]			X	X	X	X								
Serum BAFF levels			X		X	X			X				X	
Immunoglobulins (total IgG, IgG subclasses)		X	X	X	X	X	X	X	X	X	X	X	X	X
IgA, IgM, IgE[n]			X			X		X					X	
ITP-specific autoantibodies[o]			X					X						X
ITP bleeding scale		X	X		X	X		X		X		X		X
NFI-MS			X					X		X		X		X
Headache questionnaire[p]			X	X	X	X	X	X	X	X	X	X	X	X
Subject exit interview[q]														X

AE=adverse event; BAFF=B cell activating factor; BL=Baseline; CSF=cerebrospinal fluid; CT=computed tomography; d=day(s); DMC=Data Monitoring Committee; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EOS=End of Study; EW=Early Withdrawal; [redacted] HIV=human immunodeficiency virus; Ig=immunoglobulin; IMP=investigational medicinal product; ITP=immune thrombocytopenia; IXRS= interactive voice/web response system; LP=lumbar puncture; RNA=ribonucleic acid; MRI=magnetic resonance imaging; NFI-MS=Neurological Fatigue Index for multiple sclerosis; [redacted]

[a] Frequency of assessments on dosing days is detailed in Table 5-4.
[b] Visits 8, 10, and 12 can be performed at home with a healthcare professional visiting the subject at his/her home.
[c] The End-of-Study Visit is 8 weeks following the final dose.

[d] A visit window of ±2 days is allowed for the dosing visits. The visit window of ±2 days is relative to the first dosing visit date. However, there should be a minimum interval of 5 days and maximum interval of 9 days as compared to the previous dose.
[e] The visit windows in the Observation Period are relative to the final dosing visit date.
[f] Additional informed consent is needed for participation in the exploratory genomic substudy. All samples will be collected prior to dosing with IMP.
[g] Prior to dosing at Visit 2, 2 platelet samples will be taken. One sample will be analyzed locally and the value will be used to check inclusion criteria. The other platelet sample will be sent to the central laboratory. At subsequent dosing visits, a platelet sample will be assessed locally prior to dosing to evaluate withdrawal criterion of platelet count >$350x10^9$/L.
[h] The first 6 subjects will be enrolled in the Dose Arm 1 group. Safety data for these 6 subjects up to 7 days after the last dose will be reviewed by the DMC. Following this review the DMC will make a decision to open Dose Arm 2 for enrollment. If Dose Arm 2 is opened, the subsequent subjects will be randomly assigned in 1:1 ratio to either Dose Arm 1 or Dose Arm 2 using an IXRS. Once 15 subjects are enrolled in Dose Arm 1 and safety data review of at least 3 subjects in Dose Arm 2 is done, the subsequent subjects will be randomly assigned in 1:1 ratio to either Dose Arm 2 or Dose Arm 3 using an IXRS. Once 15 subjects are in Dose Arm 2 or 6 subjects are enrolled in Dose Arm 3, the respective dose arm will be closed.
[i] Subjects can withdraw at any time during the study, based on the criteria in Section 6.4.
[j] A complete physical examination will be performed at Screening and EOS/EW Visit. At all other visits (where physical examination is performed), an abbreviated physical examination will be conducted.
[k] The ECG should be performed in triplicate prior to blood collection for assessment of laboratory parameters. Three ECGs should be recorded in a time frame of 5 minutes with at least 1 minute difference, 1-2 minutes between the ECGs.
[l] At the Screening Visit, 2 separate blood samples will be obtained on the same day for evaluation of platelet count.
[m] Blood sample for cytokines will be obtained only in case of infusion reactions.
[n] In case the number of infusions to be administered are reduced after DMC review of safety data, then the scheduled Visit 5 assessment for IgA, IgM, and IgE will be performed earlier at the last dosing visit.
[o] [redacted]
[p] This assessment is applicable only to subjects experiencing severe headaches and will be performed daily until resolution (ie, if headache becomes moderate or mild, normal collection of AEs should apply); this assessment will be followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.
[q] A semi-structured interview guide will be used and the interview will be recorded. In case of early withdrawal from the study, the subject exit interview should be performed at End-of-Study Visit only.

Change #24

Section 5.2 Schedule of study assessments

NEW table:

Table 5-3: Schedule of assessments for the UCB7665 4mg/kg twice weekly dose arm (Dose Arm 3)

Assessments		Screening Period	Dosing Period					Observation Period							
			Dose 1	Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	**1**	**2**[a]	**3**[a]	**4**[a]	**5**[a]	**6**[a]	**7**	**8**	**9**[b]	**10**	**11**[b]	**12**	**13**[b]	**14**
			BL Visit												**EOS/EW**[c]
	Day	**-28 to -1**	**1**	**4**	**8**	**11**	**15**	**18**	**22**	**29**	**36**	**43**	**50**	**57**	**71**
	Week		**1**	**1**	**2**	**2**	**3**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**11**
	Visit Window			**+1d**[d]	**+1d**[d]	**+1d**[d]	**+1d**[d]	**±1d**	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]
Written informed consent[f]		X													
Demographic data		X													
Verification of inclusion/exclusion criteria		X	X												
Platelets for inclusion/ withdrawal check (local laboratory)[g]			X	X	X	X	X								
Randomization[h]			X												
Withdrawal criteria[i]			X	X	X	X	X								
General medical/procedures history		X													

Table 5-3: Schedule of assessments for the UCB7665 4mg/kg twice weekly dose arm (Dose Arm 3)

Assessments		Screening Period	Dosing Period					Observation Period							
			Dose 1	Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a] BL Visit	3[a]	4[a]	5[a]	6[a]	7	8	9[b]	10	11[b]	12	13[b]	14 EOS/EW[c]
	Day	-28 to -1	1	4	8	11	15	18	22	29	36	43	50	57	71
	Week		1	1	2	2	3	3	4	5	6	7	8	9	11
	Visit Window			+1d[d]	+1d[d]	+1d[d]	+1d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
ITP history		X													
Prior and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medical procedures			X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight		X													X
Height		X													
Recording of AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[j]		X	X	X	X	X	X		X		X		X		X
12-lead ECG[k]		X	X	X	X	X	X		X						X
Karnofsky Performance Status		X													
Laboratory parameters (hematology, chemistry, urinalysis)		X[l]	X	X	X	X	X	X	X	X	X	X	X	X	X
Serology test for HIV,		X													

Table 5-3: Schedule of assessments for the UCB7665 4mg/kg twice weekly dose arm (Dose Arm 3)

Assessments		Screening Period	Dosing Period					Observation Period							
			Dose 1	Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	**1**	**2**[a]	**3**[a]	**4**[a]	**5**[a]	**6**[a]	**7**	**8**	**9**[b]	**10**	**11**[b]	**12**	**13**[b]	**14**
			BL Visit												**EOS/EW**[c]
	Day	**-28 to -1**	**1**	**4**	**8**	**11**	**15**	**18**	**22**	**29**	**36**	**43**	**50**	**57**	**71**
	Week		**1**	**1**	**2**	**2**	**3**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**11**
	Visit Window			**+1d**[d]	**+1d**[d]	**+1d**[d]	**+1d**[d]	**±1d**	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]
hepatitis B, and hepatitis C															
Blood sample for cytokines			X	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]
Whole blood sample for DNA (optional)			X				X								
Whole blood sample for RNA (optional)			X	X			X								X
Serum pregnancy test		X													
Urine pregnancy test			X	X	X	X	X								X
Call to IXRS for treatment kit number			X	X	X	X	X								
Administration of IMP			X	X	X	X	X								
Blood sampling for plasma concentration of UCB7665			X	X	X	X	X	X	X						
Anti-UCB7665 antibodies/IgG depletion assay			X	X	X	X	X	X	X	X		X		X	X

Table 5-3: Schedule of assessments for the UCB7665 4mg/kg twice weekly dose arm (Dose Arm 3)

Assessments		Screening Period	Dosing Period					Observation Period							
			Dose 1	Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a] BL Visit	3[a]	4[a]	5[a]	6[a]	7	8	9[b]	10	11[b]	12	13[b]	14 EOS/EW[c]
	Day	-28 to -1	1	4	8	11	15	18	22	29	36	43	50	57	71
	Week		1	1	2	2	3	3	4	5	6	7	8	9	11
	Visit Window			+1d[d]	+1d[d]	+1d[d]	+1d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Serum complements (C3 and C4) and plasma complements (C3a and C5a)			X		X			X				X			
Serum biomarkers [redacted]			X	X	X	X	X	X	X	X	X	X	X	X	
Serum biomarkers [redacted]			X	X	X	X	X								
Serum BAFF levels			X	X	X	X	X			X				X	
Immunoglobulins (total IgG, IgG subclasses)		X	X	X	X	X	X	X	X	X	X	X	X	X	X
IgA, IgM, IgE[n]			X				X		X					X	
ITP-specific autoantibodies[o]			X						X						X
ITP bleeding scale		X	X	X	X	X	X		X		X		X		X
NFI-MS			X						X		X		X		X

Table 5-3: Schedule of assessments for the UCB7665 4mg/kg twice weekly dose arm (Dose Arm 3)

Assessments		Screening Period	Dosing Period					Observation Period							
			Dose 1	Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a] BL Visit	3[a]	4[a]	5[a]	6[a]	7	8	9[b]	10	11[b]	12	13[b]	14 EOS/EW[c]
	Day	-28 to -1	1	4	8	11	15	18	22	29	36	43	50	57	71
	Week		1	1	2	2	3	3	4	5	6	7	8	9	11
	Visit Window			+1d[d]	+1d[d]	+1d[d]	+1d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Headache questionnaire[p]			X	X	X	X	X	X	X	X	X	X	X	X	X
Subject exit interview[q]															X

AE=adverse event; BAFF=B cell activating factor; BL=Baseline; CSF=cerebrospinal fluid; CT=computed tomography; d=day(s); DMC=Data Monitoring Committee; DNA=deoxyribonucleic acid ; ECG=electrocardiogram; EOS=End of Study; EW=Early Withdrawal; [redacted] HIV=human immunodeficiency virus; Ig=immunoglobulin; IMP=investigational medicinal product; ITP=immune thrombocytopenia; IXRS= interactive voice/web response system; LP=lumbar puncture; MRI=magnetic resonance imaging; NFI-MS=Neurological Fatigue Index for multiple sclerosis; [redacted] RNA=ribonucleic acid; [redacted]

[a] Frequency of assessments on dosing days is detailed in Table 5-4.

[b] Visits 9, 11, and 13 can be performed at home with a healthcare professional visiting the subject at his/her home.

[c] The End-of-Study Visit is 8 weeks following the final dose.

[d] A visit window of +1 day is allowed for the dosing visits, with at least 3 days in between 2 successive doses.

[e] The visit windows in the Observation Period are relative to the final dosing visit date.

[f] Additional informed consent is needed for participation in the exploratory genomic substudy. All samples will be collected prior to dosing with IMP.

[g] Prior to dosing at Visit 2, 2 platelet samples will be taken. One sample will be analyzed locally and the value will be used to check inclusion criteria. The other platelet sample will be sent to the central laboratory. At subsequent dosing visits, a platelet sample will be assessed locally prior to dosing to evaluate withdrawal criterion of platelet count >350x10^9/L.

[h] Dose Arm 3 will be opened once 15 subjects are enrolled in Dose Arm 1 and safety data review of at least 3 subjects in Dose Arm 2 is done. Subsequent subjects will be randomly assigned in 1:1 ratio to either Dose Arm 2 or Dose Arm 3 using an IXRS. Once 15 subjects are in Dose Arm 2 or 6 subjects are enrolled in Dose Arm 3, the respective dose arm will be closed.

[i] Subjects can withdraw at any time during the study, based on the criteria in Section 6.4.

[j] A complete physical examination will be performed at Screening and EOS/EW Visit. At all other visits (where physical examination is performed), an abbreviated physical examination will be conducted.

[k] The ECG should be performed in triplicate prior to blood collection for assessment of laboratory parameters. Three ECGs should be recorded in a time frame of 5 minutes with at least 1 minute difference, 1-2 minutes between the ECGs.
[l] At the Screening Visit, 2 separate blood samples will be obtained on the same day for evaluation of platelet count.
[m] Blood sample for cytokines will be obtained only in case of infusion reactions.
[n] In case the number of infusions to be administered are reduced after DMC review of safety data, then the scheduled Visit 6 assessment for IgA, IgM, and IgE will be performed earlier at the last dosing visit.
[o] [redacted]
[p] This assessment is applicable only to subjects experiencing severe headaches and will be performed daily until resolution (ie, if headache becomes moderate or mild, normal collection of AEs should apply); this assessment will be followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.
[q] A semi-structured interview guide will be used and the interview will be recorded. In case of early withdrawal from the study, the subject exit interview should be performed at End-of-Study Visit only.

Change #25

Section 5.2 Schedule of study assessments

Table 5-3: Schedule of investigations on the dosing days

	Predose	End of infusion	2h after end of infusion	4h after end of infusion
Withdrawal criteria	X			
Platelet count (local laboratory) for inclusion check at Visit 2 and for withdrawal criterion at other dosing visits	X			
Prior and concomitant medications	X			
Concomitant medical procedures	X			
Vital signs[a]	X	X	X	X
Physical examination	X			
12-lead ECG	X			
Hematology	X			
Clinical chemistry	X			

Table 5-3: Schedule of investigations on the dosing days

	Predose	End of infusion	2h after end of infusion	4h after end of infusion
Urinalysis	X			
Urine pregnancy test	X			
Immunoglobulins[b]	X			
ITP-specific autoantibodies[c]	X			
Blood sampling for UCB7665 plasma concentration	X			
Anti-UCB7665 antibodies/IgG depletion assay	X			
Serum (C3 and C4) and plasma complements (C3a and C5a)[d]	X			
Serum biomarkers [redacted]	X		X	X
Serum BAFF levels	X		X	X
Blood sampling for cytokines[e]	X			
ITP bleeding scale	X			
AEs	X	X	X	X
NFI-MS[f]	X			

AE=adverse event; BAFF=B cell activating factor; ECG=electrocardiogram; h=hours; Ig=immunoglobulin; IMP=investigational medicinal product; ITP=immune thrombocytopenia; NFI-MS=Neurological Fatigue Index for multiple sclerosis; [redacted] PRO=Patient Reported Outcomes; [redacted]

[a] In addition to time points mentioned, vital signs will be evaluated every 15 minutes during infusion. Respiratory rate will be assessed only once predose.
[b] Total IgG and IgG subclasses.
[c] Evaluation of ITP-specific autoantibodies will be performed prior to dose 1 only.
[d] Serum and plasma complement levels will be assessed prior to dose 1 and dose 3 only.
[e] Blood sample for Baseline cytokine values will be obtained at Visit 2 for all subjects at predose and at other visits in case of infusion reactions.
[f] PRO endpoint (NFI-MS) will be assessed prior to dose 1 only.

Has been changed to:

Table 5–4: Schedule of investigations on the dosing days

	Predose	End of infusion	2h after end of infusion	4h after end of infusion
Withdrawal criteria	X			
Platelet count (local laboratory) for inclusion check at Visit 2 and for withdrawal criterion at other dosing visits	X			
Prior and concomitant medications	X			
Concomitant medical procedures	X			
Vital signs[a]	X	X	X	X
Physical examination	X			
12-lead ECG[b]	X			
Hematology	X			
Clinical chemistry	X			
Urinalysis	X			
Urine pregnancy test	X			
Immunoglobulins[c]	X			
ITP-specific autoantibodies[d]	X			
Blood sampling for UCB7665 plasma concentration	X			
Anti-UCB7665 antibodies/IgG depletion assay	X			
Serum (C3 and C4) and plasma complements (C3a and C5a)[e]	X			
Serum biomarkers [redacted]	X		X	X
Serum BAFF levels	X		X	X

Table 5–4: Schedule of investigations on the dosing days

	Predose	End of infusion	2h after end of infusion	4h after end of infusion
Blood sampling for cytokines[f]	X			
Whole blood sample for DNA and RNA (optional)[g]	X			
ITP bleeding scale	X			
AEs	X	X	X	X
NFI-MS[h]	X			

AE=adverse event; BAFF=B cell activating factor; DNA=deoxyribonucleic acid; ECG=electrocardiogram; h=hours; Ig=immunoglobulin; IMP=investigational medicinal product; ITP=immune thrombocytopenia; NFI-MS=Neurological Fatigue Index for multiple sclerosis; [redacted] PRO=Patient Reported Outcomes; RNA=ribonucleic acid; [redacted]

[a] In addition to time points mentioned, vital signs will be evaluated every 15 minutes during infusion. Respiratory rate will be assessed only once predose.

[b] The ECG should be performed in triplicate prior to blood collection for assessment of laboratory parameters. Three ECGs should be recorded in a time frame of 5 minutes with at least 1 minute difference, 1-2 minutes between the ECGs.

[c] Total IgG and IgG subclasses.

[d] Evaluation of ITP-specific autoantibodies will be performed prior to dose 1 only.

[e] Serum and plasma complements (C3a and C5a) will be assessed prior to dose 1 and dose 3 only.

[f] Blood sample for Baseline cytokine values will be obtained at Visit 2 for all subjects at predose and at other visits in case of infusion reactions.

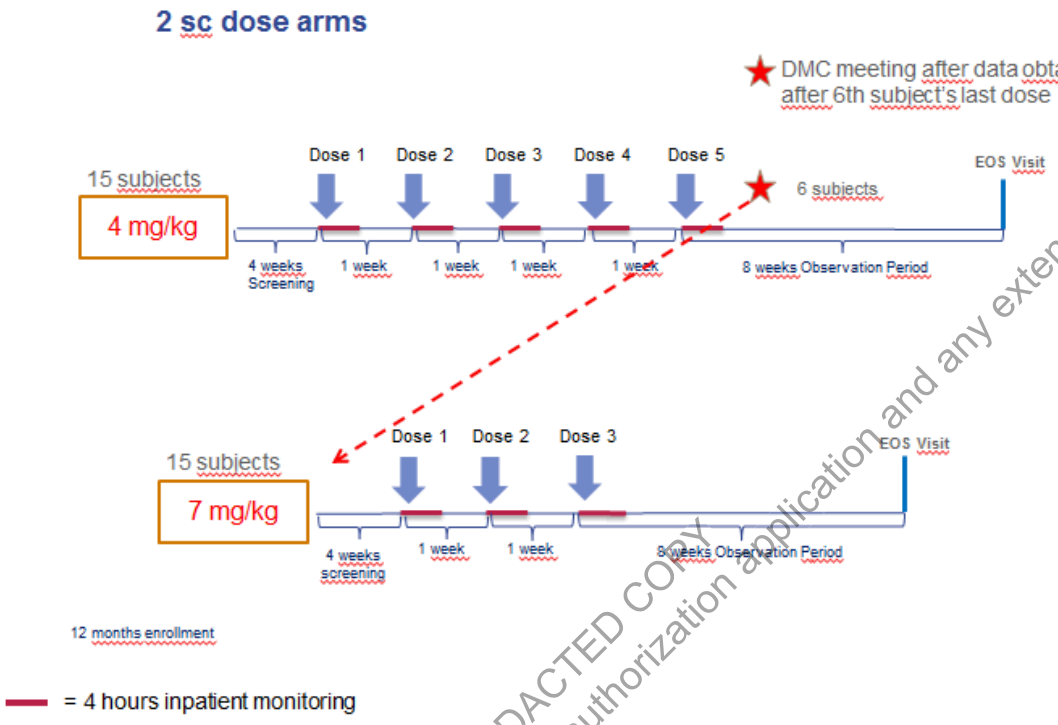
[g] For DNA, samples are taken at Baseline (Visit 2) and last dose only. For RNA, samples are taken at Baseline (Visit 2), Visit 3, at last dose, and End of Study Visit. All samples collected prior to dosing (if applicable for visit).

[h] PRO endpoint (NFI-MS) will be assessed prior to dose 1 only.

Change #26

Section 5.3 Schematic diagram

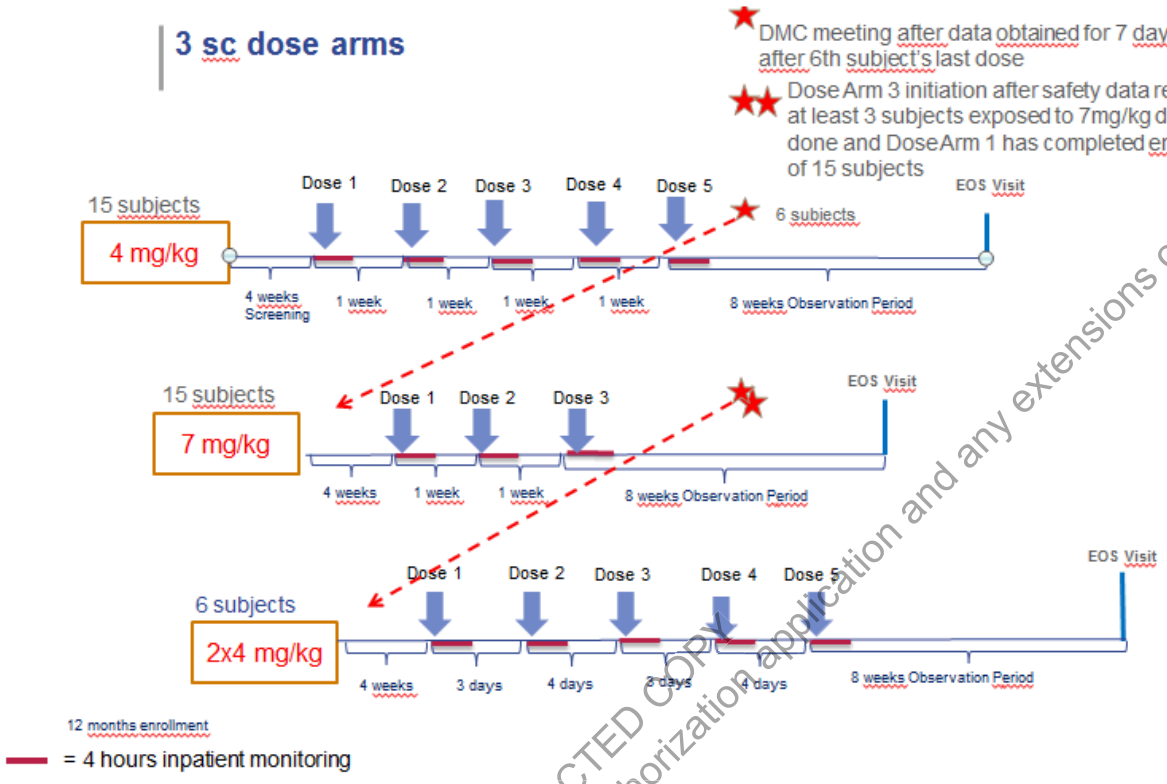
Figure 5–1: Schematic diagram



DMC=Data Monitoring Committee; EOS=End of Study; sc=subcutaneous

Has been changed to:

Figure 5–1: Schematic diagram



DMC=Data Monitoring Committee; EOS=End of Study; sc=subcutaneous
Note: 2x4mg/kg refers to UCB7665 4mg/kg dose given twice weekly.

Change #27

Section 5.4.5 Rationale for dose selection

Paragraph #5:

Therefore, doses of UCB7665 4mg/kg given once weekly for 5 weeks and UCB7665 7mg/kg given once weekly for 3 weeks have been selected to evaluate the safety, tolerability and effect on platelet count in subjects with primary persistent or chronic ITP.

Has been changed to:

Therefore, doses of UCB7665 4mg/kg given once weekly for 5 weeks and UCB7665 7mg/kg given once weekly for 3 weeks have been selected as the initial doses to evaluate the safety, tolerability and effect on platelet count in subjects with primary persistent or chronic ITP. However, modelled data has shown a similar IgG reduction in a 4mg/kg twice weekly dosing regimen as in a 7mg/kg weekly dosing regimen. Therefore, a third dosing arm of UCB7665 4mg/kg twice weekly has been integrated into the study design to explore the PD effect of UCB7665 administered as an sc infusion in subjects with ITP following a more frequent dosing regimen. This dose arm will be initiated after safety data review of at least 3 subjects in Dose Arm 2 is done and Dose Arm 1 has completed enrollment of 15 subjects.

Change #28

NEW Section 5.4.6 Justification for additional genomic analyses

DNA analysis

A genetic component in ITP has long been suspected to predispose some persons to develop ITP when exposed to a provocative event.

Further, the hypothesis of underlying genetic risk for ITP is supported by rare anecdotal and case reports of familial ITP. Affected members of these families present with ITP that meets the clinical criteria for primary ITP, but demonstrates a convincing pattern of inheritance. A 2006 review of the Pediatric and Adult Registry of Chronic ITP (PARC-ITP) (Johnsen, 2012) found that 10 of 445 (2.2%) of pediatric patients reported a positive family history of ITP. However, identification of susceptibility genes in ITP, via family linkage studies or genome wide association studies, have not yet been forthcoming, likely due to the rarity of familial ITP families available for study and the heterogeneity of ITP sporadic cases. Identification and characterization of a genetic and/or epigenetic component of familial ITP will lead to important clues into the pathogenesis of more common forms of ITP and possibly advance understanding of drug response phenotypes.

RNA analysis

Gene expression (mRNA) analyses have identified distinct gene transcription signatures from whole blood associated with many autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus, and ITP. Such signatures have provided molecular insight into disease biology and can facilitate patient stratification via gene expression panels predictive of therapeutic response and clinical outcomes.

Collection of blood for RNA analysis will enable identification of candidate markers for treatment effect and safety, and determine the feasibility of patient stratification.

MicroRNA analysis

MicroRNA are short (19-25 nucleotides) evolutionarily conserved single-stranded RNA molecules that regulate the expression of genes involved in diverse biological processes. The effect of miRNA on mRNA is mediated through the binding of the miRNA to the target mRNA ribonucleoprotein complex resulting in altered expression and decreased protein translation.

Regulated miRNA in ITP significantly affect both gene and protein expression in T cells, indicating that they may be important regulatory molecules involved in the loss of immune tolerance in ITP.

In summary, the genetic, epigenetic, and genomic elements of ITP are complex and require further elucidation to understand the cause, progression, and appropriate treatment of ITP. Through the voluntary collection of blood DNA/and RNA samples from consenting subjects, this substudy will help enable further investigation of this complex disease.

Change #29

Section 6.1 Inclusion criteria

7. Female subjects of childbearing potential must have a negative serum pregnancy test at the Screening Visit, which is confirmed to be negative by urine testing prior to the first dose of IMP at Week 1 (Visit 2) and prior to further dosing at each study visit thereafter.

   Female subjects of childbearing potential must agree to use a highly effective method of birth control, during the study and for a period of 3 months after their final dose of IMP. Highly effective forms of birth control are methods which achieve a failure rate of less than 1% per year when used consistently and correctly. Highly effective methods of birth control include:

   …

Has been changed to:

7. Female subjects of childbearing potential must have a negative serum pregnancy test at the Screening Visit, which is confirmed to be negative by urine testing prior to the first dose of IMP at Week 1 (Visit 2) and prior to further dosing at each study visit thereafter.

   Female subjects of childbearing potential must agree to use a highly effective method of birth control, during the study and for a period of 2 months after their final dose of IMP. Highly effective forms of birth control are methods which achieve a failure rate of less than 1% per year when used consistently and correctly. Highly effective methods of birth control include:

   …

Change #30

Section 6.5 Study stopping rules

Paragraph #2:

More detailed criteria for stopping a cohort will be defined in the DMC charter.

Has been changed to:

More detailed criteria for stopping a dose arm will be defined in the DMC charter.

Change #31

Section 7.2 Treatment to be administered

Paragraph #1: Dose Arm 3 details added as follows:

Subjects in the Dose Arm 3 will receive 5 sc doses of UCB7665 4mg/kg at 3 to 4 day intervals (ie, approximately twice a week).

Change #32

Section 7.4 Labeling

Clinical drug supplies will be labeled in accordance with the current International Conference on Harmonisation (ICH) guidelines on GCP and GMP and will include any locally required statements. If necessary, labels will be translated into the local language.

Has been changed to:

Clinical drug supplies will be labeled in accordance with the current International Council for Harmonisation (ICH) guidelines on GCP and GMP and will include any locally required statements. If necessary, labels will be translated into the local language.

Change #33

Section 7.10 Randomization and numbering of subjects

Paragraph #2:

The first 6 subjects (and those treated before DMC assessment after the 6 subjects) will not be randomized. Once the DMC has approved opening of Dose Arm 2 for enrollment, subsequent subjects will be randomized to 1 of the 2 dose arms in a 1:1 ratio. Once 15 subjects are in the 4mg/kg group, the remaining subjects will not be randomized. They will be allocated to the 7mg/kg group.

Has been changed to:

The first 6 subjects (and those treated before DMC assessment after the 6 subjects) will not be randomized. Once the DMC has approved opening of Dose Arm 2 for enrollment, subsequent subjects will be randomly assigned to 1 of the 2 dose arms (ie, Dose Arm 1 and Dose Arm 2) in a 1:1 ratio. Once 15 subjects are enrolled in the Dose Arm 1 and safety data review of at least 3 subjects in Dose Arm 2 is done, the remaining subjects will be randomly assigned in 1:1 ratio to either Dose Arm 2 or Dose Arm 3. Once 15 subjects are enrolled in the Dose Arm 2 or 6 subjects are enrolled in Dose Arm 3, the respective dose arm will be closed.

Change #34

Section 8.1.1 Visit 1 (Day -28 to -1) Screening Visit

Has been changed to:

Section 8.1.1 Visit 1 (Day -28 to -1) Screening Visit (all Dose Arms)

Detail regarding informed consent process for exploratory genomic analyses added as follows:

Subjects will also have the option of providing additional voluntary informed consent for collection of whole blood samples for exploratory DNA and RNA analyses.

NEW bullet:

- Obtain informed consent for substudy involving DNA and RNA analyses

Change #35

Section 8.2 Dosing Period

Has been changed to:

Section 8.2 Dosing Period for Dose Arms 1 and 2 (weekly dosing regimen)

Change #36

Section 8.2.1 Visit 2 (Week 1/Day 1) Baseline Visit

Paragraphs #2, #3, and #4:

Eligible subjects will be treated with IMP at Visit 2. The first 6 subjects will be enrolled in Dose Arm 1, subsequent subjects will be randomized to 1 of the 2 dose arms. Once 15 subjects are in Dose Arm 1, the remaining subjects will not be randomized. They will be allocated to Dose Arm 2.

Eligible subjects will be treated with IMP at Visit 2. The first 6 subjects will be enrolled in Dose Arm 1, subsequent subjects will be randomized to 1 of the 2 dose arms. Once 15 subjects are in Dose Arm 1, the remaining subjects will not be randomized. They will be allocated to Dose Arm 2.

Subjects allocated to Dose Arm 1 (UCB7665 4mg/kg sc) will receive a total of 5 doses of IMP at Visit 2 (Day 1, Week 1), Visit 4 (Week 2), Visit 5 (Week 3), Visit 6 (Week 4), and Visit 7 (Week 5).

Subjects allocated to Dose Arm 2 (UCB7665 7mg/kg sc) will receive a total of 3 doses of IMP at Visit 2 (Day 1, Week 1), Visit 4 (Week 2), and Visit 5 (Week 3).

Has been changed to:

Section 8.2.1 Visit 2 (Week 1/Day 1) Baseline Visit [UCB7665 4mg/kg weekly and UCB7665 7mg/kg weekly]

Eligible subjects will be treated with IMP at Visit 2. The first 6 subjects will be enrolled in Dose Arm 1; subsequent subjects will be randomly assigned to 1 of the 2 dose arms (ie, Dose Arm 1 and Dose Arm 2). Once 15 subjects are in Dose Arm 1 and at least 3 subjects are in Dose Arm 2, the remaining subjects will be randomly assigned in 1:1 ratio to either Dose Arm 2 or Dose Arm 3. Once 15 subjects are in Dose Arm 2 or 6 subjects are enrolled in Dose Arm 3, the respective dose arm will be closed.

Subjects allocated to Dose Arm 1 (UCB7665 4mg/kg weekly sc) will receive a total of 5 doses of IMP at Visit 2 (Day 1, Week 1), Visit 4 (Week 2), Visit 5 (Week 3), Visit 6 (Week 4), and Visit 7 (Week 5).

Subjects allocated to Dose Arm 2 (UCB7665 7mg/kg weekly sc) will receive a total of 3 doses of IMP at Visit 2 (Day 1, Week 1), Visit 4 (Week 2), and Visit 5 (Week 3).

NEW bullet:

- Collection of whole blood for exploratory DNA and RNA analyses

Change #37

Section 8.2.2 Visit 3 (Week 1/Day 4)

Has been changed to:

Section 8.2.2 Visit 3 (Week 1/Day 4) [UCB7665 4mg/kg weekly and UCB7665 7mg/kg weekly]

New bullet:

- For Dose Arm 1 and 2, collection of whole blood for exploratory RNA analyses

Change #38

Section 8.2.3 Visit 4 (Week 2/Day 8)

Has been changed to:

Section 8.2.3 Visit 4 (Week 2/Day 8) [UCB7665 4mg/kg weekly and UCB7665 7mg/kg weekly]

Change #39

Section 8.2.4 Visit 5 (Week 3/Day 15)

Has been changed to:

Section 8.2.4 Visit 5 (Week 3/Day 15) [UCB7665 4mg/kg weekly and UCB7665 7mg/kg weekly]

New bullet:

- For Dose Arm 2 only, collection of whole blood for exploratory DNA and RNA analyses

Change #40

Section 8.2.5 Visit 6 (Week 4/Day 22) [UCB7665 4mg/kg only]

Has been changed to:

Section 8.2.5 Visit 6 for Dose Arm 1 (Week 4/Day 22) [UCB7665 4mg/kg only]

Change #41

Section 8.2.6 Visit 7 (Week 5/Day 29) [UCB7665 4mg/kg only]

Has been changed to:

Section 8.2.6 Visit 7 for Dose Arm 1 (Week 5/Day 29) [UCB7665 4mg/kg only]

New bullet:

- For Dose Arm 1 only, collection of whole blood for DNA and RNA analyses

Change #42

NEW Sections 8.3, 8.3.1, 8.3.2, 8.3.3, 8.3.4, and 8.3.5:

Section 8.3 Dosing for Dose Arm 3 (twice weekly dosing regimen)

Subjects allocated to Dose Arm 3 (UCB7665 4mg/kg twice weekly sc) will receive a total of 5 doses of IMP at Visit 2 (Day 1, Week 1), Visit 3 (Day 4, Week 1), Visit 4 (Day 8, Week 2), Visit 5 (Day 11, Week 2), and Visit 6 (Day 15, Week 3).

Section 8.3.1 Visit 2 (Week 1 Day 1) Baseline Visit [UCB7665 4mg/kg twice weekly]

The same conditions and assessments are required at this Visit as are detailed in Section 8.2.1.

Section 8.3.2 Visit 3 (Week 1/Day 4) [UCB7665 4mg/kg twice weekly]

This is the second dosing visit and a window of +1 day is allowed for this visit. However, there should be a minimum of 3 days (72 hours) interval between two doses.

The assessments at this visit are identical to those detailed in Section 8.2.3. Additional to the assessments mentioned in Section 8.2.3, whole blood samples will be collected for RNA analyses.

Section 8.3.3 Visit 4 (Week 2/Day 8) [UCB7665 4mg/kg twice weekly]

This is the third dosing visit and a window of +1 day is allowed for this visit, relative to Dose 1 at the Visit 2 date. However, there should be a minimum of 3 days (72 hours) interval between two doses.

The assessments at this visit are identical to those detailed in Section 8.2.4.

Section 8.3.4 Visit 5 (Week 2/Day 11) [UCB7665 4mg/kg twice weekly]

This is the fourth dosing visit and a window of +1 day is allowed for this visit, relative to Dose 1 at the Visit 2 date. However, there should be a minimum of 3 days (72 hours) interval between two doses.

The assessments at this visit are identical to those detailed in Section 8.2.5.

Section 8.3.5 Visit 6 (Week 3/Day 15) [UCB7665 4mg/kg twice weekly]

This is the fifth dosing visit and a window of +1 day is allowed for this visit, relative to Dose 1 at the Visit 2 date. However, there should be a minimum of 3 days (72 hours) interval between two doses.

The assessments at this visit are identical to those detailed in Section 8.2.6. Blood samples will be collected for DNA and RNA analyses.

Change #43

Section 8.3 Observation Period

Paragraph #2:

For UCB7665 4mg/kg dose, the following visits will be performed: Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13, Visit 14, and Visit 15, corresponding to UCB7665 7mg/kg Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, and Visit 13.

Has been changed to:

Section 8.4 Observation Period

For UCB7665 4mg/kg weekly dose (Dose Arm 1), the following visits will be performed: Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13, Visit 14, and Visit 15, corresponding to UCB7665 7mg/kg weekly dose (Dose Arm 2) on Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, and Visit 13.

For the UCB7665 4mg/kg twice weekly dose (Dose Arm 3), the following visits will be performed: Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13, and Visit 14.

Change #44

Section 8.3.1 Visit 8 (Week 5/Day 32) [UCB7665 4mg/kg]/ Visit 6 (Week 3/Day 18) [UCB7665 7mg/kg]

Has been changed to:

Section 8.4.1 Visit 8 (Week 5/Day 32) [UCB7665 4mg/kg weekly]/ Visit 6 (Week 3/Day 18) [UCB7665 7mg/kg weekly]/ Visit 7 (Week 3/Day 18) [UCB7665 4mg/kg twice weekly]

Change #45

Section 8.3.2 Visit 9 (Week 6/Day 36) [UCB7665 4mg/kg]/ Visit 7 (Week 4/Day 22) [UCB7665 7mg/kg]

A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. The following assessments will be performed at this visit:

…

Has been changed to:

Section 8.4.2 Visit 9 (Week 6/Day 36) [UCB7665 4mg/kg weekly]/ Visit 7 (Week 4/Day 22) [UCB7665 7mg/kg weekly]/ Visit 8 (Week 4/Day 22) [UCB7665 4mg/kg twice weekly]

This is the second visit in the Observation Period. A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. The following assessments will be performed at this visit:

…

Change #46

Section 8.3.3 Visit 10 (Week 7/Day 43) [UCB7665 4mg/kg]/ Visit 8 (Week 5/Day 29) [UCB7665 7mg/kg]

A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. This visit can be performed at home with a healthcare professional visiting the subject at his/her home. The following assessments will be performed at this visit:

…

Has been changed to:

Section 8.4.3 Visit 10 (Week 7/Day 43) [UCB7665 4mg/kg weekly]/
Visit 8 (Week 5/Day 29) [UCB7665 7mg/kg weekly]/
Visit 9 (Week 5/Day 29) [UCB7665 4mg/kg twice weekly]

This is the third visit in the Observation Period. A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. This visit can be performed at home with a healthcare professional visiting the subject at his/her home. The following assessments will be performed at this visit:

…

Change #47

Section 8.3.4 Visit 11 (Week 8/Day 50) [UCB7665 4mg/kg]/ Visit 9 (Week 6/Day 36) [UCB7665 7mg/kg]

A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. The following assessments will be performed at this visit:

…

Has been changed to:

Section 8.4.4 Visit 11 (Week 8/Day 50) [UCB7665 4mg/kg weekly]/ Visit 9 (Week 6/Day 36) [UCB7665 7mg/kg weekly]/ Visit 10 (Week 6/Day 36) [UCB7665 4mg/kg twice weekly]

This is the fourth visit in the Observation Period. A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. The following assessments will be performed at this visit:

…

Change #48

Section 8.3.5 Visit 12 (Week 9/Day 57) [UCB7665 4mg/kg]/ Visit 10 (Week 7/Day 43) [UCB7665 7mg/kg]

A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. This visit can be performed at home with a healthcare professional visiting the subject at his/her home. The following assessments will be performed at this visit:

…

Has been changed to:

Section 8.4.5 Visit 12 (Week 9/Day 57) [UCB7665 4mg/kg weekly]/ Visit 10 (Week 7/Day 43) [UCB7665 7mg/kg weekly]/ Visit 11 (Week 7/Day 43) [UCB7665 4mg/kg twice weekly]

This is the fifth visit in the Observation Period. A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. This visit can be performed at home with a healthcare professional visiting the subject at his/her home. The following assessments will be performed at this visit:

…

Change #49

Section 8.3.6 Visit 13 (Week 10/Day 64) [UCB7665 4mg/kg]/ Visit 11 (Week 8/Day 50) [UCB7665 7mg/kg]

A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. The following assessments will be performed at this visit:

…

Has been changed to:

Section 8.4.6 Visit 13 (Week 10/Day 64) [UCB7665 4mg/kg weekly]/Visit 11 (Week 8/Day 50) [UCB7665 7mg/kg weekly]/ Visit 12 (Week 8/Day 50) [UCB7665 4mg/kg twice weekly]

This is the sixth visit in the Observation Period. A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. The following assessments will be performed at this visit:

…

Change #50

Section 8.3.7 Visit 14 (Week 11/Day 71) [UCB7665 4mg/kg weekly]/Visit 12 (Week 9/Day 57) [UCB7665 7mg/kg weekly]/ Visit 13 (Week 9/Day 57) [UCB7665 4mg/kg twice weekly]

A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. This visit can be performed at home with a healthcare professional visiting the subject at his/her home. The following assessments will be performed at this visit:

…

Has been changed to:

Section 8.4.7 Visit 14 (Week 11/Day 71) [UCB7665 4mg/kg weekly]/Visit 12 (Week 9/Day 57) [UCB7665 7mg/kg weekly]/ Visit 13 (Week 9/Day 57) [UCB7665 4mg/kg twice weekly]

This is the seventh visit in the Observation Period. A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. This visit can be performed at home with a healthcare professional visiting the subject at his/her home. The following assessments will be performed at this visit:

…

Change #51

Section 8.3.8 End-of-Study Visit: Visit 15 (Week 13/Day 85) [UCB7665 4mg/kg]/ Visit 13 (Week 11/Day 71) [UCB7665 7mg/kg]

Has been changed to:

Section 8.4.8 End-of-Study Visit: Visit 15 (Week 13/Day 85) [UCB7665 4mg/kg weekly]/ Visit 13 (Week 11/Day 71) [UCB7665 7mg/kg weekly]/ Visit 14 (Week 11/Day 71) [UCB7665 4mg/kg twice weekly]

NEW bullet:

- For all dose arms, collection of whole blood for exploratory RNA analyses

Change #52

Section 8.4 Early Withdrawal Visit

Paragraph #3:

The assessments to be done at both the Early Withdrawal Visit as well as the End-of-Study Visit are the same as those at Visit 15 for the UCB7665 4mg/kg group or Visit 13 for the UCB7665 7mg/kg group, except for the subject exit interview which will be performed at the End-of-Study Visit only.

Has been changed to:

Section 8.5 Early Withdrawal Visit

The assessments to be done at both the Early Withdrawal Visit as well as the End-of-Study Visit are the same as those at Visit 15 for the UCB7665 4mg/kg weekly (Dose Arm 1) group, Visit 13 for the UCB7665 7mg/kg weekly (Dose Arm 2) group, or Visit 14 for the UCB7665 4mg/kg twice weekly (Dose Arm 3) group, except for the subject exit interview which will be performed at the End-of-Study Visit only.

Change #53

Section 9.1 Platelet counts

NEW variables:

- Baseline-corrected AUEC for platelet count calculated from Baseline to the end of study visit
- Clinical Response: platelet count $\geq 30x10^9$/L and $<100x10^9$/L with at least 2-fold increase from Baseline value and absence of bleeding
- Time to Clinical Response: time from starting treatment to achievement of Clinical Response
- Duration of Clinical Response: measured from achievement of Clinical Response to loss of Clinical Response (loss of Clinical Response defined as platelet count $<30x10^9$/L or less than 2-fold increase from Baseline platelet count or presence of bleeding)
- Complete Clinical Response: platelet count $\geq 100x10^9$/L and absence of bleeding
- Time to Complete Clinical Response: time from starting treatment to achievement of Complete Clinical Response
- Duration of Complete Clinical Response: measured from achievement of Complete Clinical Response to loss of Complete Clinical Response (loss of Complete Clinical Response defined as platelet count $<100x10^9$/L or presence of bleeding)
- No Clinical Response: platelet count $<30x10^9$/L and less than 2-fold increase from Baseline or presence of bleeding

Change #54

Section 11 Assessment of other immunological variables

NEW assessment:

- Lymphocyte counts (B and T)

Change #55

Section 12.1.1 Definition of adverse event

Paragraph #4:

Bleeding events should not be reported as an AE since these events will be assessed and reported during the ITP-BAT assessment. Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or more bleeding events should be reported as AEs.

Has been changed to:

Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or 2 bleeding events should not be reported as an AE since these events will be assessed and reported during the ITP-BAT assessment; CTCAE grade 3 or more bleeding events should be reported as AEs.

Change #56

Section 12.1.9 Safety signal detection

Paragraph #1:

The safety variables and ADA results available after 7 days of the final dose of 3 and 6 subjects in the UCB7665 4mg/kg dose arm will be reviewed by a DMC (interim analysis 1 and 2) comprising at least 1 external expert, the UCB study physician, the UCB DS representative, and a biostatistician and will be summarized on an ongoing basis during the study so as to continuously evaluate the safety of subjects. The DMC will meet and reach a decision on whether or not the study can continue as planned, and whether or not the next dose arm can be started. Subsequently, safety variables and ADA results available after 7 days of the final dose of 3 and 6 subjects in the UCB7665 7mg/kg dose arm (together with all available data from the UCB7665 4 mg/kg dose arm) will be reviewed by the DMC (interim analysis 3 and 4).

Has been changed to:

The safety variables and ADA results available after 7 days of the final dose of 3 and 6 subjects in the UCB7665 4mg/kg weekly group (Dose Arm 1) will be reviewed by the DMC (interim analysis 1 and 2) comprising at least 1 external expert, the UCB study physician, the UCB PS representative, and a biostatistician and will be summarized on an ongoing basis during the study so as to continuously evaluate the safety of subjects. The DMC will meet and reach a decision on whether or not the study can continue as planned, and whether or not Dose Arm 2 can be started. Subsequently, safety variables and ADA results available after 7 days of the final dose of 3 and 6 subjects in the UCB7665 7mg/kg weekly (Dose Arm 2) (together with all available data from Dose Arm 1 and 2) will be reviewed by the DMC (interim analysis 3 and 4).

Change #57

Section 12.7 Laboratory measurements

Table 12-2 Laboratory measurements

Deletion of: B and T Lymphocyte count

Addition of: γ-globulin

Change #58

Section 12.7.1 Evaluation of PDILI

Table 12-3 Required investigations and follow up for PDILI

Deletion of: ≥8xULN row

Addition of: Hepatology consult required if ALT or AST ≥8xULN to≥5xULN (and ≥2x Baseline) row immediate consultation requirements

Change #59

Section 12.8.512-Lead ECG

Paragraph #1:

A standard 12-lead ECG will be performed at visits as specified in the schedule of study assessments (Section 5.2). Care should be taken to assure proper lead placement and quality ECG recordings. Subjects should rest in a supine position in a controlled, calm environment for at least 15 minutes prior to the recording and should be motionless during the recording. The ECG will be performed in triplicate prior to blood collection for assessment of laboratory parameters.

Has been changed to:

A standard 12-lead ECG will be performed at visits as specified in the schedule of study assessments (Section 5.2). Care should be taken to assure proper lead placement and quality ECG recordings. Subjects should rest in a supine position in a controlled, calm environment for at least 15 minutes prior to the recording and should be motionless during the recording.

The ECG will be performed in triplicate prior to blood collection for assessment of laboratory parameters. Three ECGs should be recorded in a time frame of 5 minutes with at least 1 minute difference, 1-2 minutes between the ECGs.

Change #60

Section 14.1 Definition of analysis sets

Full Analysis Set (FAS):

The FAS will consist of all subjects who have received at least 1 infusion (full infusion) of IMP and, in addition, have a Baseline and at least 1 post-Baseline measurement for platelet count.

The analysis of the PD, efficacy, and immunologic variables will be performed on the FAS. Selected outputs may be repeated for the Per Protocol Set (PPS). Further details will be provided in the SAP.

Has been changed to:

The FAS will consist of all subjects who have received at least 1 infusion (full infusion) of IMP and, in addition, have a Baseline and at least 1 post-Baseline measurement for platelet count.

The analysis of the PD (excluding total IgG, IgG subclasses, and IgG depletion assay), efficacy, and immunologic variables will be performed on the FAS. Selected outputs may be repeated for the PD Per Protocol Set (PD-PPS). Further details will be provided in the SAP.

Change #61

Section 14.1 Definition of analysis sets

NEW analysis set:

Pharmacodynamic Per Protocol Set (PD-PPS)

The PD-PPS is a subset of the FAS, consisting of those subjects who had no important protocol deviations potentially affecting the serum concentration of total IgG, as confirmed during a pre-analysis review of the data prior to database lock.

The PD-PPS will be used for the analysis of the total IgG, IgG subclasses, and IgG depletion assay.

Change #62

Section 14.2 General statistical considerations

All analyses will be performed using SAS® version 9.2 or later (SAS Institute, Cary, NC, USA). Continuous variables will be summarized by visit (where applicable) with the statistics including the number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized by visit (where applicable) with frequency counts and percentages. Analyses will be performed by dose arm, unless otherwise stated. In the event that the number of infusions in the planned dose arms (3x7mg/kg and 5x4mg/kg) are modified following review by the DMC, the data will be summarized based on the actual dose arms completing the study. For example, if the 5x4 mg/kg dose arm is modified such that some subjects receive only 4 infusions, then the data will be summarized separately for this new dose regimen.

Has been changed to:

All analyses will be performed using SAS® version 9.2 or later (SAS Institute, Cary, NC, USA). Continuous variables will be summarized by visit (where applicable) with the statistics including the number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized by visit (where applicable) with frequency counts and percentages. Analyses will be performed by dose arm, unless otherwise stated. In the event that the number of planned infusions in Dose Arms 1 and 2 (5x4mg/kg and 3x7mg/kg weekly) are modified following review by the DMC, the data will be summarized based on the actual dose arms completing the study. For example, if the weekly 5x4mg/kg dose arm is modified such that some subjects receive only 4 infusions, then the data will be summarized separately for this new dose regimen.

Change #63

Section 14.3.2 Other safety analyses

Paragraph #1 and #2:

The absolute and relative frequencies for subjects with a given TEAE with respect to the preferred term according to the latest available version of the MedDRA, as well as the absolute frequencies of the individual TEAEs that have occurred, will be determined within each system organ class. Additional tables will summarize TEAEs by maximum intensity and causal relationship with UCB7665, as judged by the investigator. Adverse events will be categorized by severity according to the CTCAE version 4.03 grading. In case the CTCAE grading is not available, the intensity (mild/moderate/severe) will be utilized. The TEAEs leading to discontinuation of IMP and treatment-emergent SAEs will also be summarized. The action taken, time of onset relative to dosing, and duration of each AE will be listed only.

For the continuous laboratory variables, the values and changes from Baseline will be summarized at each time point. For categorized values according to the reference range, shift tables from Baseline to each post-Baseline time point will be presented for selected variables to be defined in the SAP. Values outside the reference range will be flagged in the data listings.

Has been changed to:

The absolute and relative frequencies for subjects with a given TEAE with respect to the preferred term according to the latest available version of the MedDRA, as well as the absolute frequencies of the individual TEAEs that have occurred, will be determined within each system organ class. Additional tables will summarize TEAEs by maximum intensity and causal relationship with UCB7665, as judged by the investigator. Adverse events will be categorized by severity according to the CTCAE version 4.03 grading. In case the CTCAE grading is not available, the intensity (mild/moderate/severe) will be utilized. For the purpose of the tabulations CTCAE grades will be aligned with the intensity classifications (mild/moderate/severe) to enable pooling of the AEs in the summaries. The TEAEs leading to discontinuation of IMP and treatment-emergent SAEs will also be summarized. The action taken, time of onset relative to dosing, and duration of each AE will be listed only.

For the continuous laboratory variables, the values and changes from Baseline will be summarized at each time point. For categorized values according to the reference range, shift tables from Baseline to each post-Baseline time point will be presented for selected variables to be defined in the SAP. Values outside the reference range will be flagged in the data listings. The number and percentage of subjects with markedly abnormal laboratory results (based on CTCAE grading) will be tabulated for each dose arm.

Change #64

Section 14.4.1 Efficacy analyses

The main efficacy variable is the maximum increase from Baseline in platelet count during the study. The maximum increase from Baseline and maximum platelet count during the study will be summarized by dose arm.

In addition, all measurements of platelet count will be summarized by dose arm and time point using descriptive statistics (including changes from Baseline).

For each dose arm a 1-sided t-test will be applied to assess if the average maximum increase from Baseline is greater than zero. In case the assumptions for the-t-test are not fulfilled a variance-stabilizing transformation may be applied in addition and/or an alternative nonparametric method may be considered. Further details will be provided in the SAP.

The Response rate, Complete Response rates, and platelet count $\geq 50x10^9$/L rate will be summarized (number of subjects and percentages) and presented with 90% 2-sided confidence intervals for the rate of responders at each time point and overall (across all time points). Response and Complete Response are defined in Section 4.2.

Time to Response, time to Complete Response, time to platelet count $\geq 50x10^9$/L, duration of Response, duration of Complete Response, and duration of platelet count $\geq 50x10^9$/L will be calculated and summarized by dose arm.

The results from the ITP bleeding scale will be summarized at each time point and will include the grades for each of the 3 major domains: skin (S), visible mucosae (M), and organs (O).

Results of the NFI-MS will be summarized at each time point, using summary scores where applicable. Changes from Baseline will be calculated and summarized.

Has been changed to:

The main efficacy variable is the maximum increase from Baseline in platelet count during the study. The maximum increase from Baseline and maximum platelet count during the study will be summarized by dose arm.

In addition, all measurements of platelet count will be summarized by dose arm and time point using descriptive statistics (including changes from Baseline).

For Dose Arm 1 and 2, a 1-sided t-test will be applied to assess if the average maximum increase from Baseline is greater than zero. In case the assumptions for the-t-test are not fulfilled, an alternative nonparametric method may be considered. Further details will be provided in the SAP.

The Response, Complete Response, and platelet count $\geq 50x10^9$/L will be summarized (number of subjects and percentages) and presented with 90% 2-sided confidence intervals for the rate of responders at each time point and overall (across all time points). Response and Complete Response are defined in Section 4.2. The analysis will be repeated for the Clinical Response variables defined in Section 4.2.

Time to Response, time to Complete Response, time to platelet count $\geq 50x10^9$/L, duration of Response, duration of Complete Response, duration of platelet count $\geq 50x10^9$/L, and Baseline-corrected AUEC for platelet count will be calculated and summarized by dose arm. The time to first response will be analyzed using a log-rank test and displayed using Kaplan-Meier curves. The time taken Response, time to Complete Response, and respective durations will be summarized by dose arm.

The results from the ITP bleeding scale will be summarized at each time point and will include the grades for each of the 3 major domains: skin (S), visible mucosae (M), and organs (O). In addition the number and percentage of subjects with severe or clinically relevant bleeding and number and percentage of subjects with absence of bleeding will be summarized at each time point.

Results of the NFI-MS will be summarized at each time point, using summary scores where applicable. Changes from Baseline will be calculated and summarized.

Additional subgroup analyses may be performed as needed and further details will be provided in SAP regarding these analyses.

Change #65

Section 14.4.3 Pharmacodynamic analyses

For all PD variables, descriptive statistics for the values and change from Baseline and/or percentage change from Baseline will be tabulated by time point. If appropriate, measurements will be log-transformed.

The PD variables will include ITP-specific autoantibodies [redacted] total IgG, and IgG subclasses. In addition, for total IgG, the maximum decrease from Baseline and minimum value will be evaluated and summarized. Figures of mean values over time and changes from Baseline will be presented.

Has been changed to:

For all PD variables, descriptive statistics for the values and change from Baseline and/or percentage change from Baseline will be tabulated by time point.

The PD variables will include ITP-specific autoantibodies [redacted] total IgG, IgG subclasses, and total and endogenous IgG measured via IgG depletion assay. In addition, for total IgG, the maximum decrease from Baseline and minimum value will be evaluated and summarized. Figures of mean values over time and changes from Baseline will be presented.

Change #66

Section 14.4.4 Immunologic variables

Paragraphs #1 and #2:

All immunologic variables including concentrations of immunoglobulins (IgA, IgE, and IgM), serum (C3 and C4) and plasma (C3a and C5a) complement levels, serum biomarkers [redacted] serum BAFF levels and the results of the IgG depletion assay will be summarized by dose arm over time (including changes from Baseline) using descriptive statistics. Figures of mean values over time and changes from Baseline may be presented.

The ADA status (negative/positive) and changes in relative mass units from Baseline will be summarized by dose arm; figures will also be presented.

Has been changed to:

All immunologic variables including concentrations of immunoglobulins (IgA, IgE, and IgM), serum (C3 and C4) and plasma (C3a and C5a) complement levels, serum biomarkers [redacted], serum BAFF levels, and lymphocyte counts (B and T) will be summarized by dose arm over time (including changes from Baseline) using descriptive statistics. Figures of mean values over time and changes from Baseline may be presented.

The ADA status (negative/positive) will be summarized by dose arm at each visit and overall; figures will also be presented in conjunction with PK concentrations of UCB7665 and with IgG depletion assay results.

Change #67

Section 14.4.5.2 Subject characteristics

Bullet #3:

- Prior and concomitant medications

Has been changed to:

- Past, prior, and concomitant medications

Change #68

Section 14.7 Planned interim analysis and data monitoring

Paragraphs #2, #4, #6, #8, and #13:

For the sequential adaptive design in this study, at least 4 interim analyses will be performed. Safety data from the interim analyses will be reviewed by the DMC to monitor the safety, to adapt the dose regimen, and to decide when and if the UCB7665 7mg/kg dose arm should be opened. Planned dosing may be discontinued for all subjects on a dose arm (see Section 6.5).

If the study continues without modifications, the next interim analysis will take place after data from 3 additional subjects are available. Based on the available combined data of the first 6 subjects, the DMC will decide if the 3x7mg/kg dose arm can be initiated. If the new dose arm will be initiated and if the 5x4mg/kg will be continued, new subjects will be randomized to 1 of the 2 dose arms in an allocation ratio of 1:1(Once 15 subjects are in the 4mg/kg group, the remaining subjects will not be randomized. They will be allocated to the 7mg/kg group).

The fourth interim analysis and review of data by DMC will take place after safety data (7 days after final dose) is available for the first 6 subjects in Dose Arm 2.

The potential decisions based on the fourth and subsequent interim analysis for the UCB7665 7mg/kg cohort are in line with the decisions described above for the UCB7665 4mg/kg cohort.

A detailed description of the DMC composition, processes and responsibilities, criteria to escalate to the next dose arm, and criteria to stop a dose arm will be provided in a separate DMC charter.

Has been changed to:

For the sequential adaptive design in this study, at least 4 interim analyses will be performed. Safety data from the interim analyses will be reviewed by the DMC to monitor the safety, to adapt the dose regimen, and to decide when and if the UCB7665 7mg/kg weekly group (Dose Arm 2) should be opened. Planned dosing may be discontinued for all subjects in a dose arm (see Section 6.5).

If the study continues without modifications, the next interim analysis will take place after data from 3 additional subjects are available. Based on the available combined data of the first 6 subjects, the DMC will decide if the 3x7mg/kg dose arm can be initiated. If the new dose arm

will be initiated and if the 5x4mg/kg will be continued, new subjects will be randomly assigned to 1 of the 2 dose arms in an allocation ratio of 1:1.

The fourth planned interim analysis and review of data by DMC will take place after safety data (7 days after final dose) is available for the first 6 subjects in Dose Arm 2.

The potential decisions based on the fourth and subsequent interim analysis for the UCB7665 7mg/kg group (Dose Arm 2) are in line with the decisions described above for the UCB7665 4mg/kg weekly group (Dose Arm 1).

A detailed description of the DMC composition, processes and responsibilities, criteria to escalate to the next dose arm, and criteria to stop, or continue a dose arm will be provided in a separate DMC charter.

Change #69

Section 14.8 Determination of sample size

Paragraph #1:

The sample size of 15 subjects, in each dose arm, is mainly based on the efficacy objective of the study. In addition the 2x15 subjects ensure that sufficient data are available to form conclusions about the safety of administering UCB7665.

Has been changed to:

The sample size of 15 subjects in Dose Arms 1 and 2, is mainly based on the efficacy objective of the study. In addition the 15 subjects in Dose Arms 1 and 2 ensure that sufficient data are available to form conclusions about the safety of administering UCB7665. Six subjects in Dose Arm 3 were judged to be sufficient in order to explore IgG reductions for the 5x4mg/kg/2 weeks dose regimen.

Change #70

Section 15.1 Informed consent

NEW paragraph #6:

Subjects have the right to withdraw their consent for the exploratory genomic substudy at any point without any impact on their care or participation in the main study. In this case, any data already generated on the samples will be retained and used, but no further analysis will occur.

Change #71

Section 15.4 Subject privacy

NEW paragraphs #3 and #4:

Genetic analysis data will not be shared with the subjects and will be subject to the highest level of data protection, as per European regulations.

Samples may be shared with collaborators working within UCB and may be analyzed at a third party site, but only in relation to the aims of this exploratory analysis as detailed in this study protocol. Samples may be stored for up to 20 years and maybe used at any time up to that point. Samples will remain under the control of UCB at all times and may be destroyed at any point before the 20 year expiration date.

Change #72

Section 17 References

NEW reference:

Johnsen J. Pathogenesis in immune thrombocytopenia: new insights. Hematology Am Soc Hematol Educ Program. 2012;2012:306-12.

18.9 Protocol Amendment 3

Rationale for the amendment

The primary purpose of this substantial amendment is to include three additional cohorts and a non-mandatory genomic substudy.

The previous protocol amendment (Protocol Amendment 2) was written to introduce a third cohort of 4mg/kg sc twice weekly. However, based on preliminary emerging data, it was expected that the planned inclusion of a 3rd dose arm with 4mg/kg of sc UCB7665 given twice per week would not create additional insight regarding the safety and the tolerability of UCB7665 in subjects with ITP. Therefore the planned implementation of protocol amendment #02 has been canceled. Instead, protocol amendment 3 will enable to further explore the safety, tolerability and PD effect of the same cumulative dose of UCB7665 administered with higher doses given in less sc infusions by integrating three new dose arms into the study.

Dose Arm 3 (10mg/kg weekly) with a cumulative dose of 20mg/kg will be opened as per DMC recommendation after review of the safety data of at least 6 subjects of Dose Arm 2 (7mg/kg weekly).

Dose Arm 4 with a single dose of 15mg/kg will be activated after review of the safety data of at least 6 subjects of Dose Arm 3 (10mg/kg weekly) and the DMC recommends this 4th dose increase.

Dose Arm 5 with a single dose of 20mg/kg will be activated after review of the safety data of at least 6 subjects of Dose Arm 4 (15mg/kg weekly) and the DMC recommends this 4th dose increase.

During this amendment, additional exploratory genomic (DNA and RNA) analyses have been added as an optional substudy to evaluate the genomic components of ITP to understand the molecular etiology, progression, and treatment of the disease.

All of the changes that were made in protocol amendment 2 that are still applicable to the current amendment 3 will be included in this section.

Modifications and changes

Global changes

- The following changes were made throughout the protocol:
- Addition of a new dose arm 10mg/kg administered once per week, a total of 2 sc doses.
- Addition of a new dose arm 15mg/kg administered in one sc dose.
- Addition of a new dose arm 20mg/kg administered in one sc dose.
- Additional exploratory genomic analyses added as an optional substudy.
- Addition of detailed tuberculosis assessment to ensure the subject safety
- Study variables were rearranged into ‘primary and others and exploratory variables.’
- [redacted]
- Serum biomarkers were changed to exploratory safety biomarkers throughout.

- The Clinical Response upper limit of normal (<$100x10^9$/L) was deleted.
- The IgG depletion assay was removed.
- Clarification was added that ECG is done in triplicate.

Specific changes

Change #1

STUDY CONTACT INFORMATION

Sponsor Study Physician

Name:	[redacted], MD
Address:	UCB BIOSCIENCES GmbH Alfred-Nobel-Straße 10 40789 Monheim GERMANY
Phone:	[redacted]
Fax:	

Has been changed to:

Name:	[redacted], MD
Address:	UCB BIOSCIENCES Inc. 8010 Arco Corporation Drive, Suite 175 Raleigh NC 27617, USA
Phone:	[redacted]
Fax:	

Change #2

Clinical Project Manager

Name:	[redacted]
Address:	UCB Biopharma SPRL Allée de la Recherche 60 B-1070 Brussels BELGIUM
Phone:	[redacted]
Fax:	

Has been changed to:

Name:	[redacted]
Address:	UCB BioSciences GmbH Alfred-Nobel-Strasse 10 40789 Monheim Germany
Phone:	[redacted]
Fax:	

Change #3

LIST OF ABBREVIATIONS

ICH International Conference on Harmonisation

Has been changed to:

ICH International Council for Harmonisation

Change #4

LIST OF ABBREVIATIONS

The following additions were made to the list of abbreviations:

AUEC area under the effect curve

DNA deoxyribonucleic acid

EOS End of Study

IGRA interferon-gamma release assay

LTB	latent tuberculosis
mRNA	messenger ribonucleic acid
miRNA	micro ribonucleic acid
NTMBI	nontuberculosis myobacterial infection
PD-PPS	Pharmacodynamic Per Protocol Set
RNA	ribonucleic acid
TB	tuberculosis

Change #5

LIST OF ABBREVIATIONS

The following abbreviation was deleted:

[redacted]

Change #6

Section 1 SUMMARY

Paragraph #3

TP0001 is a Phase 2, multicenter, open-label, multiple-dose, 2-dose-arm study to evaluate the safety, tolerability, and efficacy of UCB7665 administered as subcutaneous (sc) doses of 4mg/kg or 7mg/kg, in subjects ≥18 years of age with persistent (>3 months up to 12 months after diagnosis) or chronic (more than 12 months after diagnosis) primary ITP.

Has been changed to:

TP0001 is a Phase 2, multicenter, open-label, multiple-dose, multiple-arm study to evaluate the safety, tolerability, and efficacy of UCB7665 administered as subcutaneous (sc) doses of 4mg/kg, 7mg/kg, and 10mg/kg, 15mg/kg, and 20mg/kg (resulting in cumulative doses of 20mg/kg, 21mg/kg, 20mg/kg 15 mg/kg and 20mg/kg respectively), in subjects ≥18 years of age with persistent (>3 months up to 12 months after diagnosis) or chronic (more than 12 months after diagnosis) primary ITP.

Change #7

Section 1 SUMMARY

Paragraph #4:

The study is planned to be conducted at approximately 25 sites in Europe and Australia. A total of 30 subjects are planned to enter the Dosing Period in the study. The maximum study duration for study participation for an individual subject is approximately 16 weeks.

Has been changed to:

The study is planned to be conducted at up to approximately 45 sites in Europe and Australia. A total of approximately 48 to 66 subjects (dependent on emerging safety data and corresponding

DMC recommendation) are planned to enter the Dosing Period in the study. The maximum study duration for study participation for an individual subject is approximately 16 weeks.

Change #8

Section 1 SUMMARY

Paragraph #5:

The study will evaluate 2 dose arms of UCB7665. Subjects in Dose Arm 1 will receive 5 doses of UCB7665 4mg/kg sc at 1 week intervals and subjects in Dose Arm 2 will receive 3 doses of UCB7665 7mg/kg sc at 1 week intervals.

Has been changed to:

The study is intended to evaluate 5 dose arms of UCB7665. Subjects in Dose Arm 1 will receive 5 doses of UCB7665 4mg/kg sc at 1 week intervals, subjects in Dose Arm 2 will receive 3 doses of UCB7665 7mg/kg sc at 1 week intervals, subjects in Dose Arm 3 will receive 2 doses of UCB7665 10mg/kg sc at 1 week intervals, Dose Arm 4 will receive 1 dose of UCB7665 15mg/kg sc and Dose Arm 5 will receive 1 dose of UCB7665 20mg/kg sc.

Change #9

Section 1 SUMMARY

Paragraph #6:

The study consists of a Screening Period (up to 4 weeks), Dosing Period of 2 to 4 weeks, and an Observation Period of 8 weeks. The Screening Visit corresponds to Visit 1 of the study. The Dosing Period will commence at Visit 2 (Baseline Visit), with dosing visits scheduled at weekly intervals. The Observation Period will start after the final dose administration with a visit scheduled 3 days after the final dose and weekly thereafter (ie, weekly after final dose) for a period of 8 weeks. The End-of-Study Visit will be performed at the end of the Observation Period, ie, 8 weeks after the final dose of investigational medicinal product (IMP).

Has been changed to:

The study consists of a Screening Period (up to 4 weeks), Dosing Period of 1 day to 4 weeks, and an Observation Period of 8 weeks. The Screening Visit corresponds to Visit 1 of the study. The Dosing Period will commence at Visit 2 (Baseline Visit), with dosing visits scheduled at weekly intervals for Dose Arms 1, 2 and 3 and only one visit scheduled for Dose Arms 4 and 5. The Observation Period will start after the last dose administration (or only dose administration for Dose Arms 4 and 5) with a visit scheduled 3 days after the last dose and weekly visits thereafter (ie, weekly after last or only dose) for a period of 8 weeks. The End-of-Study Visit will be performed at the end of the Observation Period, ie, 8 weeks after the last or only dose of investigational medicinal product (IMP).

Change #10

Paragraph #7:

The first 6 subjects will be enrolled in Dose Arm 1 only. While recruitment is ongoing, safety data for the first 3 subjects up to 7 days after the final dose will be reviewed by a Data Monitoring Committee (DMC). During a second DMC meeting, safety data for the first 6

subjects up to 7 days after the final dose will be reviewed. Following this review, the DMC will make a decision on whether to open Dose Arm 2 for enrollment. Once the DMC has approved initiation of Dose Arm 2, subsequent subjects will be randomized to 1 of the 2 dose arms using an interactive voice/web response system (IXRS). The aim is to have 15 subjects in each dose arm. The DMC may also decide to reduce the number of doses in each of the dose arms based on review of data during the study. Safety data will also be reviewed on an ongoing basis during the study so as to continuously evaluate the safety of subjects.

Has been changed to:

The first 6 subjects will be enrolled in Dose Arm 1 only. While recruitment is ongoing, safety data for the first 3 subjects up to 7 days after the last dose of the third subject will be reviewed by the Data Monitoring Committee (DMC). During a second DMC meeting, all available safety data up to cut off date defined as 7 days after the last dose of the sixth subject will be reviewed. Following this review, the DMC will make a recommendation on whether to open Dose Arm 2 for enrollment. Once the DMC has advocated the initiation of Dose Arm 2, the subsequent subjects for the first 2 arms will be randomly assigned in 1:1 ratio to either Dose Arm 1 or Dose Arm 2 using an interactive voice/web response system (IXRS). Once 15 subjects are enrolled in Dose Arm 1, the subsequently enrolled subjects will be enrolled in Dose Arm 2.

Change #11

Paragraph #8 modified and NEW paragraphs #9 and #10 added:

After the safety data review of at least 6 subjects in Dose Arm 2 is done, the DMC will make a recommendation on whether to open Dose Arm 3 for enrollment. Once the DMC has advocated the initiation of Dose Arm 3 and the enrollment of 15 subjects in Dose Arm 2 has been completed, the subsequent subjects will be assigned to Dose Arm 3 only. After every third subject has been enrolled, DMC will review all available safety data up to cut off date defined as 7 days after the last dose. Depending on the emerging safety data of 6 subjects in Dose Arm 3, the DMC will recommend whether to open Dose Arm 4 for enrollment or to include additional subjects in Dose Arm 3. If applicable, this step is planned to be done stepwise in groups of 3 subjects. A maximum of 12 subjects are planned for Dose Arm 3. The DMC will recommend to open Dose Arm 4 for enrollment in a subsequent DMC meeting, if applicable.

Once the DMC has advocated the initiation of Dose Arm 4, the enrollment of Dose Arm 3 will be closed and all subsequently enrolled subjects will be assigned to Dose Arm 4. After every third subject that has been enrolled, DMC will review all available safety data up to cut off date defined as 7 days after the dosing of the third subject in Dose Arm 3. Depending on the emerging safety data of 6 subjects in Dose Arm 4, the DMC will recommend whether to open Dose Arm 5 for enrollment or to include additional subjects in Dose Arm 4. If applicable, this step is planned to be done stepwise in groups of 3 subjects. A maximum of 12 subjects are planned for Dose Arm 4. The DMC will recommend to open Dose Arm 5 for enrollment in a subsequent meeting, if applicable.

Once the DMC has advocated the initiation of Dose Arm 5, the enrollment of Dose Arm 4 will be closed and the subsequently enrolled subjects will be assigned to Dose Arm 5. After every third subject is enrolled, the DMC will review all available safety data up to the cutoff date defined as 7 days after the dosing of the third subject in Dose Arm 4. Depending on the emerging safety data of 6 subjects in Dose Arm 5, the DMC will recommend to include additional subjects

in Dose Arm 5. If applicable, this step is planned to be done stepwise in groups of 3. A maximum of 12 subjects are planned for Dose Arm 5.

The DMC may also decide to reduce the number of doses in each of the dose arms, to stop a dose arm or not to open a dose arm based on review of safety data during the study. Safety data will also be reviewed on an ongoing basis by CRO medical monitor and UCB physician during the study so as to continuously evaluate the safety of subjects.

Change #12

Section 1 SUMMARY

Paragraph #12:

The following efficacy variables will be assessed: Response (platelet count $\geq 30x10^9$/L and at least 2-fold increase of the Baseline count) during the study and by visit; Complete Response (platelet count $\geq 100x10^9$/L) during the study and by visit; platelet count $\geq 50x10^9$/L during the study and by visit; the maximum value and maximum increase from Baseline in platelet count during the study; value and change from Baseline in platelet count over time; time to Response (time from starting treatment to achievement of Response); time to Complete Response (time from starting treatment to achievement of Complete Response); time to achieving platelet count $\geq 50x10^9$/L; duration of Response (measured from achievement of Response to loss of Response [defined as platelet count below $30x10^9$/L or less than 2-fold increase of Baseline platelet count]); duration of Complete Response (measured from achievement of Complete Response to loss of Complete Response [defined as platelet count below $100x10^9$/L]); duration of platelet count $\geq 50x10^9$/L (measured from achievement of platelet count $\geq 50x10^9$/L to reduction of platelet count below $50x10^9$/L); ITP bleeding score over time; and Patient Reported Outcome (PRO), ie, Neurological Fatigue Index for Multiple Sclerosis (NFI-MS) summary score over time. Plasma concentration of UCB7665 over time will be assessed as the PK variable. The PD variables are minimum value and maximum decrease in total IgG concentration during the study; IgG subclass concentrations; and ITP-specific autoantibody [redacted] in serum over time. Other immunological variables to be evaluated are total IgA, IgE, and IgM levels; serum (C3 and C4) and plasma (C3a and C5a) complement levels; ADA status (negative/positive) and relative mass units; serum biomarkers [redacted] B cell activating factor (BAFF) levels and the results of the IgG depletion assay; and cytokines (for subjects experiencing infusion reactions). Additional exploratory biomarkers may be investigated if needed using the samples already available.

Has been changed to:

Now paragraph #13:

The following efficacy variables will be assessed: Response (platelet count $\geq 30x10^9$/L and at least 2-fold increase of the Baseline count) during the study and by visit; Complete Response (platelet count $\geq 100x10^9$/L) during the study and by visit; platelet count $\geq 50x10^9$/L during the study and by visit; the maximum value and maximum increase from Baseline in platelet count during the study; value and change from Baseline in platelet count over time; Baseline-corrected area under the effect curve (AUEC) for platelet count; time to Response (time from starting treatment to achievement of Response); time to Complete Response (time from starting treatment

to achievement of Complete Response); time to achieving platelet count ≥$50x10^9$/L; duration of Response (measured from achievement of Response to loss of Response [defined as platelet count below $30x10^9$/L or less than 2-fold increase of Baseline platelet count]); duration of Complete Response (measured from achievement of Complete Response to loss of Complete Response [defined as platelet count below $100x10^9$/L]); duration of platelet count ≥$50x10^9$/L (measured from achievement of platelet count ≥$50x10^9$/L to reduction of platelet count below $50x10^9$/L); Clinical Response (defined as platelet count ≥$30x10^9$/L with at least 2-fold increase from Baseline value and absence of bleeding); time to Clinical Response (time from starting treatment to achievement of Clinical Response); duration of Clinical Response (measured from achievement of Clinical Response to loss of Clinical Response [loss of Clinical Response defined as platelet count <$30x10^9$/L or less than 2-fold increase from Baseline platelet count or presence of bleeding]); Complete Clinical Response (defined as platelet count ≥$100x10^9$/L and absence of bleeding); time to Complete Clinical Response (time from starting treatment to achievement of Complete Clinical Response); duration of Complete Clinical Response (measured from achievement of Complete Clinical Response to loss of Complete Clinical Response [loss of Complete Clinical Response defined as platelet count <$100x10^9$/L or presence of bleeding]); no Clinical Response (defined as platelet count <$30x10^9$/L and less than 2-fold increase from Baseline or presence of bleeding); ITP bleeding score over time; and Patient Reported Outcome (PRO), ie, Neurological Fatigue Index for Multiple Sclerosis (NFI-MS) summary score over time. Plasma concentration of UCB7665 over time will be assessed as the PK variable. The PD variables are minimum value and maximum decrease in total IgG concentration during the study; IgG subclass concentrations; and ITP-specific autoantibody [redacted] in serum over time. Other immunological variables to be evaluated are total IgA, IgE, and IgM levels; serum (C3 and C4) and plasma (C3a and C5a) complement levels; ADA status (negative/positive) and relative mass units; exploratory safety biomarkers [redacted] and B cell activating factor (BAFF) levels; B and T lymphocytes; and cytokines (for subjects experiencing infusion reactions).

Change #13

Section 1 SUMMARY

Exploratory genomic analyses substudy details are added as follows:

During this study, subjects will also have the option of providing additional informed consent for exploratory deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) (ie, messenger RNA [mRNA] and micro RNA [miRNA]) analyses. Participation in this additional portion of the study is optional and does not preclude subject's eligibility for participation in the main study. The additional genomic samples must not be collected if the subject has not consented to participate in this exploratory genomic substudy.

Change #14

Section 1 SUMMARY

New paragraph added at the end of the summary:

Prior to this amendment, a protocol amendment 2 with a dose arm 4mg/kg twice weekly was planned, however the corresponding protocol amendment 2 was not implemented. These changes are highlighted in Section 18.8.

Change #15

Section 1 INTRODUCTION

Paragraph #11:

In 4-week and 13-week toxicity studies with 8-week, treatment-free recovery periods in Cynomolgus monkeys, UCB7665 induced the expected large decreases (75% to 90%) in plasma IgG in all animals which was maintained for the duration of both studies in the majority of the animals, with only minor effects on albumin levels. UCB7665 was well tolerated at the highest dose levels tested of UCB7665 150mg/kg sc and UCB7665 150mg/kg iv administered every 3 days (the no observed adverse effect level [NOAEL]).

Has been changed to:

In 4-week and 13-week toxicity studies with 8-week, treatment-free recovery periods in Cynomolgus monkeys, UCB7665 induced the expected large decreases (75% to 90%) in plasma IgG in all animals which was maintained for the duration of both studies in the majority of the animals, with only minor effects on albumin levels. UCB7665 was well tolerated at the highest dose levels tested of UCB7665 150mg/kg sc and UCB7665 150mg/kg iv administered every 3 days (there was no observed adverse effect level [NOAEL]).

Change #16

Section 1 INTRODUCTION

Paragraph #12:

Further information on the PK, PD, and safety profiles for UCB7665 from nonclinical studies, and preliminary safety information from clinical studies, can be obtained from the current version of the UCB7665 Investigator's Brochure.

Has been changed to:

Further information on the PK, PD, and safety profiles for UCB7665 from nonclinical studies, and preliminary safety information from clinical studies (including data from this study), can be obtained from the current version of the UCB7665 Investigator's Brochure.

Change #17

Section 1 INTRODUCTION

Paragraph #13:

Exploratory genomic analyses substudy details are added as follows:

Subjects will also have the option of providing additional informed consent for exploratory DNA and RNA (mRNA and miRNA) analyses as described in Section 5.1.1.

Change #18

Section 3.3 Exploratory objectives

Two additional NEW bullets:

- To evaluate the genomic components of ITP to understand the molecular etiology, progression, and treatment of the disease, applicable only for subjects consenting to participate in the optional genomic analyses substudy.
- [redacted]

Change #19

Section 4 Study Variables sub-sections were renumbered

4.1 Safety variables

4.1.1. Primary safety variables

4.1.2 Other saftey variables

4.2 Efficacy variables

4.3 Pharmacokinetic and pharmacodynamic variables

4.3.1 Pharmacokinetic variable

4.3.2 Pharmacodynamic variables

4.4 Other immunological variables

Has been changed to:

4.1 Primary variable

4.2 Others and exploratory variables

4.2.1 Safety variables

4.2.2 Efficacy variables

4.2.3 Pharmacokinetic variables

4.2.4 Pharmacodynamic variables

4.2.5 Other immunological variables

Change #20

Section 4.2.2 Efficacy variables

Additional efficacy variables listed as follows:

- Baseline-corrected AUEC for platelet count
- Clinical Response: platelet count $\geq 30x10^9$/L with at least 2-fold increase from Baseline value and absence of bleeding

- Time to Clinical Response: time from starting treatment to achievement of Clinical Response
- Duration of Clinical Response: measured from achievement of Clinical Response to loss of Clinical Response (loss of Clinical Response defined as platelet count $<30x10^9$/L or less than 2-fold increase from Baseline platelet count or presence of bleeding)
- Complete Clinical Response: platelet count $\geq100x10^9$/L and absence of bleeding
- Time to Complete Clinical Response: time from starting treatment to achievement of Complete Clinical Response
- Duration of Complete Clinical Response: measured from achievement of Complete Clinical Response to loss of Complete Clinical Response (loss of Complete Clinical Response defined as platelet count $<100x10^9$/L or presence of bleeding)
- No Clinical Response: platelet count $<30x10^9$/L or less than 2-fold increase from Baseline or presence of bleeding

Change #21

Section 4.3.2 Pharmacodynamic variables (now Section 4.2.4)

The following variable was deleted:

- The value and change from Baseline in endogenous IgG concentrations will be measured by IgG depletion assay

Change #22

Section 4.3.2 Pharmacodynamic variables (now Section 4.2.4)

- Change from Baseline in serum biomarkers [redacted] over time

Has been changed to:

Now moved to Section 4.2.1 Safety variables:

- Change from Baseline in exploratory safety biomarkers over time

Change #23

Section 4.4 Other immunological variables (now Section 4.2.5)

- Change from Baseline in serum biomarkers [redacted] over time

Has been changed to:

- Change from Baseline in exploratory biomarkers relating to mechanism of action, disease activity, treatment response, and clinical outcome

Change #24

Section 4.4 Other immunological variables (now Section 4.2.5)

Additional immunological variable listed as follows:

- Lymphocyte counts (B and T)

Change #25

Section 4.2.5 Other immunological variables

The following text was deleted:

Cytokine samples will be taken at Baseline for all subjects and at subsequent visits only if the subject experiences infusion reactions.

Change #26

Section 5.1 Study description

Paragraphs #1, #2 and #3:

This is a Phase 2, multicenter, open-label, multiple-dose, 2-dose-arm study to evaluate the safety, tolerability, and efficacy of UCB7665 in subjects with primary persistent or chronic ITP.

Dose Arm 1: UCB7665 4mg/kg sc (5 doses at an interval of 1 week)

Dose Arm 2: UCB7665 7mg/kg sc (3 doses at an interval of 1 week)

The DMC will monitor emergent safety data during the study. Refer to Section 14.7 for details.

The maximum duration of the study per subject is approximately 16 weeks, consisting of a Screening Period (1 to 28 days), a Dosing Period of 2 or 4 weeks, and an Observation Period of 8 weeks.

Has been changed to:

This is a Phase 2, multicenter, open-label, multiple-dose, multiple-arm study to evaluate the safety, tolerability, and efficacy of UCB7665 in subjects with primary persistent or chronic ITP.

Dose Arm 1 (15 subjects): UCB7665 4mg/kg sc (5 doses at an interval of 1 week)

Dose Arm 2 (15 subjects): UCB7665 7mg/kg sc (3 doses at an interval of 1 week)

Dose Arm 3 (6 to 12 subjects): UCB7665 10mg/kg sc (2 doses at an interval of 1 week)

Dose Arm 4 (6 to 12 subjects): UCB7665 15mg/kg sc (1 dose)

Dose Arm 5 (6 to 12 subjects): UCB7665 20mg/kg sc (1 dose)

The maximum duration of the study per subject is approximately 16 weeks, consisting of a Screening Period (1 to 28 days), a Dosing Period of 1 to 4 weeks, and an Observation Period of 8 weeks.

Change #27

- Section 5.1 Study description

Paragraph #5:

Dosing Period: The first 6 subjects in the study will receive UCB7665 4mg/kg. These subjects in the Dose Arm 1 will not be randomized. While recruitment is still ongoing, safety data for the first 3 subjects up to 7 days after the final dose of the third subject will be reviewed by the DMC. During a second DMC meeting, all available safety data up to cut off date defined as 7 days after the final dose of the sixth subject will be reviewed. During these reviews recruitment in the dose arm will not be stopped. Following this review, the DMC will make a decision on whether to

open Dose Arm 2 for enrollment. Once the DMC has approved opening of Dose Arm 2 for enrollment, subjects will subsequently be randomized to 1 of the 2 dose arms using IXRS. If the new dose arm will be initiated and if the UCB7665 4mg/kg arm will be continued, new subjects will be randomized to 1 of the 2 dose arms in an allocation ratio of 1:1 (Once 15 subjects are in the 4mg/kg group, the remaining subjects will not be randomized. They will be allocated to the 7mg/kg group.).

Has been changed to:

Dosing Period: The first 6 subjects in the study will receive UCB7665 4mg/kg. These subjects in the Dose Arm 1 will not be randomized. While recruitment is still ongoing, safety data for the first 3 subjects up to 7 days after the last dose of the third subject in Dose Arm 1 will be reviewed by the DMC. During a second DMC meeting, all available safety data up to cut off date defined as 7 days after the last dose of the sixth subject in Dose Arm 1 will be reviewed. During these reviews recruitment in the dose arm will not be stopped. Following this review, the DMC will make a decision on whether to open Dose Arm 2 for enrollment. Once DMC has advocated the initiation of Dose Arm 2, the subsequent subjects will be randomly assigned in 1:1 ratio to either Dose Arm 1 or Dose Arm 2 using an IXRS. Once 15 subjects are enrolled in the Dose Arm 1, the remaining subjects will be enrolled in Dose Arm 2.

After the safety data review of at least 6 subjects in Dose Arm 2 is done, the DMC will make a recommendation on whether to open Dose Arm 3 for enrollment. Once the DMC has advocated the initiation of Dose Arm 3 and the enrollment of 15 subjects in Dose Arm 2 has been completed, the subsequent subjects will be assigned to Dose Arm 3 only. After every third subject has been enrolled, the DMC will review all available safety data up to cut off date defined as 7 days after the dosing. Depending on the emerging safety data of 6 subjects in Dose Arm 3, the DMC will recommend whether to open Dose Arm 4 for enrollment or to include additional subjects in Dose Arm 3. If applicable, the latter option will be done stepwise in groups of 3 subjects. A maximum, 12 subjects will be enrolled in Dose Arm 3. The DMC will recommend to open Dose Arm 4 for enrollment in a subsequent DMC meeting, if applicable.

Once the DMC has advocated the initiation of Dose Arm 4, the enrollment of Dose Arm 3 will be closed and all subsequent subjects will be assigned to Dose Arm 4. After every third subject is enrolled, the DMC will review all available safety data up to the cutoff date defined as 7 days after the dosing. Depending on the emerging safety data of 6 subjects in Dose Arm 4, the DMC will recommend to include additional subjects in Dose Arm 4 or not. Subjects will be added stepwise in groups of 3, if applicable. A maximum of 12 subjects may be enrolled in Dose Arm 4. The DMC will recommend to open Dose Arm 5 for enrollment in a subsequent DMC meeting, if applicable.

Once the DMC has advocated the initiation of Dose Arm 5, the enrollment of Dose Arm 4 will be closed and all subsequent subjects will be assigned to Dose Arm 5. After every third subject is enrolled, the DMC will review all available safety data up to the cutoff date defined as 7 days after the dosing. Depending on the emerging safety data of 6 subjects in Dose Arm 5, the DMC will recommend to include additional subjects in Dose Arm 5 or not. Subjects will be added stepwise in groups of 3, if applicable. A maximum of 12 subjects may be enrolled in Dose Arm 5.

Change #28

Section 5.1 Study description

Paragraph #5:

At least 4 interim analyses will be performed. Based on the interim analysis, the DMC will assess the safety of UCB7665, determine whether to initiate the UCB7665 7mg/kg dose arm and may decide to adapt the dose regimen. Planned dosing may be discontinued for all subjects on a dose arm (see Section 6.5). Refer to Section 14.7 for details.

Has been changed to:

At least 11 interim analyses will be performed. Based on the interim analyses, the DMC will assess the safety of UCB7665, determine whether to initiate subsequent dose arms and may decide to adapt the dose regimen. Planned dosing may be discontinued for all subjects in a dose arm (see Section 6.5). Refer to Section 14.7 for details.

Change #29

Paragraph #6:

In case the DMC recommends reducing the number of doses (infusions) for either the UCB7665 4mg/kg dose or UCB7665 7mg/kg dose based on review of safety data, then the additional dose arms receiving a reduced number of doses will be considered as additional new dose arms for the study.

Has been changed to:

In case the DMC recommends reducing the number of doses (infusions) for any of the predefined dose arms (as applicable) based on review of safety data, then the additional dose arms receiving a reduced number of doses will be considered as additional new dose arms for the study.

Change #30

Paragraph #7:

Observation Period: Following the final dose, a visit will be scheduled 3 days postdose and weekly thereafter for 8 weeks to collect safety and efficacy data.

Has been changed to:

Observation Period: Following the last dose (or only dose administration for Dose Arms 4 and 5), a visit will be scheduled 3 days postdose and weekly thereafter for 8 weeks to collect safety and efficacy data.

Change #31

NEW Section 5.1.1 Exploratory genomic analyses

During this study, subjects will also have the option of providing additional informed consent for exploratory DNA and RNA analyses. Participation in this additional portion of the study is optional and does not preclude subject's eligibility for participation in the main study. The additional genomic samples must not be collected if the subject has not consented to participate in this exploratory genomic substudy.

Once subject provides consent, through a separate informed consent form, blood samples will be drawn as follows:

For DNA: Blood samples will be collected at Baseline (Visit 2) for all dose arms. Subsequent blood sample will be collected prior to the last dose (ie, Visit 7 for Dose Arm 1, Visit 5 for Dose Arm 2, and Visit 4 for Dose Arm 3).

For RNA: Blood samples will be collected at the following time points for different dose arms:

- Dose Arm 1: Baseline (Visit 2), 3 days after dose 1 (Visit 3), prior to the last dose (Visit 7), and End of Study Visit (Visit 15).
- Dose Arm 2: Baseline (Visit 2), 3 days after dose 1 (Visit 3), prior to the last dose (Visit 5), and End of Study Visit (Visit 13).
- Dose Arm 3: Baseline (Visit 2), 3 days after dose 1 (Visit 3), prior to the last dose (Visit 4), and End of Study Visit (Visit 12).
- Dose Arm 4: Baseline (Visit 2), 3 days after dosing (Visit 3) and End of Study Visit (Visit 10).
- Dose Arm 5: Baseline (Visit 2), 3 days after dosing (Visit 3) and End of Study Visit (Visit 10).

For each DNA blood sample a volume of 6mL whole blood is needed and for each RNA sample a volume of 2.5mL whole blood is needed.

Failure to provide consent to participate in this substudy will not impact subject's eligibility to participate in the main study.

Any exploratory biomarker or genomic analysis will only ever be related to the exploration of the underlying causes of ITP in patients, related biology, and drug response. Justification for additional genomic analyses is detailed in Section 5.4.6.

Details on the collection, storage, preparation, and shipping of samples will be presented in the Laboratory Manual provided separately.

Any results from this analysis will be reported separately and will not form a part of the main clinical study report.

Change #32

Section 5.1.3 Planned number of subjects and sites

A total of 30 subjects are planned to enter the Dosing Period in the study. This number should allow for an appropriate assessment of the safety and give information on efficacy of the treatment for planning of potential future studies. To achieve the required number of eligible subjects to enter the Dosing Period, it is anticipated that 40 subjects will need to be screened. These subjects will be enrolled at approximately 25 sites. First subject first visit is planned for Q1 2016, last subject last visit for Q3 2017.

Has been changed to:

A total of up to approximately 48 to 66 subjects are planned to enter the Dosing Periods in the study (15 subjects in each of Dose Arms 1 and 2, and 6 to 12 subjects in Dose Arms 3, 4, and 5).

To achieve the required number of eligible subjects to enter the Dosing Period, it is anticipated that approximately 90 subjects will need to be screened. These subjects will be enrolled at approximately 45 sites. First subject first visit is planned for Q1 2016, last subject last visit for Q2 2018.

Change #33

Section 5.2 Schedule of study assessments

Table 5–1 presents the tabular scheme of study assessments for UCB7665 4mg/kg dose arm and Table 5–2 presents the tabular scheme of study assessments for UCB7665 7mg/kg dose arm. Table 5–3 presents the assessments to be performed on dosing days.

Has been changed to:

Table 5–1 presents the tabular scheme of study assessments for the weekly UCB7665 4mg/kg dose arm (Dose Arm 1), Table 5–2 presents the tabular scheme of study assessments for the weekly UCB7665 7mg/kg dose arm (Dose Arm 2), Table 5-3 presents the tabular scheme of study assessments for the weekly UCB7665 10mg/kg dose arm (Dose Arm 3), Table 5-4 presents the tabular scheme of study assessments for the one dose of UCB7665 15mg/kg, Table 5-5 presents the tabular scheme of study assessments for the one dose of UCB7665 20mg/kg and Table 5–6 presents the assessments to be performed on dosing days.

Change #34

Section 5.2 Schedule of study assessments

Table 5–1: Schedule of assessments for the UCB7665 4mg/kg dose arm

Assessments		Screening Period	Dosing Period						Observation Period							
			Dose 1		Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a] BL Visit	3	4[a]	5[a]	6[a]	7[a]	8	9	10[b]	11	12[b]	13	14[b]	15 EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	22	29	32	36	43	50	57	64	71	85
	Week		1	1	2	3	4	5	5	6	7	8	9	10	11	13
	Visit Window			±1d	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Written informed consent		X														
Demographic data		X														
Verification of inclusion/exclusion criteria		X	X													
Platelets for inclusion/ withdrawal check (local laboratory)[f]			X		X	X	X	X								
Randomization[g]			X													
Withdrawal criteria[h]			X	X	X	X	X	X								
General medical/procedures history		X														
ITP history		X														

Table 5–1: Schedule of assessments for the UCB7665 4mg/kg dose arm

Assessments		Screening Period	Dosing Period						Observation Period							
			Dose 1		Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a] BL Visit	3	4[a]	5[a]	6[a]	7[a]	8	9	10[b]	11	12[b]	13	14[b]	15 EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	22	29	32	36	43	50	57	64	71	85
	Week		1	1	2	3	4	5	5	6	7	8	9	10	11	13
	Visit Window			±1d	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Prior and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medical procedures			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight		X														X
Height		X														
Recording of AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[i]		X	X		X	X	X	X		X		X		X		X
12-lead ECG		X	X		X	X	X	X		X						X
Karnofsky Performance Status		X														
Laboratory parameters (hematology, chemistry, urinalysis)		X[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 5–1: Schedule of assessments for the UCB7665 4mg/kg dose arm

Assessments		Screening Period	Dosing Period						Observation Period							
			Dose 1		Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a]	3	4[a]	5[a]	6[a]	7[a]	8	9	10[b]	11	12[b]	13	14[b]	15
			BL Visit													EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	22	29	32	36	43	50	57	64	71	85
	Week		1	1	2	3	4	5	5	6	7	8	9	10	11	13
	Visit Window			±1d	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Serology test for HIV, hepatitis B, and hepatitis C		X														
Blood sample for cytokines			X	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]
Serum pregnancy test		X														
Urine pregnancy test			X		X	X	X	X								X
Call to IXRS for treatment kit number			X		X	X	X	X								
Administration of IMP			X		X	X	X	X								
Blood sampling for plasma concentration of UCB7665			X	X	X	X	X	X	X	X						
Anti-UCB7665 antibodies/IgG depletion assay			X	X	X	X	X	X	X	X	X		X		X	X

Table 5–1: Schedule of assessments for the UCB7665 4mg/kg dose arm

Assessments		Screening Period	Dosing Period						Observation Period							
			Dose 1		Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a]	3	4[a]	5[a]	6[a]	7[a]	8	9	10[b]	11	12[b]	13	14[b]	15
			BL Visit													EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	22	29	32	36	43	50	57	64	71	85
	Week		1	1	2	3	4	5	5	6	7	8	9	10	11	13
	Visit Window			±1d	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Serum complements (C3 and C4) and plasma complements (C3a and C5a)			X			X			X				X			
Serum biomarkers [redacted]			X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum biomarkers [redacted]			X	X	X	X	X	X								
Serum BAFF levels			X		X	X	X	X			X				X	
Immunoglobulins (total IgG, IgG subclasses)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IgA, IgM, IgE[l]			X					X		X					X	
ITP-specific autoantibodies[m]			X							X						X
ITP bleeding scale		X	X		X	X	X	X		X		X		X		X
NFI-MS			X							X		X		X		X

Table 5–1: Schedule of assessments for the UCB7665 4mg/kg dose arm

Assessments		Screening Period	Dosing Period						Observation Period							
			Dose 1		Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a]	3	4[a]	5[a]	6[a]	7[a]	8	9	10[b]	11	12[b]	13	14[b]	15
			BL Visit													EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	22	29	32	36	43	50	57	64	71	85
	Week		1	1	2	3	4	5	5	6	7	8	9	10	11	13
	Visit Window			±1d	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Headache questionnaire[n]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject exit interview[o]																X

AE=adverse event; BAFF=B cell activating factor; BL=Baseline; CSF=cerebrospinal fluid; CT=computed tomography; d=day(s); DMC=Data Monitoring Committee; ECG=electrocardiogram; EOS=End of Study; EW=Early Withdrawal; [redacted]; HIV=human immunodeficiency virus; Ig=immunoglobulin; IMP=investigational medicinal product; ITP=immune thrombocytopenia; IXRS= interactive voice/web response system; LP=lumbar puncture; MRI=magnetic resonance imaging; NFI-MS=Neurological Fatigue Index for multiple sclerosis; [redacted]

[a] Frequency of assessments on dosing days is detailed in Table 5–3.

[b] Visits 10, 12, and 14 can be performed at home with a healthcare professional visiting the subject at his/her home.

[c] The End-of-Study Visit is 8 weeks following the final dose.

[d] A visit window of ±2 days is allowed for the dosing visits. The visit window of ±2 days is relative to the first dosing visit date. However, there should be a minimum interval of 5 days and maximum interval of 9 days as compared to the previous dose.

[e] The visit windows in the Observation Period are relative to the final dosing visit date.

[f] Prior to dosing at Visit 2, 2 platelet samples will be taken. One sample will be analyzed locally and the value will be used to check inclusion criteria. The other platelet sample will be sent to the central laboratory. At subsequent dosing visits, a platelet sample will be assessed locally prior to dosing to evaluate withdrawal criterion of platelet count >$350x10^9$/L.

[g] The first 6 subjects will be enrolled in the Dose Arm 1 group only. Safety data for these 6 subjects up to 7 days after the last dose will be reviewed by the DMC. Following this review the DMC will make a decision to open Dose Arm 2 for enrollment. If Dose Arm 2 is opened, subjects subsequently enrolled will be randomly assigned subsequently to 1 of the 2 dose arms using an IXRS until 15 subjects are in Dose Arm 1.

[h] Subjects can withdraw at any time during the study, based on the criteria in Section 6.4.

[i] A complete physical examination will be performed at Screening and EOS/EW Visit. At all other visits (where physical examination is performed), an abbreviated physical examination will be conducted.

[j] At the Screening Visit, 2 separate blood samples will be obtained on the same day for evaluation of platelet count.

[k] Blood sample for cytokines will be obtained only in case of infusion reactions.

[l] In case the number of infusions to be administered are reduced after DMC review of safety data, then the scheduled Visit 7 assessment for IgA, IgM, and IgE will be performed earlier at the last dosing visit.

[m] [redacted]

[n] This assessment is applicable only to subjects experiencing severe headaches and will be performed daily until resolution (ie, if headache becomes moderate or mild, normal collection of AEs should apply); this assessment will be followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

[o] A semi-structured interview guide will be used and the interview will be recorded. In case of early withdrawal from the study, the subject exit interview should be performed at End-of-Study Visit only.

Table 5–2: Schedule of assessments for the UCB7665 7mg/kg dose arm

Assessments		**Screening Period**	**Dosing Period**				**Observation Period**							
			Dose 1		**Dose 2**	**Dose 3**								
	Visit	**1**	**2[a]**	**3**	**4[a]**	**5[a]**	**6**	**7**	**8[b]**	**9**	**10[b]**	**11**	**12[b]**	**13**
			BL Visit											**EOS/ EW[c]**
	Day	**-28 to -1**	**1**	**4**	**8**	**15**	**18**	**22**	**29**	**36**	**43**	**50**	**57**	**71**
	Week		**1**	**1**	**2**	**3**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**11**
	Visit Window			**±1d**	**±2d[d]**	**±2d[d]**	**±1d**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**
Written informed consent		X												
Demographic data		X												
Verification of inclusion/exclusion criteria		X	X											
Platelets for inclusion/withdrawal check (local laboratory) [f]			X		X	X								

Table 5–2: Schedule of assessments for the UCB7665 7mg/kg dose arm

Assessments		Screening Period	Dosing Period				Observation Period							
			Dose 1		Dose 2	Dose 3								
	Visit	**1**	**2**[a]	**3**	**4**[a]	**5**[a]	**6**	**7**	**8**[b]	**9**	**10**[b]	**11**	**12**[b]	**13**
			BL Visit											**EOS/ EW**[c]
	Day	**-28 to -1**	**1**	**4**	**8**	**15**	**18**	**22**	**29**	**36**	**43**	**50**	**57**	**71**
	Week		**1**	**1**	**2**	**3**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**11**
	Visit Window			**±1d**	**±2d**[d]	**±2d**[d]	**±1d**	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]
Randomization[g]			X											
Withdrawal criteria[h]			X	X	X	X								
General medical/procedures history		X												
ITP history		X												
Prior and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medical procedures			X	X	X	X	X	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight		X												X
Height		X												
Recording of AEs		X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[i]		X	X		X	X		X		X		X		X
12-lead ECG		X	X		X	X		X						X
Karnofsky Performance Status		X												
Laboratory parameters (hematology, chemistry, urinalysis)		X[j]	X	X	X	X	X	X	X	X	X	X	X	X

Table 5–2: Schedule of assessments for the UCB7665 7mg/kg dose arm

Assessments		Screening Period	Dosing Period				Observation Period							
			Dose 1		Dose 2	Dose 3								
	Visit	**1**	**2[a]**	**3**	**4[a]**	**5[a]**	**6**	**7**	**8[b]**	**9**	**10[b]**	**11**	**12[b]**	**13**
			BL Visit											**EOS/ EW[c]**
	Day	**-28 to -1**	**1**	**4**	**8**	**15**	**18**	**22**	**29**	**36**	**43**	**50**	**57**	**71**
	Week		**1**	**1**	**2**	**3**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**11**
	Visit Window			**±1d**	**±2d[d]**	**±2d[d]**	**±1d**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**
Serology test for HIV, hepatitis B, and hepatitis C		X												
Blood sample for cytokines			X	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]
Serum pregnancy test		X												
Urine pregnancy test			X		X	X								X
Call to IXRS for treatment kit number			X		X	X								
Administration of IMP			X		X	X								
Blood sampling for plasma concentration of UCB7665			X	X	X	X	X	X						
Anti-UCB7665 antibodies/IgG depletion assay			X	X	X	X	X	X	X		X		X	X
Serum complements (C3 and C4) and plasma complements (C3a and C5a)			X			X	X				X			
Serum biomarkers [redacted]			X	X	X	X	X	X	X	X	X	X	X	
Serum biomarkers [redacted]			X	X	X	X								

Table 5–2: Schedule of assessments for the UCB7665 7mg/kg dose arm

Assessments		Screening Period	Dosing Period				Observation Period							
			Dose 1		Dose 2	Dose 3								
	Visit	**1**	**2[a]**	**3**	**4[a]**	**5[a]**	**6**	**7**	**8[b]**	**9**	**10[b]**	**11**	**12[b]**	**13**
			BL Visit											**EOS/ EW[c]**
	Day	**-28 to -1**	**1**	**4**	**8**	**15**	**18**	**22**	**29**	**36**	**43**	**50**	**57**	**71**
	Week		**1**	**1**	**2**	**3**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**11**
	Visit Window			**±1d**	**±2d[d]**	**±2d[d]**	**±1d**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**
Serum BAFF levels			X		X	X			X				X	
Immunoglobulins (total IgG, IgG subclasses)		X	X	X	X	X	X	X	X	X	X	X	X	X
IgA, IgM, IgE[l]			X			X		X					X	
ITP-specific autoantibodies[m]			X					X						X
ITP bleeding scale		X	X		X	X		X		X		X		X
NFI-MS			X					X		X		X		X
Headache questionnaire[n]			X	X	X	X	X	X	X	X	X	X	X	X
Subject exit interview[o]														X

AE=adverse event; BAFF=B cell activating factor; BL=baseline; CSF=cerebrospinal fluid CT=computed tomography; d=day(s); DMC=Data Monitoring Committee; ECG=electrocardiogram; EOS=End of Study; EW=Early Withdrawal; [redacted] HIV=human immunodeficiency virus; Ig=immunoglobulin; IMP=investigational medicinal product; ITP=immune thrombocytopenia; IXRS= interactive voice/web response system; LP=lumbar puncture; MRI=magnetic resonance imaging; NFI-MS=Neurological Fatigue Index for multiple sclerosis; [redacted]

[a] Frequency of assessments on dosing days is detailed in Table 5–3.

[b] Visits 8, 10, and 12 can be performed at home with a healthcare professional visiting the subject at his/her home.

[c] The End-of-Study Visit is 8 weeks following the final dose.

[d] A visit window of ±2 days is allowed for the dosing visits. The visit window of ±2 days is relative to the first dosing visit date. However, there should be a minimum interval of 5 days and maximum interval of 9 days as compared to the previous dose.

[e] The visit windows in the Observation Period are relative to the final dosing visit date.

[f] Prior to dosing at Visit 2, 2 platelet samples will be taken. One sample will be analyzed locally and the value will be used to check inclusion criteria. The other platelet sample will be sent to the central laboratory. At subsequent dosing visits, a platelet sample will be assessed locally prior to dosing to evaluate withdrawal criterion of platelet count >350x10^9/L.

[g] The first 6 subjects will be enrolled in the Dose Arm 1 group. Safety data for these 6 subjects up to 7 days after the last dose will be reviewed by the DMC. Following this review the DMC will make a decision to open Dose Arm 2 for enrollment. If Dose Arm 2 is opened, subjects subsequently enrolled will be randomly assigned to one of the dose arms using an IXRS until 15 subjects are in Dose Arm 1.

[h] Subjects can withdraw at any time during the study, based on the criteria in Section 6.4.

[i] A complete physical examination will be performed at Screening and EOS/EW Visit. At all other visits (where physical examination is performed), an abbreviated physical examination will be conducted.

[j] At the Screening Visit, 2 separate blood samples will be obtained on the same day for evaluation of platelet count.

[k] Blood sample for cytokines will be obtained only in case of infusion reactions.

[l] In case the number of infusions to be administered are reduced after DMC review of safety data, then the scheduled Visit 5 assessment for IgA, IgM, and IgE will be performed earlier at the last dosing visit.

[m] [redacted]

[n] This assessment is applicable only to subjects experiencing severe headaches and will be performed daily until resolution (ie, if headache becomes moderate or mild, normal collection of AEs should apply); this assessment will be followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

[o] A semi-structured interview guide will be used and the interview will be recorded. In case of early withdrawal from the study, the subject exit interview should be performed at End-of-Study Visit only.

Has been changed to:

Table 5–1: Schedule of assessments for the UCB7665 4mg/kg weekly dose arm (Dose Arm 1)

Assessments		Screening Period	Dosing Period						Observation Period							
			Dose 1		Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a]	3	4[a]	5[a]	6[a]	7[a]	8	9	10[b]	11	12[b]	13	14[b]	15
			BL Visit													EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	22	29	32	36	43	50	57	64	71	85
	Week		1	1	2	3	4	5	5	6	7	8	9	10	11	13
	Visit Window			±1d	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Written informed consent[f]		X														
Demographic data		X														
Verification of inclusion/exclusion criteria		X	X													
Platelets for inclusion/ withdrawal check (local laboratory)[g]			X		X	X	X	X								
Randomization[h]			X													
Withdrawal criteria[i]			X	X	X	X	X	X								
General medical/procedures history		X														
ITP history		X														
Prior and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 5–1: Schedule of assessments for the UCB7665 4mg/kg weekly dose arm (Dose Arm 1)

Assessments		Screening Period	Dosing Period						Observation Period							
			Dose 1		Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a] BL Visit	3	4[a]	5[a]	6[a]	7[a]	8	9	10[b]	11	12[b]	13	14[b]	15 EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	22	29	32	36	43	50	57	64	71	85
	Week		1	1	2	3	4	5	5	6	7	8	9	10	11	13
	Visit Window			±1d	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Concomitant medical procedures			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight		X														X
Height		X														
Recording of AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[j]		X	X		X	X	X	X		X		X		X		X
12-lead ECG[k]		X	X		X	X	X	X		X						X
Karnofsky Performance Status		X														
Laboratory parameters (hematology, chemistry, urinalysis)		X[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serology test for HIV, hepatitis B, and hepatitis C		X														
IGRA TB test[m]		X														

Table 5–1: Schedule of assessments for the UCB7665 4mg/kg weekly dose arm (Dose Arm 1)

Assessments		Screening Period	Dosing Period						Observation Period							
			Dose 1		Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a]	3	4[a]	5[a]	6[a]	7[a]	8	9	10[b]	11	12[b]	13	14[b]	15
			BL Visit													EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	22	29	32	36	43	50	57	64	71	85
	Week		1	1	2	3	4	5	5	6	7	8	9	10	11	13
	Visit Window			±1d	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
TB signs and symptoms questionnaire		X														X
Blood sample for cytokines			X	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]
Whole blood sample for DNA (optional)			X					X								
Whole blood sample for RNA (optional)			X	X				X								X
Serum pregnancy test		X														
Urine pregnancy test			X		X	X	X	X								X
Call to IXRS for treatment kit number			X		X	X	X	X								
Administration of IMP			X		X	X	X	X								
Blood sampling for plasma concentration of UCB7665			X	X	X	X	X	X	X	X						
Anti-UCB7665 antibodies			X	X	X	X	X	X	X	X	X		X		X	X

Table 5–1: Schedule of assessments for the UCB7665 4mg/kg weekly dose arm (Dose Arm 1)

Assessments		Screening Period	Dosing Period						Observation Period							
			Dose 1		Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a]	3	4[a]	5[a]	6[a]	7[a]	8	9	10[b]	11	12[b]	13	14[b]	15
			BL Visit													EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	22	29	32	36	43	50	57	64	71	85
	Week		1	1	2	3	4	5	5	6	7	8	9	10	11	13
	Visit Window			±1d	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Serum complements (C3 and C4) and plasma complements (C3a and C5a)			X			X			X				X			
Blood collection for exploratory safety biomarkers			X	X[o]	X	X	X	X	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	
Serum BAFF levels			X		X	X	X	X			X				X	
Blood collection for exploratory biomarker analysis			X		X	X	X	X			X				X	
Immunoglobulins (total IgG, IgG subclasses)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IgA, IgM, IgE[p]			X					X		X					X	
ITP-specific autoantibodies [q]			X							X						X
ITP bleeding scale		X	X		X	X	X	X		X		X		X		X
NFI-MS			X							X		X		X		X

Table 5–1: Schedule of assessments for the UCB7665 4mg/kg weekly dose arm (Dose Arm 1)

Assessments		Screening Period	Dosing Period						Observation Period							
			Dose 1		Dose 2	Dose 3	Dose 4	Dose 5								
	Visit	1	2[a] BL Visit	3	4[a]	5[a]	6[a]	7[a]	8	9	10[b]	11	12[b]	13	14[b]	15 EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	22	29	32	36	43	50	57	64	71	85
	Week		1	1	2	3	4	5	5	6	7	8	9	10	11	13
	Visit Window			±1d	±2d[d]	±2d[d]	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Headache questionnaire[r]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject exit interview[s]																X

AE=adverse event; BAFF=B cell activating factor; BL=Baseline; CSF=cerebrospinal fluid; CT=computed tomography; d=day(s); DMC=Data Monitoring; DNA=deoxyribonucleic acid; Committee; ECG=electrocardiogram; EOS=End of Study; EW=Early Withdrawal; [redacted] HIV=human immunodeficiency virus; Ig=immunoglobulin; IMP=investigational medicinal product; ITP=immune thrombocytopenia; IXRS= interactive voice/web response system; LP=lumbar puncture; RNA=ribonucleic acid; MRI=magnetic resonance imaging; NFI-MS=Neurological Fatigue Index for multiple sclerosis; TB=tuberculosis.

[a] Frequency of assessments on dosing days is detailed in Table 5–6.

[b] Visits 10, 12, and 14 can be performed at home with a healthcare professional visiting the subject at his/her home.

[c] The End-of-Study Visit is 8 weeks following the final dose.

[d] A visit window of ±2 days is allowed for the dosing visits. The visit window of ±2 days is relative to the first dosing visit date. However, there should be a minimum interval of 5 days and maximum interval of 9 days as compared to the previous dose.

[e] The visit windows in the Observation Period are relative to the final dosing visit date.

[f] Additional informed consent is needed for participation in the exploratory genomic substudy. All samples will be collected prior to dosing with IMP.

[g] Prior to dosing at Visit 2, 2 platelet samples will be taken. One sample will be analyzed locally and the value will be used to check inclusion criteria. The other platelet sample will be sent to the central laboratory. At subsequent dosing visits, a platelet sample will be assessed locally prior to dosing to evaluate withdrawal criterion of platelet count >$350x10^9$/L.

[h] The first 6 subjects will be enrolled in the Dose Arm 1 group only. Safety data for these 6 subjects up to 7 days after the last dose will be reviewed by the DMC. Following this review the DMC will make a decision to open Dose Arm 2 for enrollment. If Dose Arm 2 is opened, the subsequent subjects will be randomly assigned in 1:1 ratio to either Dose Arm 1 or Dose Arm 2 using an IXRS. Once 15 subjects are enrolled in Dose Arm 1 and safety data review of at least 6 subjects in Dose Arm 2 is done, the subsequently enrolled subjects will be enrolled in Dose Arm 2 until a planned number of 15 subjects are enrolled.

[i] Subjects can withdraw at any time during the study, based on the criteria in Section 6.4.

[j] A complete physical examination will be performed at Screening and EOS/EW Visit. At all other visits (where physical examination is performed), an abbreviated physical examination will be conducted.

[k] The ECG should be performed in triplicate prior to blood collection for assessment of laboratory parameters. Three ECGs should be recorded in a time frame of 5 minutes with at least 1 minute difference, 1-2 minutes between the ECGs.

[l] At the Screening Visit, 2 separate blood samples will be obtained on the same day for evaluation of platelet count.

[m] The IGRA test will be performed in a central laboratory. Any IGRA-positive subjects will be withdrawn from the study.

[o] Exploratory safety biomarker samples to be obtained on dosing days for all subjects. During non-dosing visits and during the visits in the Observation Period, the samples should be obtained only from subjects experiencing severe headaches or GI disturbances (only in case of Adverse Events of Interest, see Section 12.4).

[n] Blood sample for cytokines will be obtained and analyzed at baseline for all subjects and at subsequent visits only in subjects with infusion reactions.

[p] In case the number of infusions to be administered are reduced after DMC review of safety data, then the scheduled Visit 7 assessment for IgA, IgM, and IgE will be performed earlier at the last dosing visit.

[q] [redacted]

[r] This assessment is applicable only to subjects experiencing severe headaches and will be performed daily until resolution (ie, if headache becomes moderate or mild, normal collection of AEs should apply); this assessment will be followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

[s] A semi-structured interview guide will be used and the interview will be recorded. In case of early withdrawal from the study, the subject exit interview should be performed at End-of-Study Visit only.

Table 5–2: Schedule of assessments for the UCB7665 7mg/kg weekly dose arm (Dose Arm 2)

Assessments		Screening Period	Dosing Period				Observation Period							
			Dose 1		Dose 2	Dose 3								
	Visit	**1**	**2**[a]	**3**	**4**[a]	**5**[a]	**6**	**7**	**8**[b]	**9**	**10**[b]	**11**	**12**[b]	**13**
			BL Visit											**EOS/ EW**[c]
	Day	**-28 to -1**	**1**	**4**	**8**	**15**	**18**	**22**	**29**	**36**	**43**	**50**	**57**	**71**
	Week		**1**	**1**	**2**	**3**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**11**
	Visit Window			**±1d**	**±2d**[d]	**±2d**[d]	**±1d**	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]
Written informed consent[f]		X												
Demographic data		X												
Verification of inclusion/exclusion criteria		X	X											
Platelets for inclusion/withdrawal check (local laboratory)[g]			X		X	X								
Randomization[h]			X											
Withdrawal criteria[i]			X	X	X	X								
General medical/procedures history		X												
ITP history		X												
Prior and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medical procedures			X	X	X	X	X	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight		X												X
Height		X												
Recording of AEs		X	X	X	X	X	X	X	X	X	X	X	X	X

Table 5–2: Schedule of assessments for the UCB7665 7mg/kg weekly dose arm (Dose Arm 2)

Assessments		Screening Period	Dosing Period				Observation Period							
			Dose 1		Dose 2	Dose 3								
	Visit	**1**	**2[a]**	**3**	**4[a]**	**5[a]**	**6**	**7**	**8[b]**	**9**	**10[b]**	**11**	**12[b]**	**13**
			BL Visit											**EOS/ EW[c]**
	Day	**-28 to -1**	**1**	**4**	**8**	**15**	**18**	**22**	**29**	**36**	**43**	**50**	**57**	**71**
	Week		**1**	**1**	**2**	**3**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**11**
	Visit Window			**±1d**	**±2d[d]**	**±2d[d]**	**±1d**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**
Physical examination[j]		X	X		X	X		X		X		X		X
12-lead ECG[k]		X	X		X	X		X						X
Karnofsky Performance Status		X												
Laboratory parameters (hematology, chemistry, urinalysis)		X[l]	X	X	X	X	X	X	X	X	X	X	X	X
Serology test for HIV, hepatitis B, and hepatitis C		X												
IGRA TB test[m]		X												
TB signs and symptoms questionnaire		X												X
Blood sample for cytokines			X	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]
Whole blood sample for DNA (optional)			X			X								
Whole blood sample for RNA (optional)			X	X		X								X
Serum pregnancy test		X												
Urine pregnancy test			X		X	X								X
Call to IXRS for treatment kit number			X		X	X								

Table 5–2: Schedule of assessments for the UCB7665 7mg/kg weekly dose arm (Dose Arm 2)

Assessments		Screening Period	Dosing Period				Observation Period							
			Dose 1		Dose 2	Dose 3								
	Visit	1	2[a]	3	4[a]	5[a]	6	7	8[b]	9	10[b]	11	12[b]	13
			BL Visit											EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	18	22	29	36	43	50	57	71
	Week		1	1	2	3	3	4	5	6	7	8	9	11
	Visit Window			±1d	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Administration of IMP			X		X	X								
Blood sampling for plasma concentration of UCB7665			X	X	X	X	X	X						
Anti-UCB7665 antibodies			X	X	X	X	X	X	X		X		X	X
Serum complements (C3 and C4) and plasma complements (C3a and C5a)			X			X	X				X			
Blood collection for exploratory safety biomarkers			X	X[o]	X	X	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	
Serum BAFF levels			X		X	X			X				X	
Blood collection for exploratory biomarker analysis			X		X	X			X				X	
Immunoglobulins (total IgG, IgG subclasses)		X	X	X	X	X	X	X	X	X	X	X	X	X
IgA, IgM, IgE[p]			X			X		X					X	
ITP-specific autoantibodies[q]			X					X						X
ITP bleeding scale		X	X		X	X		X		X		X		X
NFI-MS			X					X		X		X		X

Table 5–2: Schedule of assessments for the UCB7665 7mg/kg weekly dose arm (Dose Arm 2)

Assessments		Screening Period	Dosing Period				Observation Period							
			Dose 1		Dose 2	Dose 3								
	Visit	1	2[a] BL Visit	3	4[a]	5[a]	6	7	8[b]	9	10[b]	11	12[b]	13 EOS/ EW[c]
	Day	-28 to -1	1	4	8	15	18	22	29	36	43	50	57	71
	Week		1	1	2	3	3	4	5	6	7	8	9	11
	Visit Window			±1d	±2d[d]	±2d[d]	±1d	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Headache questionnaire[r]			X	X	X	X	X	X	X	X	X	X	X	X
Subject exit interview[s]														X

AE=adverse event; BAFF=B cell activating factor; BL=Baseline; CSF=cerebrospinal fluid; CT=computed tomography; d=day(s); DMC=Data Monitoring Committee; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EOS=End of Study; EW=Early Withdrawal; [redacted] HIV=human immunodeficiency virus; Ig=immunoglobulin; IGRA= interferon-gamma release assay; IMP=investigational medicinal product; ITP=immune thrombocytopenia; IXRS= interactive voice/web response system; LP=lumbar puncture; RNA=ribonucleic acid; MRI=magnetic resonance imaging; NFI-MS=Neurological Fatigue Index for multiple sclerosis; TB=tuberculosis.

[a] Frequency of assessments on dosing days is detailed in Table 5–6.

[b] Visits 8, 10, and 12 can be performed at home with a healthcare professional visiting the subject at his/her home.

[c] The End-of-Study Visit is 8 weeks following the last dose.

[d] A visit window of ±2 days is allowed for the dosing visits. The visit window of ±2 days is relative to the first dosing visit date. However, there should be a minimum interval of 5 days and maximum interval of 9 days as compared to the previous dose.

[e] The visit windows in the Observation Period are relative to the final dosing visit date.

[f] Additional informed consent is needed for participation in the exploratory genomic substudy. All samples will be collected prior to dosing with IMP.

[g] Prior to dosing at Visit 2, 2 platelet samples will be taken. One sample will be analyzed locally and the value will be used to check inclusion criteria. The other platelet sample will be sent to the central laboratory. At subsequent dosing visits, a platelet sample will be assessed locally prior to dosing to evaluate withdrawal criterion of platelet count >350x10^9/L.

[h] The first 6 subjects will be enrolled in the Dose Arm 1 group. Safety data for these 6 subjects up to 7 days after the last dose will be reviewed by the DMC. Following this review the DMC will make a decision to open Dose Arm 2 for enrollment. If Dose Arm 2 is opened, the subsequent subjects will be randomly assigned in 1:1 ratio to either Dose Arm 1 or Dose Arm 2 using an IXRS. Once 15 subjects are enrolled in Dose Arm 1 and safety data review of at least 6 subjects in Dose Arm 2 is done, the subsequently enrolled subjects will be enrolled in Dose Arm 2 until a planned number of 15 subjects are enrolled.

[i] Subjects can withdraw at any time during the study, based on the criteria in Section 6.4.

[j] A complete physical examination will be performed at Screening and EOS/EW Visit. At all other visits (where physical examination is performed), an abbreviated physical examination will be conducted.

[k] The ECG should be performed in triplicate prior to blood collection for assessment of laboratory parameters. Three ECGs should be recorded in a time frame of 5 minutes with at least 1 minute difference, 1-2 minutes between the ECGs.

[l] At the Screening Visit, 2 separate blood samples will be obtained on the same day for evaluation of platelet count.

[m] The IGRA test will be performed in a central laboratory. Any IGRA-positive subjects will be withdrawn from the study.

[n] Blood sample for cytokines will be obtained and analyzed at baseline for all subjects and at subsequent visits only in subjects with infusion reactions.

[o] Exploratory safety biomarker samples to be obtained on dosing days for all subjects. During non-dosing visits and during the visits in the Observation Period, the samples should be obtained only from subjects experiencing severe headaches or GI disturbances (only in case of Adverse Events of Interest, see Section 12.4).

[p] In case the number of infusions to be administered are reduced after DMC review of safety data, then the scheduled Visit 5 assessment for IgA, IgM, and IgE will be performed earlier at the last dosing visit.

[q] [redacted]

[r] This assessment is applicable only to subjects experiencing severe headaches and will be performed daily until resolution (ie, if headache becomes moderate or mild, normal collection of AEs should apply); this assessment will be followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

[s] A semi-structured interview guide will be used and the interview will be recorded. In case of early withdrawal from the study, the subject exit interview should be performed at End-of-Study Visit only.

Change #35

Section 5.2 Schedule of study assessments

NEW tables added:

Table 5-3: Schedule of assessments for the UCB7665 10mg/kg once weekly dose arm (Dose Arm 3)

Assessments		Screening Period	Dosing Period							Observation Period							
			Dose 1				Dose 2										
	Visit	1	2[a] BL Visit			3	4[a]			5	6	7[b]	8	9[b]	10	11[b]	12 EOS/EW[c]
	Telephone Contact			1	2[d]			3	4[d]								
	Day	-28 to -1	1	2	3	4	8	9	10	11	15	22	29	36	43	50	64

	Week		1	1	1	1	2	2	2	2	3	4	5	6	7	8	10
	Visit Window					**±1d**	**±2d**[e]			**±1d**[f]	**±2d**[f]	**±2d**[f]	**±2d**[f]	**±2d**[f]	**±2d**[f]	**±2d**[f]	**±2d**[f]
Written informed consent[g]		X															
Demographic data		X															
Verification of inclusion/exclusion criteria		X	X														
Platelets for inclusion/ withdrawal check (local laboratory) [h]			X				X										
Withdrawal criteria[i]			X			X	X										
General medical/procedures history		X															
ITP history		X															
Prior and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medical procedures			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs		X	X			X	X			X	X	X	X	X	X	X	X
Body weight		X															X
Height		X															
Recording of AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[j]		X	X				X				X		X		X		X
12-lead ECG[k]		X	X				X				X						X
Karnofsky Performance Status		X															
Laboratory parameters (hematology, chemistry,		X[l]	X			X	X			X	X	X	X	X	X	X	X

Table 5-3: Schedule of assessments for the UCB7665 10mg/kg once weekly dose arm (Dose Arm 3)

Assessments		Screening Period	Dosing Period							Observation Period							
			Dose 1				Dose 2										
	Visit	1	2[a] BL Visit			3	4[a]			5	6	7[b]	8	9[b]	10	11[b]	12 EOS/EW[c]
	Telephone Contact			1	2[d]			3	4[d]								
	Day	-28 to -1	1	2	3	4	8	9	10	11	15	22	29	36	43	50	64
	Week		1	1	1	1	2	2	2	2	3	4	5	6	7	8	10
	Visit Window					±1d	±2d[e]			±1d[f]	±2d[f]	±2d[f]	±2d[f]	±2d[f]	±2d[f]	±2d[f]	±2d[f]
urinalysis)																	
Serology test for HIV, hepatitis B, and hepatitis C		X															
IGRA TB test[m]		X															
TB signs and symptoms questionnaire		X															X
Blood sample for cytokines			X			X[n]	X[n]			X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]
Whole blood sample for DNA (optional)			X				X										
Whole blood sample for RNA (optional)			X			X	X										X
Serum pregnancy test		X															
Urine pregnancy test			X				X										X
Call to IXRS for treatment kit number			X				X										
Administration of IMP			X				X										

Table 5-3: Schedule of assessments for the UCB7665 10mg/kg once weekly dose arm (Dose Arm 3)

Assessments		Screening Period	Dosing Period							Observation Period							
			Dose 1				Dose 2										
	Visit	1	2[a] BL Visit			3	4[a]			5	6	7[b]	8	9[b]	10	11[b]	12 EOS/EW[c]
	Telephone Contact			1	2[d]			3	4[d]								
	Day	-28 to -1	1	2	3	4	8	9	10	11	15	22	29	36	43	50	64
	Week		1	1	1	1	2	2	2	2	3	4	5	6	7	8	10
	Visit Window					±1d	±2d[e]			±1d[f]	±2d[f]	±2d[f]	±2d[f]	±2d[f]	±2d[f]	±2d[f]	±2d[f]
Blood sampling for plasma concentration of UCB7665			X			X	X			X	X						
Anti-UCB7665 antibodies			X			X	X			X	X	X		X		X	X
Serum complements (C3 and C4) and plasma complements (C3a and C5a)			X							X				X			
Blood collection for exploratory safety biomarkers			X			X[o]	X[o]			X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	
Serum BAFF levels			X				X					X				X	
Blood collection for exploratory biomarker analysis			X				X					X				X	
Immunoglobulins (total IgG, IgG subclasses)		X	X			X	X			X	X	X	X	X	X	X	X
IgA, IgM, IgE[p]			X				X				X					X	
ITP-specific autoantibodies[q]			X								X						X

Table 5-3: Schedule of assessments for the UCB7665 10mg/kg once weekly dose arm (Dose Arm 3)

Assessments		Screening Period	Dosing Period							Observation Period							
			Dose 1				Dose 2										
	Visit	1	2[a] BL Visit			3	4[a]			5	6	7[b]	8	9[b]	10	11[b]	12 EOS/EW[c]
	Telephone Contact			1	2[d]			3	4[d]								
	Day	-28 to -1	1	2	3	4	8	9	10	11	15	22	29	36	43	50	64
	Week		1	1	1	1	2	2	2	2	3	4	5	6	7	8	10
	Visit Window					±1d	±2d[e]			±1d[f]	±2d[f]	±2d[f]	±2d[f]	±2d[f]	±2d[f]	±2d[f]	±2d[f]
ITP bleeding scale		X	X				X				X		X		X		X
NFI-MS			X				X				X		X		X		X
Headache questionnaire[r]			X			X	X			X	X	X	X	X	X	X	X
Subject exit interview[s]																	X

AE=adverse event; BAFF=B cell activating factor; BL=Baseline; CSF=cerebrospinal fluid; CT=computed tomography; d=day(s); DMC=Data Monitoring Committee; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EOS=End of Study; EW=Early Withdrawal; [redacted] HIV=human immunodeficiency virus; Ig=immunoglobulin; IGRA= interferon-gamma release assay; IMP=investigational medicinal product; ITP=immune thrombocytopenia; IXRS= interactive voice/web response system; LP=lumbar puncture; RNA=ribonucleic acid; MRI=magnetic resonance imaging; NFI-MS=Neurological Fatigue Index for multiple sclerosis; TB=tuberculosis.

[a] Frequency of assessments on dosing days is detailed in Table 5–6.

[b] Visits 7, 9, and 11 can be performed at home with a healthcare professional visiting the subject at his/her home.

[c] The End-of-Study Visit is 8 weeks following the last dose.

[d] If the TC is on the same day as an on-site visit, the TC may be skipped.

[e] A visit window of ±2 days is allowed for the dosing visits. The visit window of ±2 days is relative to the first dosing visit date. However, there should be a minimum interval of 5 days and maximum interval of 9 days as compared to the previous dose.

[f] The visit windows in the Observation Period are relative to the final dosing visit date.

[g] Additional informed consent is needed for participation in the exploratory genomic substudy. All samples will be collected prior to dosing with IMP.

[h] Prior to dosing at Visit 2, 2 platelet samples will be taken. One sample will be analyzed locally and the value will be used to check inclusion criteria. The other platelet sample will be sent to the central laboratory. At subsequent dosing visits, a platelet sample will be assessed locally prior to dosing to evaluate withdrawal criterion of platelet count >350x10^9/L.

[i] Subjects can withdraw at any time during the study, based on the criteria in Section 6.4.

[j] A complete physical examination will be performed at Screening and EOS/EW Visit. At all other visits (where physical examination is performed), an abbreviated physical examination will be conducted.

[k] The ECG should be performed in triplicate prior to blood collection for assessment of laboratory parameters. Three ECGs should be recorded in a time frame of 5 minutes with at least 1 minute difference, 1-2 minutes between the ECGs.

[l] At the Screening Visit, 2 separate blood samples will be obtained on the same day for evaluation of platelet count.

[m] The IGRA test will be performed in a central laboratory. Any IGRA-positive subjects will be withdrawn from the study.

[n] Blood sample for cytokines will be obtained and analyzed at baseline for all subjects and at subsequent visits only in subjects with infusion reactions.

[o] Exploratory safety biomarker samples to be obtained on dosing days for all subjects. During non-dosing visits and during the visits in the Observation Period, the samples should be obtained only from subjects experiencing severe headaches or GI disturbances (only in case of Adverse Events of Interest, see Section 12.4).

[p] In case the number of infusions to be administered are reduced after DMC review of safety data, then the scheduled Visit 6 assessment for IgA, IgM, and IgE will be performed earlier at the last dosing visit.

[q] [redacted]

[r] This assessment is applicable only to subjects experiencing severe headaches and will be performed daily until resolution (ie, if headache becomes moderate or mild, normal collection of AEs should apply); this assessment will be followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

[s] A semi-structured interview guide will be used and the interview will be recorded. In case of early withdrawal from the study, the subject exit interview should be performed at End-of-Study Visit only.

Table 5-4: Schedule of assessments for the UCB7665 15mg/kg once dose arm (Dose Arm 4)

Assessments		Screening Period	Dosing Period			Observation Period							
			Dose 1										
	Visit	1	2[a]			3	4	5[b]	6	7b	8	9b	10
			BL Visit										EOS/EW[c]
	Telephone Contact			1	2[d]								
	Day	-28 to -1	1	2	3	4	8	15	22	29	36	43	57
	Week		1	1	1	1	2	3	4	5	6	7	9
	Visit Window					±1d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Written informed consent[f]		X											
Demographic data		X											
Verification of inclusion/exclusion criteria		X	X										
Platelets for inclusion/ withdrawal check (local laboratory)[g]			X										
Withdrawal criteria[h]			X										
General medical/procedures history		X											
ITP history		X											
Prior and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medical procedures			X	X	X	X	X	X	X	X	X	X	X
Vital signs		X	X			X	X	X	X	X	X	X	X
Body weight		X											X

Table 5-4: Schedule of assessments for the UCB7665 15mg/kg once dose arm (Dose Arm 4)

Assessments		Screening Period	Dosing Period			Observation Period							
			Dose 1										
	Visit	**1**	**2[a]**			**3**	**4**	**5[b]**	**6**	**7b**	**8**	**9b**	**10**
			BL Visit										**EOS/EW[c]**
	Telephone Contact			**1**	**2[d]**								
	Day	**-28 to -1**	**1**	**2**	**3**	**4**	**8**	**15**	**22**	**29**	**36**	**43**	**57**
	Week		**1**	**1**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**9**
	Visit Window					**±1d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**
Height		X											
Recording of AEs		X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[i]		X	X				X		X		X		X
12-lead ECG[j]		X	X				X						X
Karnofsky Performance Status		X											
Laboratory parameters (hematology, chemistry, urinalysis)		X[k]	X			X	X	X	X	X	X	X	X
Serology test for HIV, hepatitis B, and hepatitis C		X											
IGRA TB test[l]		X											
TB signs and symptoms questionnaire		X											X
Blood sample for cytokines			X			X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]
Whole blood sample for DNA (optional)			X										

Table 5-4: Schedule of assessments for the UCB7665 15mg/kg once dose arm (Dose Arm 4)

Assessments		Screening Period	Dosing Period			Observation Period							
			Dose 1										
	Visit	**1**	**2**[a]			**3**	**4**	**5**[b]	**6**	**7b**	**8**	**9b**	**10**
			BL Visit										**EOS/EW**[c]
	Telephone Contact			**1**	**2**[d]								
	Day	**-28 to -1**	**1**	**2**	**3**	**4**	**8**	**15**	**22**	**29**	**36**	**43**	**57**
	Week		**1**	**1**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**9**
	Visit Window					**±1d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]
Whole blood sample for RNA (optional)			X			X							X
Serum pregnancy test		X											
Urine pregnancy test			X										X
Call to IXRS for treatment kit number			X										
Administration of IMP			X										
Blood sampling for plasma concentration of UCB7665			X			X	X						
Anti-UCB7665 antibodies			X			X	X	X		X		X	X
Serum complements (C3 and C4) and plasma complements (C3a and C5a)			X			X				X			
Blood collection for exploratory safety biomarkers			X			X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	
Serum BAFF levels			X					X				X	

Table 5-4: Schedule of assessments for the UCB7665 15mg/kg once dose arm (Dose Arm 4)

Assessments		Screening Period	Dosing Period			Observation Period							
			Dose 1										
	Visit	1	2[a]			3	4	5[b]	6	7b	8	9b	10
			BL Visit										EOS/EW[c]
	Telephone Contact			1	2[d]								
	Day	-28 to -1	1	2	3	4	8	15	22	29	36	43	57
	Week		1	1	1	1	2	3	4	5	6	7	9
	Visit Window					±1d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Blood collection for exploratory biomarker analysis			X					X				X	
Immunoglobulins (total IgG, IgG subclasses)		X	X			X	X	X	X	X	X	X	X
IgA, IgM, IgE			X				X					X	
ITP-specific autoantibodies[o]			X				X						X
ITP bleeding scale		X	X				X		X		X		X
NFI-MS			X				X		X		X		X
Headache questionnaire[p]			X			X	X	X	X	X	X	X	X
Subject exit interview[q]													X

AE=adverse event; BAFF=B cell activating factor; BL=Baseline; CSF=cerebrospinal fluid; CT=computed tomography; d=day(s); DMC=Data Monitoring Committee; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EOS=End of Study; EW=Early Withdrawal; [redacted] HIV=human immunodeficiency virus; Ig=immunoglobulin; IGRA= interferon-gamma release assay; IMP=investigational medicinal product; ITP=immune thrombocytopenia; IXRS= interactive voice/web response system; LP=lumbar puncture; RNA=ribonucleic acid; MRI=magnetic resonance imaging; NFI-MS=Neurological Fatigue Index for multiple sclerosis; TB=tuberculosis.

[a] Frequency of assessments on dosing days is detailed in Table 5–6.

[b] Visits 5, 7, and 9 can be performed at home with a healthcare professional visiting the subject at his/her home.

[c] The End-of-Study Visit is 8 weeks following the dose.
[d] If the TC is on the same day as an on-site visit, the TC may be skipped.
[e] The visit windows in the Observation Period are relative to the dosing visit date.
[f] Additional informed consent is needed for participation in the exploratory genomic substudy. All samples will be collected prior to dosing with IMP.
[g] Prior to dosing at Visit 1, 2 platelet samples will be taken. One sample will be analyzed locally and the value will be used to check inclusion criteria. The other platelet sample will be sent to the central laboratory. At subsequent dosing visits, a platelet sample will be assessed locally prior to dosing to evaluate withdrawal criterion of platelet count >350x10^9/L.
[h] Subjects can withdraw at any time during the study, based on the criteria in Section 6.4.
[i] A complete physical examination will be performed at Screening and EOS/EW Visit. At all other visits (where physical examination is performed), an abbreviated physical examination will be conducted.
[j] The ECG should be performed in triplicate prior to blood collection for assessment of laboratory parameters. Three ECGs should be recorded in a time frame of 5 minutes with at least 1 minute difference, 1-2 minutes between the ECGs.
[k] At the Screening Visit, 2 separate blood samples will be obtained on the same day for evaluation of platelet count.
[l] IGRA test will be performed in a central laboratory. It is recommended that the QFT-GIT be the first test performed at Screening to reduce the number of screening procedures conducted for any IGRA-positive subjects that may need to be withdrawn from the study.
[m] Blood sample for cytokines will be obtained and analyzed at baseline for all subjects and at subsequent visits only in subjects with infusion reactions.
[n] Exploratory safety biomarker samples to be obtained on dosing days for all subjects. During non-dosing visits and during the visits in the Observation Period, the samples should be obtained only from subjects experiencing severe headaches or GI disturbances (only in case of Adverse Events of Interest, see Section 12.4).
[o] [redacted]
[p] This assessment is applicable only to subjects experiencing severe headaches and will be performed daily until resolution (ie, if headache becomes moderate or mild, normal collection of AEs should apply); this assessment will be followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.
[q] A semi-structured interview guide will be used and the interview will be recorded. In case of early withdrawal from the study, the subject exit interview should be performed at End-of-Study Visit only.

Table 5-5: Schedule of assessments for the UCB7665 20mg/kg once dose arm (Dose Arm 5)

Assessments		Screening Period	Dosing Period			Observation Period							
			Dose 1										
	Visit	**1**	**2**[a]			**3**	**4**	**5**[b]	**6**	**7**[b]	**8**	**9**[b]	**10**
			BL Visit										**EOS/EW**[c]
	Telephone Contact			**1**	**2**[d]								
	Day	**-28 to -1**	**1**	**2**	**3**	**4**	**8**	**15**	**22**	**29**	**36**	**43**	**57**
	Week		**1**	**1**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**9**
	Visit Window					**±1d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]
Written informed consent[f]		X											
Demographic data		X											
Verification of inclusion/exclusion criteria		X	X										
Platelets for inclusion/ withdrawal check (local laboratory)[g]			X										
Withdrawal criteria[h]			X										
General medical/procedures history		X											
ITP history		X											
Prior and concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medical procedures			X	X	X	X	X	X	X	X	X	X	X
Vital signs		X	X			X	X	X	X	X	X	X	X
Body weight		X											X

Table 5-5: Schedule of assessments for the UCB7665 20mg/kg once dose arm (Dose Arm 5)

Assessments		Screening Period	Dosing Period			Observation Period							
			Dose 1										
	Visit	**1**	**2**[a]			**3**	**4**	**5**[b]	**6**	**7**[b]	**8**	**9**[b]	**10**
			BL Visit										**EOS/EW**[c]
	Telephone Contact			**1**	**2**[d]								
	Day	**-28 to -1**	**1**	**2**	**3**	**4**	**8**	**15**	**22**	**29**	**36**	**43**	**57**
	Week		**1**	**1**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**9**
	Visit Window					**±1d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]	**±2d**[e]
Height		X											
Recording of AEs		X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[i]		X	X				X		X		X		X
12-lead ECG[j]		X	X				X						X
Karnofsky Performance Status		X											
Laboratory parameters (hematology, chemistry, urinalysis)		X[k]	X			X	X	X	X	X	X	X	X
Serology test for HIV, hepatitis B, and hepatitis C		X											
IGRA TB test[l]		X											
TB signs and symptoms questionnaire		X											X
Blood sample for cytokines			X			X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]
Whole blood sample for DNA (optional)			X										

Table 5-5: Schedule of assessments for the UCB7665 20mg/kg once dose arm (Dose Arm 5)

Assessments		Screening Period	Dosing Period			Observation Period							
			Dose 1										
	Visit	**1**	**2[a]**			**3**	**4**	**5[b]**	**6**	**7[b]**	**8**	**9[b]**	**10**
			BL Visit										**EOS/EW[c]**
	Telephone Contact			**1**	**2[d]**								
	Day	**-28 to -1**	**1**	**2**	**3**	**4**	**8**	**15**	**22**	**29**	**36**	**43**	**57**
	Week		**1**	**1**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**9**
	Visit Window					**±1d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**	**±2d[e]**
Whole blood sample for RNA (optional)			X			X							X
Serum pregnancy test		X											
Urine pregnancy test			X										X
Call to IXRS for treatment kit number			X										
Administration of IMP			X										
Blood sampling for plasma concentration of UCB7665			X			X	X						
Anti-UCB7665 antibodies			X			X	X	X		X		X	X
Serum complements (C3 and C4) and plasma complements (C3a and C5a)			X			X				X			
Blood collection for exploratory safety biomarkers			X			X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	
Serum BAFF levels			X					X				X	

Table 5-5: Schedule of assessments for the UCB7665 20mg/kg once dose arm (Dose Arm 5)

Assessments		Screening Period	Dosing Period			Observation Period							
			Dose 1										
	Visit	1	2[a]			3	4	5[b]	6	7[b]	8	9[b]	10
			BL Visit										EOS/EW[c]
	Telephone Contact			1	2[d]								
	Day	-28 to -1	1	2	3	4	8	15	22	29	36	43	57
	Week		1	1	1	1	2	3	4	5	6	7	9
	Visit Window					±1d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]	±2d[e]
Blood collection for exploratory biomarker analysis			X					X				X	
Immunoglobulins (total IgG, IgG subclasses)		X	X			X	X	X	X	X	X	X	X
IgA, IgM, IgE			X				X					X	
ITP-specific autoantibodies[o]			X				X						X
ITP bleeding scale		X	X				X		X		X		X
NFI-MS			X				X		X		X		X
Headache questionnaire[p]			X			X	X	X	X	X	X	X	X
Subject exit interview[q]													X

AE=adverse event; BAFF=B cell activating factor; BL=Baseline; CSF=cerebrospinal fluid; CT=computed tomography; d=day(s); DMC=Data Monitoring Committee; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EOS=End of Study; EW=Early Withdrawal; [redacted] HIV=human immunodeficiency virus; Ig=immunoglobulin; IGRA= interferon-gamma release assay; IMP=investigational medicinal product; ITP=immune thrombocytopenia; IXRS= interactive voice/web response system; LP=lumbar puncture; RNA=ribonucleic acid; MRI=magnetic resonance imaging; NFI-MS=Neurological Fatigue Index for multiple sclerosis; TB=tuberculosis.

[a] Frequency of assessments on dosing days is detailed in Table 5–6.

[b] Visits 5, 7, and 9 can be performed at home with a healthcare professional visiting the subject at his/her home.

[c] The End-of-Study Visit is 8 weeks following the dose.
[d] If the TC is on the same day as an on-site visit, the TC may be skipped.
[e] The visit windows in the Observation Period are relative to the dosing visit date.
[f] Additional informed consent is needed for participation in the exploratory genomic substudy. All samples will be collected prior to dosing with IMP.
[g] Prior to dosing at Visit 1, 2 platelet samples will be taken. One sample will be analyzed locally and the value will be used to check inclusion criteria. The other platelet sample will be sent to the central laboratory. At subsequent dosing visits, a platelet sample will be assessed locally prior to dosing to evaluate withdrawal criterion of platelet count >350x10^9/L.
[h] Subjects can withdraw at any time during the study, based on the criteria in Section 6.4.
[i] A complete physical examination will be performed at Screening and EOS/EW Visit. At all other visits (where physical examination is performed), an abbreviated physical examination will be conducted.
[j] The ECG should be performed in triplicate prior to blood collection for assessment of laboratory parameters. Three ECGs should be recorded in a time frame of 5 minutes with at least 1 minute difference, 1-2 minutes between the ECGs.
[k] At the Screening Visit, 2 separate blood samples will be obtained on the same day for evaluation of platelet count.
[l] The IGRA test will be performed in a central laboratory. Any IGRA-positive subjects will be withdrawn from the study.
[m] Blood sample for cytokines will be obtained and analyzed at baseline for all subjects and at subsequent visits only in subjects with infusion reactions.
[n] Exploratory safety biomarker samples to be obtained on dosing days for all subjects. During non-dosing visits and during the visits in the Observation Period, the samples should be obtained only from subjects experiencing severe headaches or GI disturbances (only in case of Adverse Events of Interest, see Section 12.4).
[o] [redacted]
[p] This assessment is applicable only to subjects experiencing severe headaches and will be performed daily until resolution (ie, if headache becomes moderate or mild, normal collection of AEs should apply); this assessment will be followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.
[q] A semi-structured interview guide will be used and the interview will be recorded. In case of early withdrawal from the study, the subject exit interview should be performed at End-of-Study Visit only.

Change #36

Section 5.2 Schedule of study assessments

Table 5–3: Schedule of investigations on the dosing days

	Predose	End of infusion	2h after end of infusion	4h after end of infusion
Withdrawal criteria	X			
Platelet count (local laboratory) for inclusion check at Visit 2 and for withdrawal criterion at other dosing visits	X			
Prior and concomitant medications	X			

Table 5–3: Schedule of investigations on the dosing days

	Predose	End of infusion	2h after end of infusion	4h after end of infusion
Concomitant medical procedures	X			
Vital signs[a]	X	X	X	X
Physical examination	X			
12-lead ECG	X			
Hematology	X			
Clinical chemistry	X			
Urinalysis	X			
Urine pregnancy test	X			
Immunoglobulins[b]	X			
ITP-specific autoantibodies[c]	X			
Blood sampling for UCB7665 plasma concentration	X			
Anti-UCB7665 antibodies/IgG depletion assay	X			
Serum (C3 and C4) and plasma complements (C3a and C5a)[d]	X			
Serum biomarkers [redacted]	X		X	X
Serum BAFF levels	X		X	X
Blood sampling for cytokines[e]	X			
ITP bleeding scale	X			
AEs	X	X	X	X
NFI-MS[f]	X			

AE=adverse event; BAFF=B cell activating factor; ECG=electrocardiogram; h=hours; Ig=immunoglobulin; IMP=investigational medicinal product; ITP=immune thrombocytopenia; NFI-MS=Neurological Fatigue Index for multiple sclerosis; [redacted] PRO=Patient Reported Outcomes; [redacted]

[a] In addition to time points mentioned, vital signs will be evaluated every 15 minutes during infusion. Respiratory rate will be assessed only once predose.
[b] Total IgG and IgG subclasses.
[c] Evaluation of ITP-specific autoantibodies will be performed prior to dose 1 only.
[d] Serum and plasma complement levels will be assessed prior to dose 1 and dose 3 only.
[e] Blood sample for Baseline cytokine values will be obtained at Visit 2 for all subjects at predose and at other visits in case of infusion reactions.
[f] PRO endpoint (NFI-MS) will be assessed prior to dose 1 only.

Has been changed to:

Table 5–6: Schedule of investigations on the dosing days

	Predose	End of infusion	2h after end of infusion	4h after end of infusion	6h after end of infusion[a]
Withdrawal criteria	X				
Platelet count (local laboratory) for inclusion check at Visit 2 and for withdrawal criterion at other dosing visits	X				
Prior and concomitant medications	X				
Concomitant medical procedures	X				
Vital signs[b]	X	X	X	X	X
Physical examination	X				
12-lead ECG[c]	X				
Hematology	X				
Clinical chemistry	X				
Urinalysis	X				
Urine pregnancy test	X				
Immunoglobulins[d]	X				
ITP-specific autoantibodies[e]	X				
Blood sampling for UCB7665 plasma concentration	X				

Table 5–6: Schedule of investigations on the dosing days

	Predose	End of infusion	2h after end of infusion	4h after end of infusion	6h after end of infusion[a]
Anti-UCB7665 antibodies	X				
Serum (C3 and C4) and plasma complements (C3a and C5a)[f]	X				
Blood collection for exploratory safety biomarkers[g]	X		X	X	
Serum BAFF levels	X				
Blood collection for exploratory biomarker analysis	X				
Blood sampling for cytokines	X[h]			X[i]	
Whole blood sample for DNA and RNA (optional)[j]	X				
ITP bleeding scale	X				
AEs	X	X	X	X	X
NFI-MS[k]	X				

AE=adverse event; BAFF=B cell activating factor; DNA=deoxyribonucleic acid; ECG=electrocardiogram; h=hours; Ig=immunoglobulin; IMP=investigational medicinal product; ITP=immune thrombocytopenia; NFI-MS=Neurological Fatigue Index for multiple sclerosis; PRO=Patient Reported Outcomes; RNA=ribonucleic acid; [redacted]

[a] For Dose Arms 3, 4 and 5 only

[b] In addition to time points mentioned, vital signs will be evaluated every 15 minutes during infusion. Respiratory rate will be assessed only once predose.

[c] The ECG should be performed in triplicate prior to blood collection for assessment of laboratory parameters. Three ECGs should be recorded in a time frame of 5 minutes with at least 1 minute difference, 1-2 minutes between the ECGs.

[d] Total IgG and IgG subclasses.

[e] Evaluation of ITP-specific autoantibodies will be performed prior to dose 1 only.

[f] Serum and plasma complements (C3a and C5a) will be assessed prior to dose 1 and dose 3 only.

[g] [redacted]

[h] Blood sample for Baseline cytokine values will be obtained and analyzed at Baseline (Visit 2) pre-dose for all subjects. Also for all subjects on Dose Arm 3, the blood sample for cytokine values will be obtained and analyzed at Visit 4 pre-dose.

[i] Additional cytokine blood sample to be taken at 4h after end of infusion only in subjects with infusion reaction.

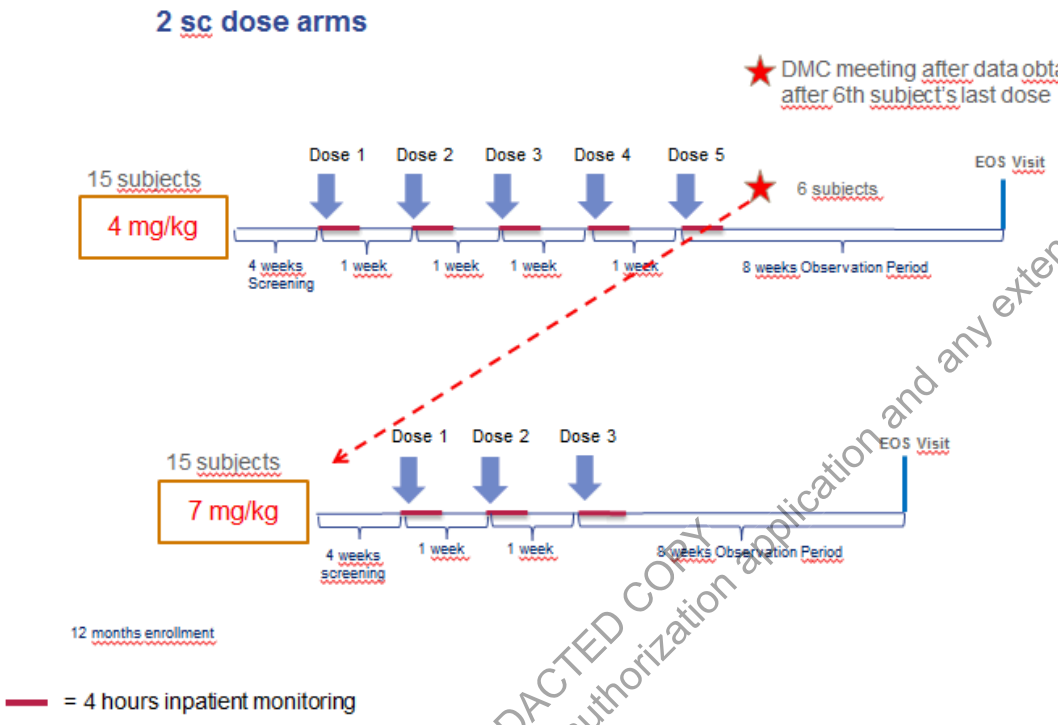
[j] For DNA, samples are taken at Baseline (Visit 2) and last dose only. For RNA, samples are taken at Baseline (Visit 2), Visit 3, at last dose, and End of Study Visit. All samples collected prior to dosing (if applicable for visit).

[k] PRO endpoint (NFI-MS) will be assessed prior to dose 1 only.

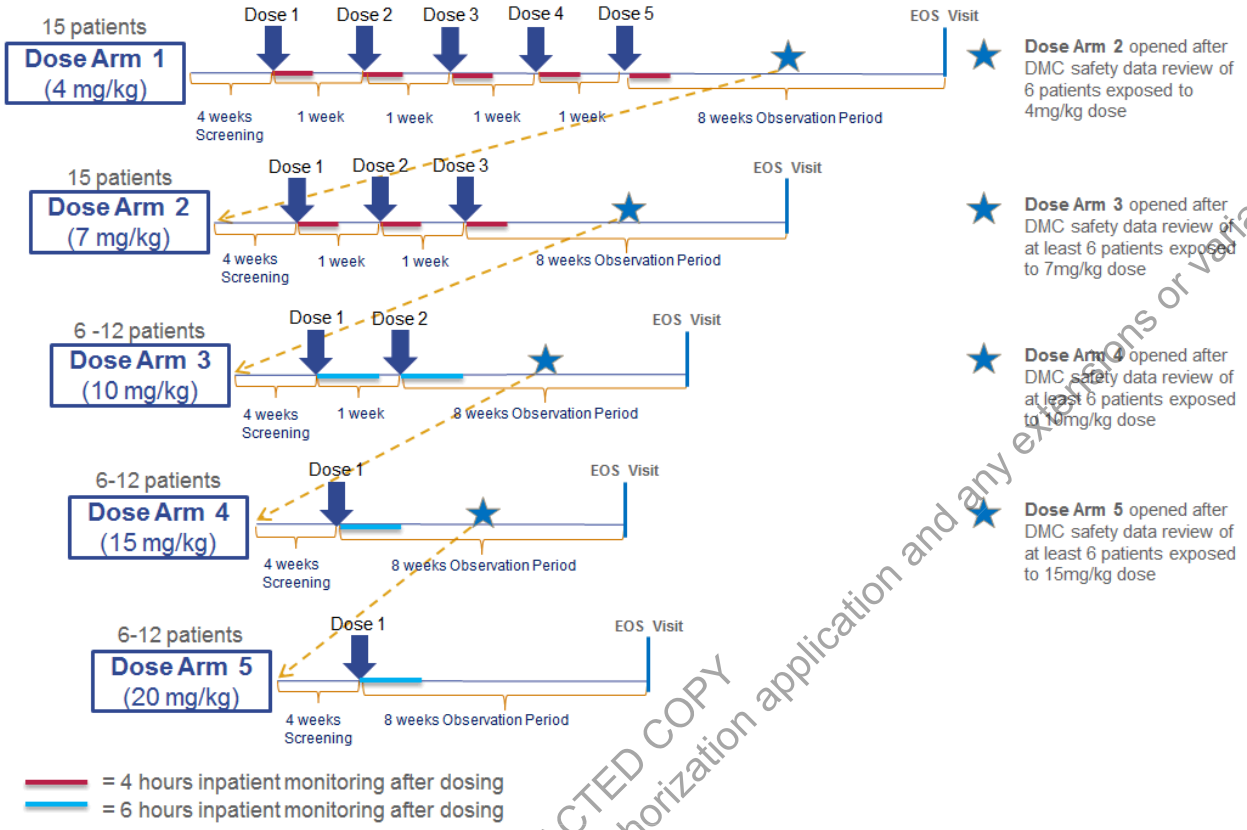
Change #37

Section 5.3 Schematic diagram

Figure 5–1: Schematic diagram



Has been changed to:



Change #38

Section 5.4.3 Choice of study design endpoints

Paragraph #1:

The primary objective of the study is evaluation of safety and tolerability of UCB7665 administered as an sc infusion in subjects with ITP. The study utilizes a sequential adaptive design with at least 4 interim analyses as described in Section 14.7. This design was chosen to permit adequate monitoring of the safety of the subjects in the study.

Has been changed to:

The primary objective of the study is evaluation of safety and tolerability of UCB7665 administered as an sc infusion in subjects with ITP. The study utilizes a sequential adaptive design with at least 11 interim analyses as described in Section 14.7. This design was chosen to permit adequate monitoring of the safety of the subjects in the study.

Change #39

5.4.5 Rationale for dose seletion

Paragraph #5:

Therefore, doses of UCB7665 4mg/kg given once weekly for 5 weeks and UCB7665 7mg/kg given once weekly for 3 weeks have been selected to evaluate the safety, tolerability and effect on platelet count in subjects with primary persistent or chronic ITP.

Has been changed to:

Therefore, doses of UCB7665 4mg/kg given once weekly for 5 weeks(Dose Arm 1) and UCB7665 7mg/kg given once weekly for 3 weeks (Dose Arm 2) have been selected as the initial doses to evaluate the safety, tolerability and effect on platelet count in subjects with primary persistent or chronic ITP. Both dose regimens have the same cumulative dose of approximately UCB7665 20mg/kg.

New paragraph #6 added:

Preliminary data from the current study indicates that the current dose regimens of UCB7665 4mg/kg and UCB7665 7mg/kg have been well tolerated. Hence the additional dose regimens of UCB7665 10mg/kg given once weekly for 2 weeks (Dose Arm 3) and of UCB7665 20mg/kg given once only (Dose Arm 5) are planned to further investigate the safety, tolerability and effect on platelet count of the same cumulative dose of UCB7665 20mg/kg but administered in dose regimes with higher dosages given in less infusions. The dose of UCB7665 15mg/kg given once only (Dose Arm 4) has been selected in addition as a risk mitigation as it is bridging the dose of UCB7665 10mg/kg given once weekly for 2 weeks (Dose Arm 3) and the dose of UCB7665 20mg/kg given once only (Dose Arm 5).

Change #40

NEW Section 5.4.6 Justification for additional genomic analyses

DNA analysis

A genetic component in ITP has long been suspected to predispose some persons to develop ITP when exposed to a provocative event.

Further, the hypothesis of underlying genetic risk for ITP is supported by rare anecdotal and case reports of familial ITP. Affected members of these families present with ITP that meets the clinical criteria for primary ITP, but demonstrates a convincing pattern of inheritance. A 2006 review of the Pediatric and Adult Registry of Chronic ITP (PARC-ITP) (Johnsen, 2012) found that 10 of 445 (2.2%) of pediatric patients reported a positive family history of ITP. However, identification of susceptibility genes in ITP, via family linkage studies or genome wide association studies, have not yet been forthcoming, likely due to the rarity of familial ITP families available for study and the heterogeneity of ITP sporadic cases. Identification and characterization of a genetic and/or epigenetic component of familial ITP will lead to important clues into the pathogenesis of more common forms of ITP and possibly advance understanding of drug response phenotypes.

RNA analysis

Gene expression (mRNA) analyses have identified distinct gene transcription signatures from whole blood associated with many autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus, and ITP. Such signatures have provided molecular insight into disease biology and can facilitate patient stratification via gene expression panels predictive of therapeutic response and clinical outcomes.

Collection of blood for RNA analysis will enable identification of candidate markers for treatment effect and safety, and determine the feasibility of patient stratification.

MicroRNA analysis

MicroRNA are short (19-25 nucleotides) evolutionarily conserved single-stranded RNA molecules that regulate the expression of genes involved in diverse biological processes. The effect of miRNA on mRNA is mediated through the binding of the miRNA to the target mRNA ribonucleoprotein complex resulting in altered expression and decreased protein translation.

Regulated miRNA in ITP significantly affect both gene and protein expression in T cells, indicating that they may be important regulatory molecules involved in the loss of immune tolerance in ITP.

In summary, the genetic, epigenetic, and genomic elements of ITP are complex and require further elucidation to understand the cause, progression, and appropriate treatment of ITP. Through the voluntary collection of blood DNA/and RNA samples from consenting subjects, this substudy will help enable further investigation of this complex disease.

Change #41

Section 6.1 Inclusion criteria

7. Female subjects of childbearing potential must have a negative serum pregnancy test at the Screening Visit, which is confirmed to be negative by urine testing prior to the first dose of IMP at Week 1 (Visit 2) and prior to further dosing at each study visit thereafter.

   Female subjects of childbearing potential must agree to use a highly effective method of birth control, during the study and for a period of 3 months after their final dose of IMP. Highly effective forms of birth control are methods which achieve a failure rate of less than 1% per year when used consistently and correctly. Highly effective methods of birth control include:

   …

Has been changed to:

7. Female subjects of childbearing potential must have a negative serum pregnancy test at the Screening Visit, which is confirmed to be negative by urine testing prior to the first dose of IMP at Week 1 (Visit 2) and prior to further dosing at each study visit thereafter.

   Female subjects of childbearing potential must agree to use a highly effective method of birth control, during the study and for a period of 2 months after their final dose of IMP. Highly effective forms of birth control are methods which achieve a failure rate of less than 1% per year when used consistently and correctly. Highly effective methods of birth control include:

   …

Change #42

Section 6.2.1 Exclusion criteria related to health status

9. Subject has renal impairment, defined as:

   Serum creatinine level of ≥1.4 mg/dL for females and ≥1.5 mg/dL for males at Screening Visit.

10. Subject has liver impairment, defined as:

Subject has >1.5xULN of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP), or >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If the subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

…

Has been changed to:

9. Subject has renal impairment, defined as:

Serum creatinine level of ≥1.4mg/dL for females and ≥1.5mg/dL for males at Screening Visit.

10. Subject has 2xULN of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP), or >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If the subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

…

Change #43

6.2.2 Exclusion criteria related to medical history

NEW exclusion criteria added:

25. Subjects with known tuberculosis (TB) infection, at high risk of acquiring TB infection, or with latent TB (LTB) infection or current history of nontuberculous mycobacterial infection (NTMBI) infection are excluded.

a. Known TB infection whether present or past is defined as:

- Active TB infection or clinical signs and symptoms suggestive of TB (pulmonary or extrapulmonary).
- History of active TB infection involving any organ system or findings in other organ systems consistent with TB infection.
- Any historical evidence by radiography or other imaging modalities consistent with previously active TB infection.
- b. High risk of acquiring TB infection is defined as:
- Known exposure to another person with active TB infection within the 3 months prior to Screening.
- Time spent in a healthcare delivery setting or institution where individuals infected with TB are housed and where the risk of transmission of infection is high.

c. LTB infection (refer to Section 12.8.1 for further details and instructions).

d. NTMBI is defined as a group of lung infections caused by mycobacteria different from mycobacterium tuberculosis infections.

26 Subjects with known TB infection, at high risk of acquiring TB infection, or LTB infection, or current/history of NTMBI are excluded.

Change #44

6.4 Withdrawal criteria

2. Subject develops an illness or has a change in health status that would interfere with his/her continued participation, including but not limited to:

- Subject has a serious infective episode requiring hospitalization or iv antibiotic therapy (including but not limited to bacteremia or sepsis, bacterial meningitis, osteomyelitis or septic arthritis, bacterial pneumonia, or visceral abscess).
- Subject experiences a severe AE of gastrointestinal disturbance or headache which is considered related to the IMP in the opinion of the investigator.
- Subject has a severe infusion reaction requiring corticosteroid and/or epinephrine therapy.
- Subject has an anaphylactic reaction requiring corticosteroid and/or epinephrine therapy.
- Subject has a life threatening bleeding event.

Has been changed to:

2. Subject develops an illness or has a change in health status that would interfere with his/her continued participation, including but not limited to:

- Subject has a serious infective episode requiring hospitalization or iv antibiotic therapy (including but not limited to bacteremia or sepsis, bacterial meningitis, osteomyelitis or septic arthritis, bacterial pneumonia, or visceral abscess).
- Subject experiences a severe AE of gastrointestinal disturbance or headache which is considered related to the IMP in the opinion of the investigator.
- Subject has a severe infusion reaction requiring corticosteroid and/or epinephrine therapy.
- Subject has an anaphylactic reaction requiring corticosteroid and/or epinephrine therapy.
- Subject has a life threatening bleeding event.
- Subject has a TB test that is confirmed positive or any further evidence suggestive of potential TB infection (eg, close exposure) and further examinations result in a diagnosis of active TB or LTB. Refer to Section 12.8.1 for further details and instructions.
- If an NTMBI infection is identified during a study, the same withdrawal procedures as those used for an active TB infection identified during the study should be followed.

Change #45

6.4 Withdrawal criteria

Subjects MUST stop treatment with the IMP if the platelet count is >350x10^9/L during the Dosing Period. Subjects should continue in the study and attend the protocol defined visits in the Observation Period.

Subjects with PDILI must be assessed to determine if IMP must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

Has been changed to:

Subjects MUST stop treatment with the IMP if the platelet count is >350x10^9/L during the Dosing Period. Subjects should continue in the study and attend the protocol defined visits in the Observation Period.

6.4.1 Potential drug induced liver injury IMP discontinuation criteria

Subjects with PDILI must be assessed to determine if IMP must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

Change #46

6.5 Study stopping rules

More detailed criteria for stopping a cohort will be defined in the DMC charter.

Has been changed to:

More detailed criteria for stopping a dose arm will be defined in the DMC charter.

Change #47

Section 7.2 Treatment to be administered

Subjects in Dose Arm 1 will receive 5 sc doses of UCB7665 4mg/kg at 1-week intervals.
Subjects in Dose Arm 2 will receive 3 sc doses of UCB7665 7mg/kg at 1-week intervals.

Has been changed to:

Subjects in Dose Arm 1 will receive 5 sc doses of UCB7665 4mg/kg at 1-week intervals.
Subjects in Dose Arm 2 will receive 3 sc doses of UCB7665 7mg/kg at 1-week intervals.
Subjects in Dose Arm 3 will receive 2 sc doses of UCB7665 10mg/kg at a 1-week interval.

Subjects in Dose Arm 4 will receive 1 sc dose of UCB7665 15mg/kg.

Subjects in Dose Arm 5 will receive 1 sc dose of UCB7665 20mg/kg.

Change #48

Section 7.4 Labeling

Clinical drug supplies will be labeled in accordance with the current International Conference on Harmonisation (ICH) guidelines on GCP and GMP and will include any locally required statements. If necessary, labels will be translated into the local language.

Has been changed to:

Clinical drug supplies will be labeled in accordance with the current International Council for Harmonisation (ICH) guidelines on GCP and GMP and will include any locally required statements. If necessary, labels will be translated into the local language.

Change #49

7.8.3 Rescue medication

In the case of prolonged hypogammaglobulinemia the subject will be considered for treatment with prophylactic antimicrobial therapy. Subjects will be followed up until immunoglobulin levels return to within the normal range.

In case of lack of efficacy and/or severe bleeding events and where appropriate, platelet substitution or treatment with a commercially available iv immunoglobulin may be considered.

Has been changed to:

In the case of prolonged hypogammaglobulinemia the subject will be considered for treatment with prophylactic antimicrobial therapy. Subjects will be followed up until immunoglobulin levels return to within the normal range.

In case of lack of efficacy and/or severe bleeding events and where appropriate, platelet substitution or treatment with a commercially available iv immunoglobulin may be considered.

If such rescue medication must be given when the subject is still in the dosing period, the subject should be withdrawn from the study treatment and complete all Observation visits, if possible.

If such rescue medication is given when the subject has completed the study treatment, the subject should continue the Observation Visits, as per schedule of study assessments (Section 5.2).

Change #50

Section 7.10 Randomization and numbering of subjects

Paragraph #2:

The first 6 subjects (and those treated before DMC assessment after the 6 subjects) will not be randomized. Once the DMC has approved opening of Dose Arm 2 for enrollment, subsequent subjects will be randomized to 1 of the 2 dose arms in a 1:1 ratio. Once 15 subjects are in the 4mg/kg group, the remaining subjects will not be randomized. They will be allocated to the 7mg/kg group.

Has been changed to:

An IXRS will be used for assigning eligible subjects to a treatment regimen based on a predetermined production randomization and/or packaging schedule provided by PAREXEL Informatics. The IXRS will generate individual assignments for subject kits of IMP, as appropriate, according to the dose arm and subject's weight.

The first 6 subjects (and those treated before DMC assessment after the 6 subjects) will not be randomized. Once the DMC has advocated the initiation of Dose Arm 2 for enrollment, subsequent subjects will be randomly assigned to 1 of the 2 dose arms (ie, Dose Arm 1 and Dose Arm 2) in a 1:1 ratio. Once 15 subjects are enrolled in the Dose Arm 1, the remaining subjects will be enrolled in Dose Arm 2 until Dose Arm 2 is completed with 15 subjects.

After Dose Arm 2, there will be no randomization between dose arms.

Change #51

Section 8.1.1 Visit 1 (Day -28 to -1) Screening Visit

Has been changed to:

Section 8.1.1 Visit 1 (Day -28 to -1) Screening Visit (all Dose Arms)

Detail regarding informed consent process for exploratory genomic analyses added as follows:

Subjects will also have the option of providing additional voluntary informed consent for collection of whole blood samples for exploratory DNA and RNA analyses.

Change #52

Section 8.1.1 Visit (Day -28 to -1) Screening Visit

…

- 12-lead ECG
- Karnofsky Performance Status
- Recording of AEs
- Urine sample for urinalysis
- Blood sample for the following laboratory parameters:
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry*
  - Serum pregnancy test for women of childbearing potential
  - Serum total IgG and IgG subclasses concentration
  - Serum HbA1c
  - Serology tests for HIV, hepatitis B, and hepatitis C
- ITP bleeding scale

  *Two blood samples for assessment of platelet count to be obtained via 2 separate blood collections

Has been changed to:

…

- 12-lead ECG (triplicate)
- Karnofsky Performance Status
- Recording of AEs
- Urine sample for urinalysis
- Blood sample for the following:

- Standard safety laboratories: hematology including coagulation parameters, clinical chemistry (two blood samples for assessment of platelet count to be obtained via 2 separate blood collections)
- Serum pregnancy test for women of childbearing potential
- Serum total IgG and IgG subclasses concentration
- Serum HbA1c
- Serology tests for HIV, hepatitis B, and hepatitis C

- ITP bleeding scale

NEW bullet points added:

…

- Obtain informed consent for substudy involving DNA and RNA analyses

…

- IGRA TB test

- TB signs and symptoms questionnaire

Change #53

Section 8.2 Dosing Period

Has been changed to:

Section 8.2 Dosing Period for all Dose Arms

Change #54

Section 8.2.1 Visit 2 (Week 1/Day 1) Baseline Visit

Paragraphs #2, #3, and #4:

Eligible subjects will be treated with IMP at Visit 2. The first 6 subjects will be enrolled in Dose Arm 1, subsequent subjects will be randomized to 1 of the 2 dose arms. Once 15 subjects are in Dose Arm 1, the remaining subjects will not be randomized. They will be allocated to Dose Arm 2.

Eligible subjects will be treated with IMP at Visit 2. The first 6 subjects will be enrolled in Dose Arm 1, subsequent subjects will be randomized to 1 of the 2 dose arms. Once 15 subjects are in Dose Arm 1, the remaining subjects will not be randomized. They will be allocated to Dose Arm 2.

Subjects allocated to Dose Arm 1 (UCB7665 4mg/kg sc) will receive a total of 5 doses of IMP at Visit 2 (Day 1, Week 1), Visit 4 (Week 2), Visit 5 (Week 3), Visit 6 (Week 4), and Visit 7 (Week 5).

Subjects allocated to Dose Arm 2 (UCB7665 7mg/kg sc) will receive a total of 3 doses of IMP at Visit 2 (Day 1, Week 1), Visit 4 (Week 2), and Visit 5 (Week 3).

Has been changed to:

Eligible subjects will be treated with IMP at Visit 2.

Subjects allocated to Dose Arm 1 (UCB7665 4mg/kg weekly sc) will receive a total of 5 doses of IMP at Visit 2 (Day 1, Week 1), Visit 4 (Week 2), Visit 5 (Week 3), Visit 6 (Week 4), and Visit 7 (Week 5).

Subjects allocated to Dose Arm 2 (UCB7665 7mg/kg weekly sc) will receive a total of 3 doses of IMP at Visit 2 (Day 1, Week 1), Visit 4 (Week 2), and Visit 5 (Week 3).

Subjects allocated to Dose Arm 3 (UCB7665 10mg/kg weekly sc) will receive a total of 2 doses of IMP at Visit 2 (Day 1, Week 1) and Visit 4 (Day 8, Week 2).

Subjects allocated to Dose Arm 4 (UCB7665 15mg/kg) will receive 1 dose of IMP at Visit 2 (Day 1, Week 1).

Subjects allocated to Dose Arm 5 (UCB7665 20mg/kg) will receive 1 dose of IMP at Visit 2 (Day 1, Week 1).

Change #55

8.2.1 Visit 2 (Week 1/Day 1) Baseline Visit

- 12-lead ECG
- Urine pregnancy test for women of childbearing potential
- Urine sample for urinalysis
- Blood sample for the following laboratory parameters:
  - Plasma concentration of UCB7665
  - Anti-UCB7665 antibodies/IgG depletion assay
  - Serum total IgG and IgG subclasses concentration
  - Serum IgA, IgM, and IgE concentration
  - ITP-specific autoantibodies [redacted]
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Additional platelet sample for analysis in local laboratory for evaluation of the inclusion criteria of platelet count $<35x10^9$/L at Baseline
  - Serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a)
  - Serum biomarkers [redacted] and serum BAFF levels. Blood samples are taken prior to dosing, 2 and 4 hours after end of infusion for serum biomarkers and BAFF
  - Serum cytokines

NEW bullet points:

- Subjects in Dose Arms 1 and 2 will stay on site for 4 hours after the end of infusion for inpatient observation at the site.
- Subjects in Dose Arms 3, 4 and 5 will stay on site for 6 hours after the end of infusion for inpatient observation at the site.

Has been changed to:

- 12-lead ECG (triplicate)
- Urine pregnancy test for women of childbearing potential
- Urine sample for urinalysis
- Blood sample for the following:
  - Plasma concentration of UCB7665
  - Anti-UCB7665 antibodies
  - Serum total IgG and IgG subclasses concentration
  - Serum IgA, IgM, and IgE concentration
  - ITP-specific autoantibodies [redacted]
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Additional platelet sample for analysis in local laboratory for evaluation of the inclusion criteria of platelet count $<35x10^9$/L at Baseline
  - Serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a)
  - Exploratory safety biomarkers [redacted]. Blood samples are taken prior to dosing, 2 and 4 hours after end of infusion for exploratory safety biomarkers
  - Serum BAFF levels
  - Exploratory biomarker analysis
  - Serum cytokines mandatory for all subjects at pre-dose, and only in case of infusion reactions at 4 hours after end of infusion
- Collection of whole blood for exploratory DNA and RNA analyses

Change #56

8.2.2 Visit 3 (Week 1/Day 4)

…

- Blood sample for the following laboratory parameters:

- Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
- Plasma concentration of UCB7665
- Anti-UCB7665 antibodies/IgG depletion assay
- Serum total IgG and IgG subclasses concentration
- Serum biomarkers [redacted]

- Review withdrawal criteria
- Serum cytokines, only in case of infusion reactions

…

Has been changed to:

8.2.2 Visit 3 (Week 1/Day 4) [UCB7665 4mg/kg, UCB7665 7mg/kg, and UCB7665 10mg/kg]

…

- Blood sample for the following:
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Plasma concentration of UCB7665
  - Anti-UCB7665 antibodies
  - Serum total IgG and IgG subclasses concentration
  - Exploratory safety biomarkers [redacted] only from subjects experiencing severe headaches or GI disturbances (only in case of Adverse Events of Interest, see Section 12.4)
- Review withdrawal criteria
- Serum cytokines, only in case of late infusion reactions visible during the visit

For Dose Arm 1, 2, and 3 collection of whole blood for exploratory RNA analyses

…

Change #57

8.2.3 Visit 4 (Week 2/Day 8)

…

- 12-lead ECG
- Urine pregnancy test for women of childbearing potential
- Urine sample for urinalysis
- Call IXRS to obtain treatment kit number(s)

- Blood sample for the following laboratory parameters:
  - Plasma concentration of UCB7665
  - Anti-UCB7665 antibodies/IgG depletion assay
  - Serum total IgG and IgG subclasses concentration
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Additional platelet sample for analysis in local laboratory for evaluation of the withdrawal criteria of platelet count >350x10^9/L
  - Serum biomarkers [redacted] and serum BAFF levels. Blood samples are taken prior to dosing, 2 and 4 hours after end of infusion for serum biomarkers and BAFF

…

Has been changed to:

8.2.3 Visit 4 (Week 2/Day 8) [UCB7665 4mg/kg, UCB7665 7mg/kg and UCB7665 10mg/kg]

…

- 12-lead ECG (triplicate)
- Urine pregnancy test for women of childbearing potential
- Urine sample for urinalysis
- Call IXRS to obtain treatment kit number(s)
- Blood sample for the following:
  - Plasma concentration of UCB7665
  - Anti-UCB7665 antibodies
  - Serum total IgG and IgG subclasses concentration
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Additional platelet sample for analysis in local laboratory for evaluation of the withdrawal criteria of platelet count >350x10^9/L
  - Exploratory safety biomarkers [redacted] Blood samples are taken prior to dosing, 2 and 4 hours after end of infusion for exploratory serum biomarkers
  - Serum BAFF levels
  - Exploratory biomarker analysis

…

NEW bullet points:

- Subjects in Dose Arms 1 and 2 will stay on site for 4 hours after the end of infusion for inpatient observation at the site.
- Subjects in Dose Arms 3, 4 and 5 will stay on site for 6 hours after the end of infusion for inpatient observation at the site.
- For Dose Arm 3, only collection of whole blood for exploratory DNA and RNA analyses

…

  – Serum cytokines at pre-dose mandatory for subjects on Dose Arm 3 (10mg/kg), and at 4 hours after end of infusion (for all dose arms)

Change #58

8.2.4 Visit 5 (Week 3/Day 15)

…

- 12-lead ECG
- Urine pregnancy test for women of childbearing potential
- Urine sample for urinalysis
- Call IXRS to obtain treatment kit number(s)
- Blood sample for the following laboratory parameters:
  – Plasma concentration of UCB7665
  – Anti-UCB7665 antibodies/IgG depletion assay
  – Serum total IgG and IgG subclasses concentration
  – Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  – Additional platelet sample for analysis in local laboratory for evaluation of the withdrawal criteria of platelet count >350x10^9/L
  – Serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a)
  – Serum IgA, IgM, and IgE concentration (UCB7665 7mg/kg only)
  – Serum biomarkers [redacted] and serum BAFF levels. Blood samples are taken prior to dosing, 2 and 4 hours after end of infusion for serum biomarkers and BAFF

Has been changed to:

8.2.4 Visit 5 (Week 3/Day 15) [UCB7665 4mg/kg and UCB7665 7mg/kg]

…

- 12-lead ECG (triplicate)
- Urine pregnancy test for women of childbearing potential

- Urine sample for urinalysis
- Call IXRS to obtain treatment kit number(s)
- Blood sample for the following:
  - Plasma concentration of UCB7665
  - Anti-UCB7665 antibodies
  - Serum total IgG and IgG subclasses concentration
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Additional platelet sample for analysis in local laboratory for evaluation of the withdrawal criteria of platelet count >350x10^9/L
  - Serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a)
  - Serum IgA, IgM, and IgE concentration (UCB7665 7mg/kg only)
  - Exploratory safety biomarker [redacted] Blood samples are taken prior to dosing, 2 and 4 hours after end of infusion for exploratory safety biomarkers
  - Serum BAFF levels
  - Exploratory biomarker analysis
- For Dose Arm 2 only, collection of whole blood for exploratory DNA and RNA analyses

…

Change #59

Visit 6 (Week 4/Day 22) [UCB7665 4mg/kg only]

- 12-lead ECG
- Urine pregnancy test for women of childbearing potential
- Urine sample for urinalysis
- Call IXRS to obtain treatment kit number(s)
- Blood sample for the following laboratory parameters:
  - Plasma concentration of UCB7665
  - Anti-UCB7665 antibodies/IgG depletion assay
  - Serum total IgG and IgG subclasses concentration
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry

- Additional platelet sample for analysis in local laboratory for evaluation of the withdrawal criteria of platelet count >350x10^9/L

- Serum biomarkers [redacted] and serum BAFF levels. Blood samples are taken prior to dosing, 2 and 4 hours after end of infusion for serum biomarkers and BAFF

Has been changed to:

8.2.5 Visit 6 for Dose Arm 1 (Week 4/Day 22) [UCB7665 4mg/kg only]

- 12-lead ECG (triplicate)
- Urine pregnancy test for women of childbearing potential
- Urine sample for urinalysis
- Call IXRS to obtain treatment kit number(s)
- Blood sample for the following:
  - Plasma concentration of UCB7665
  - Anti-UCB7665 antibodies
  - Serum total IgG and IgG subclasses concentration
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Additional platelet sample for analysis in local laboratory for evaluation of the withdrawal criteria of platelet count >350x10^9/L
  - Exploratory safety biomarkers [redacted] Blood samples are taken prior to dosing, 2 and 4 hours after end of infusion for exploratory safety biomarkers
  - Serum BAFF levels
  - Exploratory biomarker analysis

Change #60

8.2.6 Visit 7 (Week 5/Day 29) [UCB7665 4mg/kg only]

- 12-lead ECG
- Urine pregnancy test for women of childbearing potential
- Urine sample for urinalysis
- Call IXRS to obtain treatment kit number(s)
- Blood sample for the following laboratory parameters:
  - Plasma concentration of UCB7665
  - Anti-UCB7665 antibodies/IgG depletion assay

- Serum total IgG and IgG subclasses concentration
- Serum IgA, IgM, and IgE concentration
- Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
- Additional platelet sample for analysis in local laboratory for evaluation of the withdrawal criteria of platelet count >350x10^9/L
- Serum biomarkers [redacted] and serum BAFF levels. Blood samples are taken prior to dosing, 2 and 4 hours after end of infusion for serum biomarkers and BAFF

Has been changed to:

- 12-lead ECG (triplicate)
- Urine pregnancy test for women of childbearing potential
- Urine sample for urinalysis
- Call IXRS to obtain treatment kit number(s)
- Blood sample for the following:
  - Plasma concentration of UCB7665
  - Anti-UCB7665 antibodies
  - Serum total IgG and IgG subclasses concentration
  - Serum IgA, IgM, and IgE concentration
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Additional platelet sample for analysis in local laboratory for evaluation of the withdrawal criteria of platelet count >350x10^9/L
  - Exploratory safety biomarkers [redacted] Blood samples are taken prior to dosing, 2 and 4 hours after end of infusion for exploratory safety biomarkers
  - Serum BAFF levels
  - Exploratory biomarker analysis
- For Dose Arm 1 only, collection of whole blood for DNA and RNA analyses

Change #61

NEW sections added:

8.3 Telephone Contacts

For Dose Arms 3, 4 and 5 the site must make a phone call to the subject on Day 1 and Day 2 after dosing as a safety measure.

8.3.2 Telephone Contact 1 (Week 1/Day 2) [UCB7665 10mg/kg, UCB7665 15mg/kg, UCB7665 20mg/kg]

- Concomitant medications
- Concomitant medical procedures
- Recording of AEs

8.3.3 Telephone Contact 2 (Week 1/Day 3) [UCB7665 10mg/kg, UCB7665 15mg/kg, UCB7665 20mg/kg]

- Concomitant medications
- Concomitant medical procedures
- Recording of AEs

8.3.4 Telephone Contact 3 (Week 2/Day 9) [UCB7665 10mg/kg only]

- Concomitant medications
- Concomitant medical procedures
- Recording of AEs

8.3.5 Telephone Contact 4 (Week 2/Day 10) [UCB7665 10mg/kg only]

- Concomitant medications
- Concomitant medical procedures
- Recording of AEs

Change #62

8.3 Observation Period

The Observation Period will last for 8 weeks following the final dose administration. The first visit in the Observation Period will be performed 3 days after the final dose administration and subsequent visits will be performed at weekly intervals (except for a 2-week interval before the final visit).

For UCB7665 4mg/kg dose, the following visits will be performed: Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13, Visit 14, and Visit 15, corresponding to UCB7665 7mg/kg Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, and Visit 13.

Has been changed to:

8.4 Observation Period

The Observation Period will last for 8 weeks following the final dose administration. The first visit in the Observation Period will be performed 3 days after the final dose administration and subsequent visits will be performed at weekly intervals (except for a 2-week interval before the final visit).

For UCB7665 4mg/kg weekly dose (Dose Arm 1), the following visits will be performed: Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13, Visit 14, and Visit 15, corresponding to UCB7665 7mg/kg weekly dose (Dose Arm 2) on Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, and Visit 13.

For the UCB7665 10mg/kg weekly dose (Dose Arm 3), the following visits will be performed: Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 11, and Visit 12.

For the UCB7665 15 mg/kg dose (Dose Arm 4) and the UCB7665 20mg/kg dose (Dose Arm 5), the following visits will be performed: Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8, Visit 9 and Visit 10.

Change #63

8.3.1 Visit 8 (Week 5/Day 32) [UCB7665 4mg/kg]/ Visit 6 (Week 3/Day 18) [UCB7665 7mg/kg]

…

- Blood sample for the following laboratory parameters:
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Plasma concentration of UCB7665
  - Anti-UCB7665 antibodies/IgG depletion assay
  - Serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a)
  - Serum biomarkers [redacted]
  - Serum total IgG and IgG subclasses concentration

…

Has been changed to:

8.4.1 Visit 8 (Week 5/Day 32) [UCB7665 4mg/kg]/ Visit 6 (Week 3/Day 18) [UCB7665 7mg/kg]]/ Visit 5 (Week 2/Day 11) [UCB7665 10mg/kg]

Visit 3 (Week 1/Day 4) [UCB7665 15mg/kg and UCB7665 20mg/kg]

- Blood sample for the following:
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Plasma concentration of UCB7665
  - Anti-UCB7665 antibodies
  - Serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a)
  - Exploratory safety biomarkers [redacted] only from subjects experiencing severe headaches or GI disturbances (only in case of Adverse Events of Interest, see Section 12.4)

- Serum total IgG and IgG subclasses concentration

Change #64

8.3.2 Visit 9 (Week 6/Day 36) [UCB7665 4mg/kg]/ Visit 7 (Week 4/Day 22) [UCB7665 7mg/kg]

A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. The following assessments will be performed at this visit:

…

- 12-lead ECG
- Urine sample for urinalysis
- Blood sample for the following laboratory parameters:
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Plasma concentration of UCB7665
  - Anti-UCB7665 antibodies/IgG depletion assay
  - Serum biomarkers [redacted]
  - Serum total IgG and IgG subclasses concentration
  - Serum IgA, IgM, and IgE concentration
  - ITP-specific autoantibodies [redacted]

Has been changed to:

8.4.2 Visit 9 (Week 6/Day 36) [UCB7665 4mg/kg]/ Visit 7 (Week 4/Day 22) [UCB7665 7mg/kg]]/ Visit 6 (Week 3/Day 15) [UCB7665 10mg/kg]

Visit 4 (Week 2/Day 8) [UCB7665 15mg/kg and UCB7665 20mg/kg]

This is the second visit in the Observation Period. A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. The following assessments will be performed at this visit:

…

- 12-lead ECG (triplicate)

…

- Blood sample for the following:
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Plasma concentration of UCB7665
  - Anti-UCB7665 antibodies

– Exploratory safety biomarkers [redacted] Blood samples are taken prior to dosing, 2 and 4 hours after end of infusion for exploratory safety biomarkers)

Change #65

8.3.3 Visit 10 (Week 7/Day 43) [UCB7665 4mg/kg]/ Visit 8 (Week 5/Day 29) [UCB7665 7mg/kg]

A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. This visit can be performed at home with a healthcare professional visiting the subject at his/her home. The following assessments will be performed at this visit:

…

- Blood sample for the following laboratory parameters:
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Anti-UCB7665 antibodies/IgG depletion assay
  - Serum biomarkers [redacted]
  - Serum BAFF levels
  - Serum total IgG and IgG subclasses concentration

    …

Has been changed to:

8.4.3 Visit 10 (Week 7/Day 43) [UCB7665 4mg/kg]/ Visit 8 (Week 5/Day 29) [UCB7665 7mg/kg]]/ Visit 7 (Week 4/Day 22) [UCB7665 10mg/kg]

Visit 5 (Week 3/Day 15) [UCB7665 15mg/kg and UCB7665 20mg/kg]

This is the third visit in the Observation Period. A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. This visit can be performed at home with a healthcare professional visiting the subject at his/her home. The following assessments will be performed at this visi

…

- Blood sample for the following:
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Anti-UCB7665 antibodies
  - Exploratory safety biomarkers [redacted] Blood samples are taken prior to dosing, 2 and 4 hours after end of infusion for exploratory safety biomarkers)

- Serum BAFF levels
- Exploratory biomarker analysis

…

Change #66

8.3.4 Visit 11 (Week 8/Day 50) [UCB7665 4mg/kg]/ Visit 9 (Week 6/Day 36) [UCB7665 7mg/kg]

A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. The following assessments will be performed at this visit:

…

- Blood sample for the following laboratory parameters:
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Serum biomarkers [redacted]
  - Serum total IgG and IgG subclasses concentration

    …

Has been changed to:

8.4.4 Visit 11 (Week 8/Day 50) [UCB7665 4mg/kg]/ Visit 9 (Week 6/Day 36) [UCB7665 7mg/kg]]/ Visit 8 (Week 5/Day 29) [UCB7665 10mg/kg]

Visit 6 (Week 4/Day 22) [UCB7665 15mg/kg and UCB7665 20mg/kg]

This is the fourth visit in the Observation Period. A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. The following assessments will be performed at this visit:

…

- Blood sample for the following:
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Exploratory safety biomarkers [redacted] Blood samples are taken prior to dosing, 2 and 4 hours after end of infusion for exploratory safety biomarkers)
  - Serum total IgG and IgG subclasses concentration

Change #67

8.3.5 Visit 12 (Week 9/Day 57) [UCB7665 4mg/kg]/ Visit 10 (Week 7/Day 43) [UCB7665 7mg/kg]

A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. This visit can be performed at home with a healthcare professional visiting the subject at his/her home. The following assessments will be performed at this visit:

…

- Blood sample for the following laboratory parameters:
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Anti-UCB7665 antibodies/IgG depletion assay
  - Serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a)
  - Serum biomarkers [redacted]
  - Serum total IgG and IgG subclasses concentration

Has been changed to:

8.4.5 Visit 12 (Week 9/Day 57) [UCB7665 4mg/kg]/
Visit 10 (Week 7/Day 43) [UCB7665 7mg/kg]/ Visit 9 (Week 6/Day 36) [UCB7665 10mg/kg]
Visit 7 (Week 5/Day 29) [UCB7665 15mg/kg and UCB7665 20mg/kg]

This is the fifth visit in the Observation Period. A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. This visit can be performed at home with a healthcare professional visiting the subject at his/her home. The following assessments will be performed at this visit:

…

- 12-lead ECG (triplicate)

…

- Blood sample for the following:
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Anti-UCB7665 antibodies
  - Serum complement levels (C3 and C4) and plasma complement levels (C3a and C5a)
  - Exploratory safety biomarkers [redacted] Blood samples are taken prior to dosing, 2 and 4 hours after end of infusion for exploratory safety biomarkers)
  - Serum total IgG and IgG subclasses concentration
- Serum cytokines, only in case of late infusion reactions visible during the visit

Change #68

Visit 13 (Week 10/Day 64) [UCB7665 4mg/kg]/ Visit 11 (Week 8/Day 50) [UCB7665 7mg/kg]

A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. The following assessments will be performed at this visit:

…

- Blood sample for the following laboratory parameters:
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Serum total IgG and IgG subclasses concentration
  - Serum biomarkers [redacted]

    …

Has been changed to:

8.4.6 Visit 13 (Week 10/Day 64) [UCB7665 4mg/kg]/ Visit 11 (Week 8/Day 50) [UCB7665 7mg/kg]]/ Visit 10 (Week 7/Day 43) [UCB7665 10mg/kg]

Visit 8 (Week 6/Day 36) [UCB7665 15mg/kg and UCB7665 20mg/kg]

This is the sixth visit in the Observation Period. A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. The following assessments will be performed at this visit:

- Blood sample for the following:
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Serum total IgG and IgG subclasses concentration
  - Exploratory safety biomarker [redacted] Blood samples are taken prior to dosing, 2 and 4 hours after end of infusion for exploratory safety biomarkers)

Change #69

8.3.7 Visit 14 (Week 11/Day 71) [UCB7665 4mg/kg]/ Visit 12 (Week 9/Day 57) [UCB7665 7mg/kg]

A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. This visit can be performed at home with a healthcare professional visiting the subject at his/her home. The following assessments will be performed at this visit:

Has been changed to:

8.3.7 Visit 14 (Week 11/Day 71) [UCB7665 4mg/kg]/
Visit 12 (Week 9/Day 57) [UCB7665 7mg/kg]/ Visit 11 (Week 8/Day 50) [UCB7665 10mg/kg]
Visit 9 (Week 7/Day 43) [UCB7665 15mg/kg and UCB7665 20mg/kg]

This is the seventh visit in the Observation Period. A visit window of ±2 days is applicable for this visit relative to the day of the final dosing visit. This visit can be performed at home with a healthcare professional visiting the subject at his/her home. The following assessments will be performed at this visit:

- Concomitant medications
- Concomitant medical procedures
- Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate)
- Recording of AEs
- Urine sample for urinalysis
- Blood sample for the following:
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Anti-UCB7665 antibodies
  - Exploratory safety biomarkers [redacted] Blood samples are taken prior to dosing, 2 and 4 hours after end of infusion for exploratory safety biomarkers)
  - Serum BAFF levels
  - Exploratory biomarker analysis

Change #70

8.3.8 End-of-Study Visit: Visit 15 (Week 13/Day 85) [UCB7665 4mg/kg]/
Visit 13 (Week 11/Day 71) [UCB7665 7mg/kg]

…

- 12-lead ECG
- Urine pregnancy test for women of childbearing potential
- Urine sample for urinalysis
- Blood sample for the following laboratory parameters:
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Anti-UCB7665 antibodies/IgG depletion assay
  - Serum total IgG and IgG subclasses concentration
  - ITP-specific autoantibodies [redacted]
- ITP bleeding scale

- NFI-MS
- Subject exit interview
- Serum cytokines, only in case of infusion reactions
- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.

Has been changed to:

8.4.8 End-of-Study Visit: Visit 15 (Week 13/Day 85) [UCB7665 4mg/kg]/
Visit 13 (Week 11/Day 71) [UCB7665 7mg/kg]/
Visit 12 (Week 10/Day 64) [UCB7665 10mg/kg]
Visit 10 (Week 9/Day 57) [UCB7665 15mg/kg and UCB7665 20mg/kg]

…

- 12-lead ECG (triplicate)

…

- Blood sample for the following:
  - Standard safety laboratories: hematology including coagulation parameters, clinical chemistry
  - Anti-UCB7665 antibodies
  - Serum total IgG and IgG subclasses concentration
  - ITP-specific autoantibodies [redacted]
- For all dose arms, collection of whole blood for exploratory RNA analyses
- NFI-MS
- Subject exit interview
- Serum cytokines, only in case of late infusion reactions visible during the visit
- Headache questionnaire, only if subject experiences severe headaches, followed by a neurological assessment (including fundoscopy). Additionally, other diagnostic procedures including but not limited to CT scan, MRI and/or LP for CSF collection to be performed if indicated at the discretion of the investigator, considering the local guidelines for performing LP in subjects with ITP.
- TB signs and symptoms questionnaire

Change #71

8.4 Early Withdrawal Visit

Paragraph #3

The assessments to be done at both the Early Withdrawal Visit as well as the End-of-Study Visit are the same as those at Visit 15 for the UCB7665 4mg/kg group or Visit 13 for the UCB7665 7mg/kg group, except for the subject exit interview which will be performed at the End-of-Study Visit only.

Has been changed to:

The assessments to be done at both the Early Withdrawal Visit as well as the End-of-Study Visit are the same as those at Visit 15 for the UCB7665 4mg/kg weekly (Dose Arm 1) group, Visit 13 for the UCB7665 7mg/kg weekly (Dose Arm 2) group, Visit 12 for the UCB7665 10mg/kg weekly (Dose Arm 3) group, or Visit 10 for the UCB7665 15mg/kg (Dose Arm 4) and UCB7665 20mg/kg (Dose Arm 5) groups, except for the subject exit interview which will be performed at the End-of-Study Visit only.

Change #72

9.1 Platelet counts

NEW bullet points added:

- Baseline-corrected AUEC for platelet count calculated from Baseline to the end of study visit
- Clinical Response: platelet count $\geq 30x10^9$/L and at least 2-fold increase from Baseline value and absence of bleeding
- Time to Clinical Response: time from starting treatment to achievement of Clinical Response
- Duration of Clinical Response: measured from achievement of Clinical Response to loss of Clinical Response (loss of Clinical Response defined as platelet count $<30x10^9$/L or less than 2-fold increase from Baseline platelet count or presence of bleeding)
- Complete Clinical Response: platelet count $\geq 100x10^9$/L and absence of bleeding
- Time to Complete Clinical Response: time from starting treatment to achievement of Complete Clinical Response
- Duration of Complete Clinical Response: measured from achievement of Complete Clinical Response to loss of Complete Clinical Response (loss of Complete Clinical Response defined as platelet count $<100x10^9$/L or presence of bleeding)
- No Clinical Response: platelet count $<30x10^9$/L or less than 2-fold increase from Baseline or presence of bleeding

NEW paragraph added:

The clinical response variables will be assessed only for visits for which both platelet counts and the ITP bleeding score are assessed (with the exception of the confirmatory platelet assessments which may be obtained at any visit [scheduled or unscheduled] provided that they meet the criteria below). In order to define a clinical response, the platelet count must be confirmed on 2 separate occasions at least 7 days apart (ie, the second assessment should be ≥168 hours after the first assessment). The time to response will be taken as the time to the first platelet assessment (obtained at the same time as the corresponding ITP bleeding score assessment). If the second assessment does not fulfill the required criteria for a clinical response, the subject will be considered as a nonresponder at the respective visits. In order to define a clinical response (or no

clinical response), the platelet count must be confirmed on 2 separate occasions; further details will be provided in the SAP. Absence of bleeding is indicated by Grade 0 for all domains of the SMOG. Presence of bleeding is indicated by a Grade of 1 or above, for at least one domain of the SMOG.

Change #73

9.1 Platelet counts

Refer to Section 14 for details of statistical analysis of these parameters.

Has been changed to:

Refer to Section 14 for details of statistical analysis of these variables.

Change #74

11 Assessment of other immunological variables

…

- Serum biomarkers levels over time

- Serum BAFF levels
- Plasma anti-UCB7665 antibodies/IgG depletion assay
- Cytokines

Cytokine samples will be taken at Baseline Visit for all subjects. At subsequent visits, cytokine samples will be taken only when the subject experiences infusion reactions.

Has been changed to:

…

- Serum BAFF levels
- Lymphocyte counts (B and T)
- Anti-UCB7665 antibodies
- Cytokines

Cytokine samples will be taken at Baseline Visit for all subjects. At subsequent visits, cytokine samples will be taken only when the subject experiences infusion reactions.

Change #75

12.1.1 Definition of adverse event

Paragraph #4:

Bleeding events should not be reported as an AE since these events will be assessed and reported during the ITP-BAT assessment. Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or more bleeding events should be reported as AEs.

Has been changed to:

Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or 2 bleeding events should not be reported as an AE since these events will be assessed and reported during the ITP-BAT assessment; CTCAE grade 3 or more bleeding events should be reported as AEs.

Change #76

12.1.9 Safety signal detection

Paragraph #1:

The safety variables and ADA results available after 7 days of the final dose of 3 and 6 subjects in the UCB7665 4mg/kg dose arm will be reviewed by the DMC (interim analysis 1 and 2) comprising at least 1 external expert, the UCB study physician, the UCB PS representative, and a biostatistician and will be summarized on an ongoing basis during the study so as to continuously evaluate the safety of subjects. The DMC will meet and reach a decision on whether or not the study can continue as planned, and whether or not the next dose arm can be started. Subsequently, safety variables and ADA results available after 7 days of the final dose of 3 and 6 subjects in the UCB7665 7mg/kg dose arm (together with all available data from the UCB7665 4 mg/kg dose arm) will be reviewed by the DMC (interim analysis 3 and 4).

Has been changed to:

The safety variables and ADA results available after 7 days of the final dose of 3 and 6 subjects in the UCB7665 4mg/kg weekly group (Dose Arm 1) will be reviewed by the DMC (interim analysis 1 and 2) comprising at least 1 external expert, the UCB study physician, the UCB PS representative, and a biostatistician and will be summarized on an ongoing basis during the study so as to continuously evaluate the safety of subjects. The DMC will meet and reach a decision on whether or not the study can continue as planned, and whether or not Dose Arm 2 can be started. Subsequently, safety variables and ADA results available after 7 days of the final dose of 3 and 6 subjects in the UCB7665 7mg/kg weekly (Dose Arm 2) (together with all available data from Dose Arm 1 and 2) will be reviewed by the DMC (interim analysis 3 and 4). The DMC will also meet and review safety data to add additional subjects to subsequent dose arms or to open subsequent dose arms. Further details are described in Section 5.1

The DMC may also decide to reduce the number of doses in each of the dose arms, to stop a dose arm or not to open a dose arm based on review of data during the study.

Change #77

12.5 Immediate reporting of adverse events

The following AEs must be reported immediately:

- SAE: AE that the investigator classifies as serious by the above definitions regardless of causality
- Suspected transmission of an infectious agent via a medicinal product
- AE of special interest (see Section 12.3)
- AE of interest (see Section 12.4)

Has been changed to:

The following AEs must be reported immediately using the SAE Report Form according to the procedure in Section 12.2.2:

- SAE: AE that the investigator classifies as serious by the above definitions regardless of causality
- Suspected transmission of an infectious agent via a medicinal product
- AE of special interest (see Section 12.3)
- AE of interest (see Section 12.4)
- Confirmed LTB, active TB, and NTBI (see Section 12.8.1)

Change #78

Table 12–2: Laboratory measurements				
Hematology	**Chemistry**	**Coagulation parameters**	**Urinalysis**	**Pregnancy test**
Basophils[a]	Calcium	INR	pH	Urine[b] HCG
Eosinophils[a]	Phosphate	Prothrombin time	Protein	Serum[c] HCG
Neutrophils[a]	Chloride	aPTT	Creatinine	
Lymphocytes[a]	Magnesium	Fibrinogen	Glucose	**Others**
Monocytes[a]	Potassium		Ketones	HbA1c
Hematocrit	Sodium		Urobilinogen	HIV
Hemoglobin	BUN		Bilirubin	Hepatitis B (HBsAg, anti-HBs, anti-HBc)
Platelet count	AST		Blood	Hepatitis C (anti-HCV)
RBC count	ALT		Nitrite	
WBC count	GGT		Albumin	
B- and T-Lymphocyte count	Total bilirubin		Leucocytes	
	Direct bilirubin (if indicated)			

Table 12–2: Laboratory measurements				
Hematology	**Chemistry**	**Coagulation parameters**	**Urinalysis**	**Pregnancy test**
	LDH			
	Total cholesterol			
	Triglycerides			
	ALP			
	Total protein			
	Albumin			
	α1-globulin, α2-globulin, and β-globulin			
	Creatinine			
	hs-CRP			
	Amylase			

ALP=alkaline phosphatase; ALT=alanine aminotransferase; anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; anti-HCV=hepatitis C virus antibody; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen;GGT=gamma-glutamyltransferase; HbA1c=glycosylated hemoglobin; HBsAg=hepatitis B surface antigen; HCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; hs-CRP=high-sensitivity C-reactive protein; INR=International Normalized Ratio; LDH=lactate dehydrogenase; RBC=red blood cell; WBC=white blood cell

[a] Absolute as well as percentages for the differential leucocyte counts will be performed.

[b] Urine pregnancy test will be performed predose on dosing days and at End-of-Study Visit.

[c] Serum pregnancy test is done at Visit 1 (Screening) and to confirm results of positive urine test if applicable.

Has been changed to:

Table 12–2: Laboratory measurements

Hematology	Chemistry	Coagulation parameters	Urinalysis	Pregnancy test
Basophils[a]	Calcium	INR	pH	Urine[b] HCG
Eosinophils[a]	Phosphate	Prothrombin time	Protein	Serum[c] HCG
Neutrophils[a]	Chloride	aPTT	Creatinine	
Lymphocytes[a]	Magnesium	Fibrinogen	Glucose	**Others**
Monocytes[a]	Potassium		Ketones	HbA1c
Hematocrit	Sodium		Urobilinogen	HIV
Hemoglobin	BUN		Bilirubin	Hepatitis B (HBsAg, anti-HBs, anti-HBc)
Platelet count	AST		Blood	Hepatitis C (anti-HCV)
RBC count	ALT		Nitrite	Tuberculosis[d]
WBC count	GGT		Albumin	
	Total bilirubin		Leucocytes	**Safety Biomarkers**[e]
	Direct bilirubin (if indicated)			[redacted]
	LDH			[redacted]
	Total cholesterol			[redacted]
	Triglycerides			[redacted]
	ALP			[redacted]
	Total protein			
	Albumin			
	α1-globulin, α2-globulin, β-globulin, γ-globulin			
	Creatinine			
	hs-CRP			
	Amylase			

[a] Absolute as well as percentages for the differential leucocyte counts will be performed.
ALP=alkaline phosphatase; ALT=alanine aminotransferase; anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; anti-HCV=hepatitis C virus antibody; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen;GGT=gamma-glutamyltransferase;

HbA1c=glycosylated hemoglobin; HBsAg=hepatitis B surface antigen; HCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; hs-CRP=high-sensitivity C-reactive protein; INR=International Normalized Ratio; LDH=lactate dehydrogenase; RBC=red blood cell; WBC=white blood cell

[b] Urine pregnancy test will be performed predose on dosing days and at End-of-Study Visit.

[c] Serum pregnancy test is done at Visit 1 (Screening) and to confirm results of positive urine test if applicable.

[d] Interferon-gamma release assay by central laboratory.

[e] May include but not limited to the biomarkers listed in the table. Samples collected for safety biomarkers at Baseline (Visit 2) and 4 hours post dosing (Visit 2) for all subjects and during follow up only in subjects with severe headache and/or moderate to severe GI disturbances. The Baseline samples will only be analysed in case he subject experienced a severe headache and/or moderate to severe GI disturbance

Change #79

Table 12-3: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN[b]	NA	Hepatology consult[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 12.7.1.3); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values.[d]
≥8xULN	NA	NA				
≥3xULN	NA	Yes		Immediate, temporary or permanent, IMP discontinuation.		
≥3xULN (and ≥2x baseline) and <5xULN	<2xULN	No	Discussion with Medical Monitor required if the criterion that allows for IMP continuation is met.	Further investigation – immediate IMP discontinuation not required (see Section 12.7.1.2).	Not required unless otherwise medically indicated (at discretion of investigator).	

Table 12-3: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥5xULN (and ≥2x baseline)	<2xULN	No	Discussion with Medical Monitor required.	Immediate, permanent IMP discontinuation.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 12.7.1.3).	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values. [d]

Table 12-3: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
ALP=alkaline phosphatase; ALT=alanine aminotransferase; ASAP=as soon as possible; AST=aspartate aminotransferase; HCP=healthcare practitioner; IMP=investigational medicinal product; NA=not applicable; PDILI=potential drug-induced liver injury; ULN=upper limit of normal [a] Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause). [b] If the subject also has ≥2xULN ALP, the possibility of an indication of biliary obstruction should be discussed with the Medical Monitor. [c] Details provided in Section12.7.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. [d] Unless an alternative monitoring schedule is agreed by the investigator and UCB responsible physician. Determination of stabilization is at the discretion of the investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.						

Has been changed to:

Table 12-3: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN[b]	NA	Hepatology consult[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 12.7.1.3); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline values.[d]
≥3xULN	NA	Yes		Immediate, temporary or permanent, IMP discontinuation.		
≥3xULN (and ≥2x Baseline) and <5xULN	<2xULN	No	Discussion with Medical Monitor required if the criterion that allows for IMP continuation is met.	Further investigation – immediate IMP discontinuation not required (see Section 12.7.1.2).	Not required unless otherwise medically indicated (at discretion of investigator).	
≥5xULN (and ≥2x Baseline)	<2xULN	No	Discussion with Medical Monitor required. Hepatology consult required if ALT or AST ≥8xULN.	Immediate, permanent IMP discontinuation.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 12.7.1.3).	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline values.[d]

Table 12-3: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**

ALP=alkaline phosphatase; ALT=alanine aminotransferase; ASAP=as soon as possible; AST=aspartate aminotransferase; HCP=healthcare practitioner; IMP=investigational medicinal product; NA=not applicable; PDILI=potential drug-induced liver injury; ULN=upper limit of normal

[a] Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

[b] If the subject also has ≥2xULN ALP, the possibility of an indication of biliary obstruction should be discussed with the Medical Monitor.

[c] Details provided in Section 12.7.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

[d] Unless an alternative monitoring schedule is agreed by the investigator and UCB responsible physician. Determination of stabilization is at the discretion of the investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

Change #80

Section 12.8 Other safety measurements

NEW sections added:

12.8.1 Assessment and management of TB and TB risk factors

With the currently available data, TB is not considered as an important potential or identified risk for treatment with UCB7665. As immunomodulation may carry a risk of new or activation of latent TB, UCB has conservatively developed TB detection and management procedures taking into account the most current recommendations of international guidelines (2010 WHO) and most recent literature, covering any infection by the mycobacteria tuberculosis complex.

Appropriate rigorous precautions are being taken within this protocol to monitor for the risk of TB infection prior to study entry and during the study (see Section 6.2.2 (Exclusion Criterion #25) and Section 6.4. Following are the key considerations of these procedures:

12.8.1.1 TB Tests at Screening

The interferon-gamma release assay (IGRA) and TB questionnaire are required as indicated in Schedule of Assessments.

- TB screening is mandatory both before study entry and during the conduct of the study. The preferred screening test is **IGRA performed at a Central Laboratory**.
    - The IGRA result must be negative for subjects to enroll in this study
    - Subjects who test positive for IGRA test should be excluded from the study and referred for appropriate medical evaluation according to the local medical practice guidelines.
    - If the result of the IGRA test is indeterminate, the particular IGRA test previously performed may be repeated once; if positive or indeterminate on retest, the subject may not be randomized to study drug and, if already randomized, must undergo appropriate study specified withdrawal procedures. The retest must be done during the protocol-defined Screening window.

12.8.1.2 Monitoring for TB during the study

Subjects will be monitored for signs/symptoms of TB using routine pharmacovigilance measures for Adverse Events. Subjects reporting AEs related to signs/symptoms of TB will be evaluated for LTB and active TB according to the local medical practice guidelines.

Subjects with confirmed LTB or active TB or NTMBI infection will be immediately withdrawn from the study as described in Withdrawal Criteria. Confirmed LTB, active TB and NTMBI must be reported to the Sponsor immediately regardless of seriousness using the SAE Report Form. Additional information received by the Investigator should be provided within 24 hours of awareness.

Once withdrawn from study treatment, subjects should return for the POET, complete all early withdrawal assessments, and complete the follow-up visits.

12.8.1.3 TB tests at Final /End of Study Visit

Subjects will be evaluated for signs and symptoms of latent or active TB infection and for risk factors of exposure to TB, using the TB questionnaire, at the Final /End of Study (EOS) Visit. See the 'TB signs and symptoms questionnaire' section for further instructions on using the questionnaire.

12.8.1.4 Signs and symptoms of Tuberculosis

The Investigator should consider all potential sites of infection when assessing for TB during the physical examination, and other evaluations, and based on the subject's history.

Common symptoms with which the subject may present with include cough, blood in sputum, night sweats, lymphadenitis, joint pain/swelling, spinal deformity, headache/confusion, abdominal pain mimicking inflammatory bowel disease, frequent or painful urination, scrotal mass in men and pelvic inflammatory disease in women as well as other symptoms, or nonspecific symptoms. This is not an exhaustive list and unusual presentations should always be considered.

12.8.1.4.1 TB signs and symptoms questionnaire

The questionnaire "Evaluation of signs and symptoms of tuberculosis" should be used as a source document. The questionnaire will assist with the identification of subjects who may require therapy for TB. A subject who answers "Yes" to the question [redacted] at Screening is excluded. A "Yes" response to any of the other questions within the questionnaire at Screening should trigger further careful assessment to determine if subject has latent or active TB (see Section 6.2.2 (Exclusion Criterion #25). A "Yes" response to any of the questions during/end of the study should trigger further assessments as per local medical guidelines to determine if the subject has either LTB or active TB infection.

12.8.1.4.2 LTB infection, active TB or other NTMBI identified during study

During the study, subjects who develop evidence of LTB infection or active TB or NTMBI must immediately stop further administration of study drug and will be referred to an appropriate medical specialist for further evaluation.

Confirmed LTB or active TB or NTMBI must be reported to the Sponsor immediately as described above.

Change #81

Section 12.8.5 12-Lead ECG

Paragraph #1:

A standard 12-lead ECG will be performed at visits as specified in the schedule of study assessments (Section5.2). Care should be taken to assure proper lead placement and quality ECG recordings. Subjects should rest in a supine position in a controlled, calm environment for at least 15 minutes prior to the recording and should be motionless during the recording. The ECG will be performed in triplicate prior to blood collection for assessment of laboratory parameters.

Has been changed to:

A standard 12-lead ECG will be performed at visits as specified in the schedule of study assessments (Section 5.2). Care should be taken to assure proper lead placement and quality

ECG recordings. Subjects should rest in a supine position in a controlled, calm environment for at least 15 minutes prior to the recording and should be motionless during the recording.

NEW paragraph #2 added:

The ECG will be performed in triplicate prior to blood collection for assessment of laboratory parameters. Three ECGs should be recorded in a time frame of 5 minutes with at least 1 minute difference, 1-2 minutes between the ECGs.

Change #82

Section 14.1 Definition of analysis sets

Paragraph #4:

The analysis of the PD, efficacy, and immunologic variables will be performed on the FAS. Selected outputs may be repeated for the Per Protocol Set (PPS). Further details will be provided in the SAP.

Paragraph #5 and #6:

Per Protocol Set:

The PPS is a subset of the FAS, consisting of those subjects who had received all foreseen sc infusions, had a platelet count measurement during the Observation Period, and no important protocol deviations that may potentially affect the platelet count as confirmed during a pre-analysis review of the data prior to database lock. Protocol deviations may not necessarily lead to total exclusion of a subject from the PPS but may lead to exclusion of specific data.

Pharmacokinetic Per Protocol Set (PK-PPS):

The PK-PPS is a subset of the FAS, consisting of those subjects who had no important protocol deviations potentially affecting the plasma concentration of UCB7665, as confirmed during a pre-analysis review of the data prior to database lock.

Has been changed to:

The analysis of the PD (excluding total IgG, and IgG subclasses), efficacy, and immunologic variables will be performed on the FAS. Selected outputs may be repeated for the PD Per Protocol Set (PD-PPS). Further details will be provided in the SAP.

Pharmacokinetic Per Protocol Set (PK-PPS):

The PK-PPS is a subset of the FAS, consisting of those subjects who had no important protocol deviations potentially affecting the plasma concentration of UCB7665, as confirmed during a pre-analysis review of the data prior to database lock. Protocol deviations may not necessarily lead to total exclusion of a subject from the PK-PPS but may lead to exclusion of specific data.

Pharmacodynamic Per Protocol Set (PD-PPS)

The PD-PPS is a subset of the FAS, consisting of those subjects who had no important protocol deviations potentially affecting the serum concentration of total IgG, as confirmed during a pre-analysis review of the data prior to database lock. Protocol deviations may not necessarily lead to total exclusion of a subject from the PD-PPS but may lead to exclusion of specific data.

The PD-PPS will be used for the analysis of the total IgG, and IgG subclasses.

Change #83

Section 14.3.2 Other safety analysis

Paragraphs #1 and #2:

The absolute and relative frequencies for subjects with a given TEAE with respect to the preferred term according to the latest available version of the MedDRA, as well as the absolute frequencies of the individual TEAEs that have occurred, will be determined within each system organ class. Additional tables will summarize TEAEs by maximum intensity and causal relationship with UCB7665, as judged by the investigator. Adverse events will be categorized by severity according to the CTCAE version 4.03 grading. In case the CTCAE grading is not available, the intensity (mild/moderate/severe) will be utilized. The TEAEs leading to discontinuation of IMP and treatment-emergent SAEs will also be summarized. The action taken, time of onset relative to dosing, and duration of each AE will be listed only.

For the continuous laboratory variables, the values and changes from Baseline will be summarized at each time point. For categorized values according to the reference range, shift tables from Baseline to each post-Baseline time point will be presented for selected variables to be defined in the SAP. Values outside the reference range will be flagged in the data listings.

Has been changed to:

The absolute and relative frequencies for subjects with a given TEAE with respect to the preferred term according to the latest available version of the MedDRA, as well as the absolute frequencies of the individual TEAEs that have occurred, will be determined within each system organ class. Additional tables will summarize TEAEs by maximum intensity and causal relationship with UCB7665, as judged by the investigator. Adverse events will be categorized by severity according to the CTCAE version 4.03 grading. In case the CTCAE grading is not available, the intensity (mild/moderate/severe) will be utilized. For the purpose of the tabulations CTCAE grades will be aligned with the intensity classifications (mild/moderate/severe) to enable pooling of the AEs in the summaries. The TEAEs leading to discontinuation of IMP and treatment-emergent SAEs will also be summarized. The action taken, time of onset relative to dosing, and duration of each AE will be listed only.

For the continuous laboratory variables, the values and changes from Baseline will be summarized at each time point. For categorized values according to the reference range, shift tables from Baseline to each post-Baseline time point will be presented for selected variables to be defined in the SAP. Values outside the reference range will be flagged in the data listings. The number and percentage of subjects with markedly abnormal laboratory results (based on CTCAE grading) will be tabulated for each dose arm.

Change #84

Section 14.4.1 Efficacy analysis

The main efficacy variable is the maximum increase from Baseline in platelet count during the study. The maximum increase from Baseline and maximum platelet count during the study will be summarized by dose arm.

In addition, all measurements of platelet count will be summarized by dose arm and time point using descriptive statistics (including changes from Baseline).

For each dose arm a 1-sided t-test will be applied to assess if the average maximum increase from Baseline is greater than zero. In case the assumptions for the-t-test are not fulfilled a variance-stabilizing transformation may be applied in addition and/or an alternative nonparametric method may be considered. Further details will be provided in the SAP.

The Response rate, Complete Response rates, and platelet count $\geq 50x10^9$/L will be summarized (number of subjects and percentages) and presented with 90% 2-sided confidence intervals for the rate of responders at each time point and overall (across all time points). Response and Complete Response are defined in Section 4.2.

Time to Response, time to Complete Response, time to platelet count $\geq 50x10^9$/L, duration of Response, duration of Complete Response, and duration of platelet count $\geq 50x10^9$/L will be calculated and summarized by dose arm.

The results from the ITP bleeding scale will be summarized at each time point and will include the grades for each of the 3 major domains: skin (S), visible mucosae (M), and organs (O).

Results of the NFI-MS will be summarized at each time point, using summary scores where applicable. Changes from Baseline will be calculated and summarized.

Has been changed to:

The main efficacy variable is the maximum increase from Baseline in platelet count during the study. The maximum increase from Baseline and maximum platelet count during the study will be summarized by dose arm.

In addition, all measurements of platelet count will be summarized by dose arm and time point using descriptive statistics (including changes from Baseline).

For dose arms with ≥10 subjects, a 1-sided t-test will be applied to assess if the average maximum increase from Baseline is greater than zero. In case the assumptions for the-t-test are not fulfilled, an alternative nonparametric method may be considered. Further details will be provided in the SAP. The Response, Complete Response, and platelet count $\geq 50x10^9$/L will be summarized (number of subjects and percentages) and presented with 90% 2-sided confidence intervals for the rate of responders at each time point and overall (across all time points). Response and Complete Response are defined in Section 4.3. The analysis will be repeated for the Clinical Response variables defined in Section 4.3.

Time to Response, time to Complete Response, time to platelet count $\geq 50x10^9$/L, duration of Response, duration of Complete Response, duration of platelet count $\geq 50x10^9$/L, and Baseline-corrected AUEC for platelet count will be calculated and summarized by dose arm. The time to first response will be analyzed using a log-rank test and displayed using Kaplan-Meier curves. The time to Response, time to Complete Response, and respective durations will be summarized by dose arm.

The results from the ITP bleeding scale will be summarized at each time point and will include the grades for each of the 3 major domains: skin (S), visible mucosae (M), and organs (O). In addition the number and percentage of subjects with severe or clinically relevant bleeding and number and percentage of subjects with absence of bleeding will be summarized at each time point.

Results of the NFI-MS will be summarized at each time point, using summary scores where applicable. Changes from Baseline will be calculated and summarized.

Additional subgroup analyses may be performed as needed and further details will be provided in SAP regarding these analyses.

Change #85

Section 14.4.3 Pharmacodynamic analysis

For all PD variables, descriptive statistics for the values and change from Baseline and/or percentage change from Baseline will be tabulated by time point. If appropriate, measurements will be log-transformed.

The PD variables will include ITP-specific autoantibodies [redacted] total IgG, and IgG subclasses. In addition, for total IgG, the maximum decrease from Baseline and minimum value will be evaluated and summarized. Figures of mean values over time and changes from Baseline will be presented.

Has been changed to:

For all PD variables, descriptive statistics for the values and change from Baseline and/or percentage change from Baseline will be tabulated by time point.

The PD variables will include ITP-specific autoantibodies [redacted] total IgG, and IgG subclasses. In addition, for total IgG, the maximum decrease from Baseline and minimum value will be evaluated and summarized. Figures of mean values over time and changes from Baseline will be presented.

Change #86

Section 14.4.4 Immunologic variables

Paragraphs #1 and #2:

All immunologic variables including concentrations of immunoglobulins (IgA, IgE, and IgM), serum (C3 and C4) and plasma (C3a and C5a) complement levels, serum biomarkers [redacted] serum BAFF levels and the results of the IgG depletion assay will be summarized by dose arm over time (including changes from Baseline) using descriptive statistics. Figures of mean values over time and changes from Baseline may be presented.

The ADA status (negative/positive) and changes in relative mass units from Baseline will be summarized by dose arm; figures will also be presented.

Has been changed to:

All immunologic variables including concentrations of immunoglobulins (IgA, IgE, and IgM), serum (C3 and C4) and plasma (C3a and C5a) complement levels, serum BAFF levels, and lymphocyte counts (B and T) will be summarized by dose arm over time (including changes from Baseline) using descriptive statistics. Figures of mean values over time and changes from Baseline may be presented.

The ADA status (negative/positive) will be summarized by dose arm at each visit and overall; figures will also be presented in conjunction with PK concentrations of UCB7665.

Change #87

14.4.5.2 Subject characteristics

Bullet point #3:

- Prior and concomitant medications

Has been changed to:

- Past, prior, and concomitant medications

Change #88

Section 14.7 Planned interim analysis and data monitoring

Paragraph #2:

For the sequential adaptive design in this study, at least 4 interim analyses will be performed. Safety data from the interim analyses will be reviewed by the DMC to monitor the safety, to adapt the dose regimen, and to decide when and if the UCB7665 7mg/kg dose arm should be opened. Planned dosing may be discontinued for all subjects on a dose arm (see Section 6.5).

Paragraph #4:

If the study continues without modifications, the next interim analysis will take place after data from 3 additional subjects are available. Based on the available combined data of the first 6 subjects, the DMC will decide if the 3x7mg/kg dose arm can be initiated. If the new dose arm will be initiated and if the 5x4mg/kg will be continued, new subjects will be randomized to 1 of the 2 dose arms in an allocation ratio of 1:1 (Once 15 subjects are in the 4mg/kg group, the remaining subjects will not be randomized. They will be allocated to the 7mg/kg group).

Paragraph #7:

The fourth interim analysis and review of data by DMC will take place after safety data (7 days after final dose) is available for the first 6 subjects in Dose Arm 2.

The timing of further interim analysis and review of data by DMC will be decided by the DMC members at the fourth DMC meeting.

Paragraph #8:

During these reviews recruitment in the dose arms will not be stopped. If needed, subsequent DMC meetings may take place and the frequency will be detailed in the DMC charter.

Paragraph #9:

The DMC will monitor data for all reported AEs, clinical findings, including vital signs (pulse rate, blood pressure, temperature, and respiratory rate) and safety laboratory values, and immunogenicity data. Pharmacokinetic data will not be required for DMC review as blood sampling will be performed at a single time point per visit only. Thus, PK data is restricted only to the concentration data and can therefore make no plausible contribution to the assessment of safety in this particular study.

Paragraph #12:

A detailed description of the DMC composition, processes and responsibilities, criteria to escalate to the next dose arm, and criteria to stop a dose arm will be provided in a separate DMC charter.

Has been changed to:

Paragraph #2:

For the sequential adaptive design in this study, at least 11 interim analyses will be performed. Safety data from the interim analyses will be reviewed by the DMC to monitor the safety, to adapt the dose regimen, and to decide when and if the UCB7665 7mg/kg weekly group (Dose Arm 2), UCB7665 10mg/kg weekly group (Dose Arm 3), UCB7665 15mg/kg group (Dose Arm 4) and UCB7665 20mg/kg group (Dose Arm 5) should be opened. Planned dosing may be discontinued for all subjects in a dose arm (see Section 6.5).

Paragraph #4:

If the study continues without modifications, the next interim analysis will take place after data from 3 additional subjects are available. Based on the available combined data of the first 6 subjects, the DMC will decide if the 3x7mg/kg dose arm can be initiated. If the new dose arm will be initiated and if the 5x4mg/kg will be continued, new subjects will be randomly assigned to 1 of the 2 dose arms in an allocation ratio of 1:1

Paragraphs #6 and #7:

The fourth planned interim analysis and review of data by DMC will take place after safety data (7 days after final dose) is available for the first 6 subjects in Dose Arm 2.

All subsequent DMC meetings will be dependent on opening of Dose Arms 3, 4 and 5 and decisions of the previous DMC meetings. Review of data will occur after every 3 subjects. More details are included in the DMC charter.

Paragraph #8:

During the first three interim analyses, recruitment in the Dose Arms 1 and 2 will not be stopped. If needed, subsequent DMC meetings may take place and the frequency will be detailed in the DMC charter.

Paragraph #11:

A detailed description of the DMC composition, processes and responsibilities, criteria to escalate to the next dose arm, and criteria to stop, or continue a dose arm will be provided in a separate DMC charter.

Change #89

Section 14.8 Determination of sample size

Paragraph s#1 and #2

The sample size of 15 subjects, in each dose arm, is mainly based on the efficacy objective of the study. In addition the 2x15 subjects ensure that sufficient data are available to form conclusions about the safety of administering UCB7665.

An approximate sample size calculation for the efficacy variable "maximum increase from Baseline in platelet count" shows that 15 subjects would be sufficient to show a change from Baseline with 1-sided testing at 5% and power of 80%. The anticipated change is based on an assumed Baseline average of $25x10^9$/L and a clinically meaningful maximum value of $100x10^9$/L. The calculation made use of platelet count data presented in a publication by Robak T (Robak et al, 2009), but it is approximate as maximum changes from Baseline for individual subjects were not available, necessitating the use of the maximum average platelet count instead. The SD is taken from visual inspection.

Has been changed to:

The sample size of 15 subjects in Dose Arms 1 and 2, is mainly based on the efficacy objective of the study. In addition the 15 subjects in Dose Arms 1 and 2 ensure that sufficient data are available to form conclusions about the safety of administering UCB7665. Based on the safety data from dose arms 1 and 2, the sample size of 6 to 12 subjects in Dose Arms 3, 4 and 5 is judged to be sufficient in order to explore subjects' safety and IgG reductions under different dose regimens and is not based on a formal sample size calculation.

For Dose Arms 1 and 2, an approximate sample size calculation for the efficacy variable "maximum increase from Baseline in platelet count" shows that 15 subjects would be sufficient to show a change from Baseline with 1-sided testing at 5% and power of 80%. The anticipated change is based on an assumed Baseline average of $25x10^9$/L and a clinically meaningful maximum value of $100x10^9$/L. The calculation made use of platelet count data presented in a publication by Robak T (Robak et al, 2009), but it is approximate as maximum changes from Baseline for individual subjects were not available, necessitating the use of the maximum average platelet count instead. The SD is taken from visual inspection.

Change #90

Section 15.1 Informed consent

NEW paragraph added:

Subjects have the right to withdraw their consent for the exploratory genomic substudy at any point without any impact on their care or participation in the main study. In this case, any data already generated on the samples will be retained and used, but no further analysis will occur.

Change #91

Section 15.4 Subject privacy

NEW paragraphs added:

Genetic analysis data will not be shared with the subjects and will be subject to the highest level of data protection, as per European regulations.

Samples may be shared with collaborators working within UCB and may be analyzed at a third party site, but only in relation to the aims of this exploratory analysis as detailed in this study protocol. Samples may be stored for up to 20 years and maybe used at any time up to that point. Samples will remain under the control of UCB at all times and may be destroyed at any point before the 20 year expiration date.

Change #92

Section 17 References

NEW reference:

Johnsen J. Pathogenesis in immune thrombocytopenia: new insights. Hematology Am Soc Hematol Educ Program. 2012;2012:306-12.

19 DECLARATION AND SIGNATURE OF INVESTIGATOR

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.

I will ensure that all subinvestigators and other staff members read and understand all aspects of this protocol.

I have received and read all study-related information provided to me.

The objectives and content of this protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by UCB.

All rights of publication of the results reside with UCB, unless other agreements were made in a separate contract.

Investigator:

Printed name	Date/Signature

20 SPONSOR DECLARATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol and according to current Good Clinical Practice.

TP0001-Protocol Amendment 3 A multicenter, open-label, multiple-dose study to evaluate the safety, tolerability, and efficacy of UCB7665 in subjects

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
[redacted]	Clinical Approval	16-Feb-2017 15:58 GMT+01
	Clinical Approval	17-Feb-2017 13:51 GMT+01
	Clinical Approval	17-Feb-2017 14:34 GMT+01