Clinical Study Report

NGAM-10

16.1.1 Study Protocol and Study Protocol Amendments

16.1.1.1 Protocol Version 01 (30 Jan 2019)

16.1.1.2 Protocol Amendment #1 (21 May 2019)

16.1.1.3 Protocol Version 02 (21 May 2019)

16.1.1.4 Protocol Amendment #2 (05 Aug 2019)

16.1.1.5 Protocol Version 03 (05 Aug 2019)

16.1.1.6 Protocol Amendment #3 (27 Apr 2020)

16.1.1.7 Protocol Version 04 (27 Apr 2020)

16.1.1 Study Protocol and Study Protocol Amendments

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CLINICAL STUDY PROTOCOL

NGAM-10

Post-Marketing Study to Evaluate the Efficacy and Safety of PANZYGA in Pediatric Patients with Chronic Immune Thrombocytopenia (ITP)

Investigational Product:	PANZYGA
Indication:	Chronic Immune Thrombocytopenia (ITP)
Study Design:	Prospective, open-label, single-arm, multi-center study
Sponsor:	Octapharma USA 121 River Street, 12th Floor Hoboken, NJ 07030
Study Number:	NGAM-10
IND Number / BLA Number:	IND 14121 / BLA 125587
Development Phase:	Phase 4
Planned Clinical Start:	Q2/Q3 2019
Planned Clinical End:	Q1 2022
Date of Protocol:	30-Jan-2019
Version:	01

STUDY OUTLINE

Name of Sponsor/Company: Octapharma USA	
Name of Investigational Product: PANZYGA	**Protocol Identification Code:** NGAM-10
Name of Active Ingredient: Immune globulin human-ifas	**Date of Final Protocol:** 30-Jan-2019

Title of Study:

Post-Marketing Study to Evaluate the Efficacy and Safety of PANZYGA in Pediatric Patients with Chronic Immune Thrombocytopenia (ITP)

Indication:

Chronic Immune Thrombocytopenia (ITP)

Number of Study Centre(s):

Up to 8 sites in the USA

Objectives:

Primary Objective:

The primary objective is to evaluate the efficacy of PANZYGA in increasing the platelet count in pediatric patients with chronic ITP.

Secondary Objectives:

The secondary objectives of this study are to:

- Assess safety of up to 2 g/kg PANZYGA (1 g/kg PANZYGA on Day 1 and an optional dose of 1 g/kg PANZYGA on Day 3) infused in the pediatric population within the scope of the clinical study
- Determine the time to reach a platelet count of $\geq 50 \times 10^9$/L
- Determine duration of time during which the platelet count is maintained at the level $\geq 50 \times 10^9$/L
- Determine the maximum platelet count during the study

Study Design:

This is a prospective, open-label, single-arm, multicenter, Phase 4 study evaluating the efficacy and safety of PANZYGA in pediatric patients with chronic ITP.

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Number of Patients:

At least 20 patients

Patient Selection Criteria:

Inclusion Criteria:

1. Females and males aged from ≥1 year to <18 years old
2. Confirmed diagnosis of Chronic Immune Thrombocytopenia (ITP) according to American Society of Hematology (ASH) 2011 guidelines
3. Platelets count $<30x10^9$/L at the Baseline Visit
4. Voluntarily given written informed consent (provided by patient's parent or legal guardian) and assent (provided by patient [if age-appropriate per IRB requirements])
5. Females of childbearing potential have been using at least 1 acceptable form of birth control for a minimum of 30 days (or a minimum of 3 months for hormonal contraceptives) prior to the Screening visit, and must agree to use at least 1 acceptable method of contraception for 30 days after the last dose of PANZYGA. Acceptable methods of birth control for this study include: intrauterine device (IUD), hormonal contraception, male or female condom, spermicide gel, diaphragm, sponge, or cervical cap. Abstinence is not considered an acceptable method of birth control.
6. Parent or legal guardian must agree and be willing to assist the participant attend study visits, and to follow all protocol requirements and instructions of the study doctor

Exclusion Criteria:

1. Thrombocytopenia secondary to other diseases (such as Acquired Immunodeficiency Syndrome [AIDS] or systemic lupus erythematosus [SLE]), drug-related thrombocytopenia, or congenital thrombocytopenia
2. Administration of intravenous immunoglobulin (IGIV) or anti-D immunoglobulin within 3 weeks before enrollment
3. Administration of thrombopoietin receptor agonists when the dose has NOT been stable within 3 weeks before enrollment and a dosage change is planned before Day 32
4. Administration of oral immunosuppressants when the dose has NOT been stable during the preceding 2 months (2 weeks for long-term corticosteroid therapy) and a dosage change is planned before Day 32 (Note: topical agents and inhaled corticosteroid therapy use is permitted)
5. Administration of long-term anti-prolific agents or attenuated androgen therapy when the dose has NOT been stable during the preceding 2 months and no dosage change is planned until Day 32
6. Nonresponsive to previous treatment with IGIV or anti-D immunoglobulin
7. Evidence of an active major bleeding episode at Screening
8. Splenectomy in the previous 4 weeks or planned splenectomy throughout the study period
9. Evans syndrome (experiencing active disease with 2 out of 3 of the following: autoimmune thrombocytopenia, autoimmune hemolytic anemia, and/or autoimmune neutropenia)
10. Known or suspected human immunodeficiency virus (HIV), hepatitis B virus (HBV), and/or hepatitis C virus (HCV) infections
11. Emergency surgery in the previous 4 weeks
12. Severe liver and/or kidney disease (alanine aminotransferase [ALT] >3x upper limit of normal (ULN), aspartate aminotransferase [AST] >3x upper limit of normal (ULN), and/or creatinine >120 µmol/L)
13. History of severe hypersensitivity to blood or plasma derived products, or any component of the PANZYGA
14. Known immunoglobulin A (IgA) deficiency and antibodies against IgA
15. History of, or suspected alcohol or drug abuse in the previous year
16. Females who are pregnant or nursing
17. Unable or unwilling to comply with the study protocol
18. Receipt of any other investigational medicinal product within 3 months before study entry
19. Risk factors* for thromboembolic events in whom the risks outweigh the potential benefit of PANZYGA treatment.

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20. Any other condition(s), that in the Investigator's opinion, make it undesirable for the patient to participate in the study or may interfere with protocol compliance.

* Risk factors include, but are not limited to: obesity, advanced age, hypertension, diabetes, a history of atherosclerosis/vascular disease or thrombotic events, hyperlipidemia, multiple cardiovascular risk factors, acquired or inherited thrombophilic disorders, prolonged periods of immobilization, severe hypovolemia, central venous catheterization, active malignancy and/or known or suspected hyperviscosity.

Test Product, Dose, and Mode of Administration:

PANZYGA (Immune Globulin, intravenous, human-ifas). PANZYGA must be stored and transported light-protected at +2°C (36°F) to +8°C (46°F) and must be brought to room temperature before use.

Patients will receive a dose of 1 g/kg body weight PANZYGA given on Day 1 and optionally another dose of 1 g/kg PANZYGA given on Day 3; body-weight dependent doses will be based on each patient's weight collected at Baseline. Total PANZYGA doses will be 1 g/kg for patients receiving only 1 dose on Day 1 and 2 g/kg for those receiving the optional Day 3 dose. Prior to the Day 3 infusion, each patient's preinfusion platelet count will be reviewed by the Investigator. If the Day 3 platelet count shows evidence of response as indicated by the platelet count at least doubling from Baseline count AND is >50x10^9/L, the Day 3 infusion **will not be** administered. If the Baseline platelet count has doubled but is ≤50x10^9/L, the Day 3 infusion **will be** administered.

PANZYGA will be delivered by intravenous infusion according to the recommended flow rates:

- Initial infusion rate of 0.01 mL/kg/min (60 mg/kg/hr) for the first 30 minutes
- If tolerated, increase to 0.02 mL/kg/min (120 mg/kg/hr) for the second 30 minutes
- If tolerated, increase to 0.04 mL/kg/min (240 mg/kg/hr) for the third 30 minutes
- If tolerated, increase to 0.08 mL/kg/min (480 mg/kg/hr) for the remainder of the infusion.

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Infusion rates should not exceed 0.08 mL/kg/min and should not exceed 8.0 mL/min. The infusion rate may be gradually increased as tolerated by the patient.

If an adverse event (AE) occurs during infusion, the infusion rate should be reduced to half the rate at which the event occurred, or the infusion should be interrupted until symptoms subside. The infusion may then be resumed at a rate tolerated by the patient.

The batch number(s) used will be recorded in the study documentation and electronic data capture (EDC) system.

Duration of Treatment:

Screening Period: 1 week

Treatment Period: up to 3 days

Follow-up Period: 29 days

Reference Therapy, Dose, and Mode of Administration:

Not Applicable

Study Outcome Parameters (Primary and Secondary Endpoints):

Primary Endpoint:

The primary efficacy parameter is defined as an increase in platelet count at least once to ≥50x10^9/L within 7 days after the first infusion, ie, by Day 8 (increase must occur at least once on any day up to and including Day 8). This definition of clinical response will serve as the basis for the primary endpoint, the response rate (ie, the proportion of patients with an elevation of platelet count at least once to ≥50x10^9/L within 7 days [ie, by Day 8] after the first infusion).

Secondary Endpoints:

- Time to reach a platelet count of ≥50x10^9/L
- Duration of platelet response defined as the number of days the platelet count remains above ≥50x10^9/L
- Maximum platelet count during the study

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Safety Parameters:

- AEs
- Vital signs (blood pressure, heart rate, temperature, respiratory rate)
- Physical examination
- Laboratory parameters: hematology (including reticulocytes), hemolysis, platelet count, serum chemistry (including lactase dehydrogenase [LDH]).

Study Procedures:

The study will be conducted in accordance with ICH-GCP and US FDA regulations.

The Flow Chart of Assessments specifies the procedures that will be performed at each study visit.

Baseline Visit

After appropriate information about the study and PANZYGA has been provided and written informed consent/assent has been obtained, patients will be evaluated for study eligibility according to the inclusion/exclusion criteria. These evaluations will include demographics, medical/surgical history, current medications, physical examinations, blood and urine samples, along with other safety and baseline evaluations as specified in the Flow Chart of Assessments.

Infusion Visits (Day 1 and Day 3)

The first PANZYGA infusion must begin no more than 2 days after Baseline evaluations have been completed and eligibility criteria have been confirmed. If Baseline and Day 1 Visits occur on the same day, Day 1 investigations do not need to be repeated. If Baseline evaluations are completed more than 2 days before Day 1, then the platelet count must be repeated and evaluated by the Investigator prior to the first infusion.

Patients who have met all of the inclusion criteria and none of the exclusion criteria will return to the study site for their first PANZYGA infusion. Required assessments will be performed as specified in the Flow Chart of Assessments, including safety evaluations before and after each infusion. Patients will remain at the study site during the infusion and for about 30 minutes after the end of each infusion to complete vital sign measurements.

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Patients will receive a dose of 1 g/kg body weight PANZYGA on Day 1 and optionally another dose of 1 g/kg PANZYGA on Day 3; body-weight dependent doses will be based on each patient's weight collected at Baseline. Total PANZYGA doses will be 1 g/kg for patients receiving only 1 dose on Day 1 and 2 g/kg for those receiving the optional Day 3 dose.

Prior to the Day 3 infusion, the Investigator will assess each patient's preinfusion platelet count, hematocrit, and hemoglobin. If the Day 3 platelet count shows evidence of response, as indicated by the platelet count at least doubling from Baseline count AND >50x10^9/L, the Day 3 infusion will not be administered. If the Baseline platelet count has doubled but is ≤50x10^9/L, the Day 3 infusion will be administered. If any of these parameters indicate a clinically relevant change such that, in the Investigator's opinion, it is not safe to administer the second infusion the patient should be withdrawn from study treatment but will be followed for safety through Day 32.

Assessment Day 5 though Day 22

Patients will return to the study site as indicated in the Flow Chart of Assessments for continued efficacy and safety evaluations.

Day 32 (End of Study/Early Termination Visit)

Patients will return to the study site on Day 32 for final safety assessments/End of Study (EOS) visit. Patients withdrawn early from the study will be encouraged to return to the study site and complete the EOS assessments.

Statistical Analysis:

The primary endpoint for this study is the proportion of patients with an increase in platelet count to ≥50x10^9/L at least once within 7 days after the first infusion. This proportion will be assessed and presented together with its associated 95% confidence interval to facilitate comparison with results from other studies and published data. Because of the limited number of patients, no formal hypothesis test will be performed; any p-value or confidence interval presented is to be understood in the exploratory sense.

All data collected will be presented descriptively. The time to reach the desired increase in platelet count as well as the duration of response will be presented in listings and summarized in statistical tables. Individual profiles of platelet count over time will be presented as Trellis plots.

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All safety data, including tolerability assessments, abnormal laboratory values, and AEs will also be listed and summarized statistically.

Statistical presentations will be fit to the nature of individual data items and include sample characteristics, frequency counts and rates. Product-limit survival function estimates (Kaplan-Meier Plots), confidence intervals and graphs will be included as appropriate.

The following populations will be considered for the statistical analysis:

- Safety Analysis Set (SAF): All patients who received at least part of one infusion of PANZYGA.
- Full Analysis Set (FAS): All patients in the SAF who satisfy all major eligibility criteria and for whom any post-baseline data is available. This is the set of eligible patients with treatment effects measured, according to the intention-to-treat (ITT) principle.
- Per-Protocol Set I (PP1): All patients in the FAS, excluding those with significant protocol deviations before the primary efficacy assessment on day 8 is completed, and which may have an impact on the evaluation of the primary endpoint.
- Per-Protocol Set II (PP2): All patients in the FAS, excluding those with significant protocol violations potentially affecting the (secondary) efficacy evaluations.

Only protocol deviations with the potential to significantly affect the study results or to invalidate the interpretation of the data obtained will lead to exclusion of patients from the PP sets. The inclusion of each patient in the respective analysis populations will be determined before database lock in a data review meeting by a panel consisting of a medical expert from the Sponsor, the clinical study manager, the data manager, and the study statistician.

A detailed Statistical Analysis Plan (SAP) will be compiled as a separate document.

FLOW CHART OF ASSESSMENTS

Table 1: Flow Chart of Assessments

ASSESSMENTS	Scr / BL[1]	Day 1	Day 3	Day 5	Day 8	Day 15	Day 22	Day 32[12]
Visit Window (Days)	**-7 / -2**	**0**	**0**	**±1**	**±1**	**±3**	**±3**	**±5**
Informed Consent	X							
Inclusion / Exclusion Criteria Review	X	X						
Demographics	X							
Medical and Surgical History[2]	X							
Body Weight	X							
Physical Examination	X[3]	X[3]	X[4]	X[4]	X[4]	X[3]	X[4]	X[3]
Urine or Blood Pregnancy Test (females of child-bearing potential)	X							X
Hematology: CBC with white blood cell (WBC) differential, hematocrit, hemoglobin, platelet counts, reticulocytes	X	X[5,6]	X[5,6,7]	X	X	X	X	X
Hemolysis: total, direct, and indirect bilirubin	X	X	X	X	X		X	X
Serum Chemistry: ALT, AST, creatinine, Na, Ca, K, BUN, LDH	X	X	X				X	X
Viral markers (HIV, HCV, HBV nucleic acid test [NAT])	X[7]							
PANZYGA INFUSIONS		**X**	**X**[8]					
Vital Signs: heart rate, blood pressure, temperature, respiratory rate	X	X[9]	X[9]				X	X
AE Monitoring[10]		X	X	X	X	X	X	X
Prior and Concomitant Therapy (drug and non-drug)[11]	X	X	X	X	X	X	X	X

Abbreviations: BL = Baseline, Scr = Screening

1) Screening Period is 7 days. Day 1 (first PANZYGA infusion) must occur no more than 2 days after Baseline evaluations have been completed. If the Baseline visit occurs more than 2 days after Baseline evaluations have been completed, the platelet count must be repeated and evaluated by the Investigator before initiation of the Day 1 infusion. If Baseline and Day 1 visits occur on the same day, the Day 1 investigations need not be repeated.
2) Medical History will be collected for the previous year and will include the onset date of ITP. Surgical history will include the date of splenectomy (if applicable), and any other surgical procedures in the previous year.
3) Brief Physical Examination: general appearance, skin, heart, lungs, abdomen, extremities
4) Limited Physical Examination with targeted body systems per Investigator discretion
5) Pre-infusion
6) Platelet count, hematocrit, and hemoglobin results must be available and reviewed by the Investigator prior to start of the infusion
7) HIV/HCV/HBV NAT Test: Infusions may begin before the results are back if the Investigator is not aware of, and the patient isn't exhibiting clinical signs of, any viral infection.
8) If the Day 3 preinfusion platelet count shows evidence of response as indicated by the platelet count at least doubling from Baseline count AND >50x10^9/L, the Day 3 infusion **will not be** administered. If the Baseline platelet count has doubled but is ≤50x10^9/L, the Day 3 infusion **will be** administered.
9) Vital Signs: at the start of the infusion, approximately 15 minutes (±15 minutes) after each infusion rate change, and approximately 30 minutes after the end of the infusion
10) The start date and start time will be collected for any adverse events starting at Day 1 through Day 32/EOS visit
11) Prior medications will be collected for the 3 months. The start date and start time will be collected for any concomitant medications taken on Day 1 through Day 32/EOS visit
12) Day 32 visit will correspond to the Early Termination visit for patients who are withdrawn early from the study

PROTOCOL SIGNATURES

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and applicable regulatory requirements.

[redacted] _____ [redacted] _____

[redacted]

Signature Date

Octapharma Pharmazeutika Produktionsgesellschaft mbH
Oberlaaerstr. 235, A-1100 Vienna, Austria
Tel: [redacted]

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Signature Date

Octapharma Pharmazeutika Produktionsgesellschaft mbH
Oberlaaerstr. 235, A-1100 Vienna, Austria
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[redacted] _____ [redacted] _____ 31 JAN 2019

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Signature Date

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LIST OF ABBREVIATIONS

Abbreviation	Description
ADR	Adverse Drug Reaction
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
ASH	American Society of Hematology
AST	Aspartate Aminotransferase
CIDP	Chronic Inflammatory Demyelinating Poly(radiculo)neuropathy
CRO	Contract Research Organisation
DEHP	Diethylhexylphthalate
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOS	End of Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
ifas	4-letter meaningless suffix assigned by FDA at the end of newly approved biologics
IgA	immunoglobulin A
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITP	Immune Thrombocytopenia
ITT	Intention-to-Treat
IUD	Intrauterine device
IGIV	Intravenous Immunoglobulin
LDH	lactase dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MMN	Multifocal Motor Neuropathy
NAT	Nucleic Acid Test
PMR	Post-Marketing Requirement
PREA	Pediatric Research Equity Act
PP	Per-Protocol
PP1	Per-Protocol Set 1

Abbreviation	Description
PP2	Per-Protocol Set II
PVC	Polyvinyl Chloride
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SLE	systemic lupus erythematosus
SOP	Standard Operating Procedure
TEAE	Treatment-emergent Adverse Event
TNBP	tri-n-butyl phosphate
TPO-RA	Thrombopoietin Receptor Agonists
ULN	Upper Limit of Normal
USC	United States Code

1 INTRODUCTION

Since more than five decades immunoglobulins have been used to provide antibodies for the prevention of viral and bacterial diseases (replacement therapy) in immunocompromised patients. Within the last 25 years intravenous immunoglobulin (IGIV) has been proven to be useful in a wide variety of clinical conditions other than replacement therapy of immunocompromised patients, in which IGIV exhibits an immunomodulatory effect. These include Idiopathic Thrombocytopenic (ITP) in children and adults at high risk of bleeding or prior to surgery to correct the platelet count, Kawasaki disease, and Guillain-Barré syndrome (GBS). More recently, single IGIV brands have also been licensed for Multifocal Motor Neuropathy (MMN) and Chronic Inflammatory Demyelinating Poly(radiculo)neuropathy (CIDP). Experimental off-label use of IGIV mostly in other neurological and dermatological indications is widespread.

ITP is an immune-mediated (disorder characterized by increased platelet destruction. The reason for platelet destruction is the development of autoantibodies to platelet-membrane antigens. These antibodies are particularly produced in the spleen which is also the major site of platelet destruction [1]. In patients suffering from ITP, several studies have shown IGIV effective in increasing platelet counts to prevent or control bleeding [2-4] The mechanism of action in ITP is not fully elucidated but includes immunomodulatory effects, particularly the modulation of cytokines, soluble cytokine receptors and cytokine receptor antagonists with anti-inflammatory effects as well as complement modulation.

Broadly, 2 categories of agents are available for the treatment of ITP: 1) those that rapidly and transiently interfere with the process of platelet destruction for management of acute bleeding or bleeding risk (front-line therapies), and 2) those with potential to provide a more durable improvement in the platelet count (second-line therapies). Corticosteroids, IGIV, and anti-D immune globulin remain the mainstay of front-line treatment of acute bleeding symptoms in both adults and children [5]. Although corticosteroids remain the most commonly used ITP therapy, controversy still exists surrounding selection of agent, dosing, and duration of therapy. For treatment with prednisone, it is generally accepted that shorter courses are preferable to chronic therapy. The 2010 International Consensus Report on the investigation and management of primary ITP developed by an international working group address three classes of second-line therapies: splenectomy, rituximab, and the thrombopoietin receptor agonists (TPO-RA). Due to a relative lack of data, their use was recommended only in patients who were refractory to splenectomy and other therapies. Further study results in 2016 demonstrated that TPO-RA agents are being used in children with ITP of varying duration and severity. The response was similar to clinical trials, but the sustainability of response varied. Future studies need to focus on the ideal timing and rationale for these medications in pediatric patients [6].

PANZYGA is a human immunoglobulin solution with 10% protein content for intravenous administration. PANZYGA is made from a pool of at least 1000 donations of human fresh-frozen plasma per batch.

PANZYGA was granted a US approval by the US Food and Drug Administration (FDA) in August 2018. The license in 2 indications (primary humoral

immunodeficiency diseases and chronic immune thrombocytopenia) was granted based on 2 completed studies. The first study in Primary Immune Deficiency included 51 children and adults from ages 2 years to 65 years who were dosed at 200 mg/kg to 800 mg/kg body weight every 3 to 4 weeks for 360 days. The second study in Immune Thrombocytopenia included 40 adults with chronic ITP receiving 2 gm/kg body weight over 2 consecutive days. Of the 36 subjects in the full analysis set, 29 patients (81%: 95% CI: 64% to 92%) responded to PANZYGA with a rise in platelet count to at least $50x10^9$/L within 7 days after the first infusion.

Further information can be found in the Investigator's Brochure (IB).

1.1 Rationale for Conducting the Study

Under the Pediatric Research Equity Act (PREA) (21 United States Code [USC] 355c) all applications for new active ingredients, new indications, new dosage forms, new dosing regimens or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this required is waived, deferred or inapplicable.

This post-marketing requirement (PMR) study was requested by the US FDA after PANZYGA received marketing approval in the United States. The rationale for conducting this PMR study is to investigate the efficacy and safety of PANZYGA in children suffering from primary ITP.

The study will be conducted in compliance with the protocol, International Conference on Harmonisation-Good Clinical Practice (ICH-GCP), US FDA Code of Federal Regulations, and other local regulatory requirements.

1.2 Dose Rationale

According to recent guidelines, IGIV is recommended for patients with platelet counts $<30x10^9$/L in case of severe bleeding and/or mucous membrane bleeding. Standard doses should be studied (0.8 g/kg to1 g/kg on Day 1, which may be repeated once within 3 days, or 0.4 g/kg/day for 2 to 5 days). If other dosage regimens are to be applied for, they should be supported by clinical data. [7,8]. The dose option for this study is within the recommended guidelines.

1.3 Benefit-Risk Statement

The safety profile of IGIV is well characterized and, in general, the same type of adverse reactions may be expected for PANZYGA. No new or unknown safety problems are expected to emerge which are not already described in the Investigator's Brochure.

Data obtained from the clinical trials conducted with PANZYGA in the adult ITP population clearly met the recommended clinical response criteria for efficacy as set out in the relevant FDA and EU guidelines. These data are comparable with available literature data on other commercial IVIGs and formed the basis for marketing authorization in Europe and the US. The safety profile of PANZYGA is satisfactory and the number of infusional AEs are below the levels as

recommended by the FDA for products of this class. Efficacy and safety data with PANZYGA in 3 clinical studies in 51 patients (also including pediatric patients) with primary immunodeficiency (PID) and in 40 patients with immune thrombocytopenia (ITP) are available. Available data are sufficient to expect favorable benefit-risk profile of PANZYGA in the pediatric ITP population. Expected clinical benefit of using PANZYGA in this study is an increase in platelets level to control or prevent bleeding. The main known risks are listed below:

- Thrombosis may occur with immune globulin intravenous (IGIV) products, including PANZYGA. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.
- Renal dysfunction, acute renal failure, osmotic nephropathy, and death may occur with the administration of IGIV products in predisposed patients. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. PANZYGA does not contain sucrose.
- For patients at risk of thrombosis, renal dysfunction, or renal failure, administer PANZYGA at the minimum infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.
- Standard measures are taken to prevent infections resulting from the use of medicinal products prepared from human blood or plasma. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. During the manufacturing process of PANZYGA, significant viral reduction is obtained.

Inclusion and exclusion criteria, recommendations on the rate of infusion, dosage, and monitoring procedures provided in this protocol sufficiently mitigate above mentioned risks and must be adhered to.

No new or unknown safety problems are expected to emerge in pediatric ITP population, which are not listed above or described in the Investigator's Brochure.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objective is to evaluate the efficacy of PANZYGA in increasing the platelet count in pediatric patients with chronic ITP.

2.2 Secondary Objectives

The secondary objectives of this study are to:

- Assess safety of up to 2 g/kg PANZYGA (1 g/kg PANZYGA on Day 1 and an optional dose of 1 g/kg PANZYGA on Day 3) infused in the pediatric population within the scope of the clinical study
- Determine the time to reach a platelet count of $\geq 50 \times 10^9$/L
- Determine duration of time during which the platelet count is maintained at the level $\geq 50 \times 10^9$/L
- Determine the maximum platelet count during the study

3 INVESTIGATIONAL PLAN

3.1 Primary and Secondary Endpoints

3.1.1 Primary Endpoint

The primary efficacy parameter is defined as an increase in platelet count at least once to ≥50x10^9/L within 7 days after the first infusion, ie, by Day 8 (increase must occur at least once on any day up to and including Day 8). This definition of clinical response will serve as the basis for the primary endpoint, the response rate (ie, the proportion of patients with an elevation of platelet count at least once to ≥50x10^9/L within 7 days [ie, Day 8] after the first infusion).

3.1.2 Secondary Endpoints

Secondary endpoints are defined to further evaluate the efficacy and safety of the PANZYGA infused in the pediatric population.

The following parameters will be used to for efficacy assessments:

- Time to reach a platelet count of ≥50x10^9/L
- Duration of platelet response defined as the number of days the platelet count remains above ≥50x10^9/L
- Maximum platelet count during the study

The following parameters will be used for safety assessments:

- AEs
- Vital signs (blood pressure, heart rate, temperature, respiratory rate)
- Physical examination
- Laboratory parameters: hematology (including reticulocytes), hemolysis, platelet count, serum chemistry (including lactase dehydrogenase [LDH]).

3.2 Overall Study Design and Plan

This is a prospective, open-label, single-arm, multicenter, Phase 4 study evaluating the efficacy and safety of the investigational product, PANZYGA, in pediatric patients with chronic ITP.

The study will enroll at least 20 patients ≥ 1 year to <18 years old and will not be stratified by age group. A patient is considered enrolled into the study after successfully completing all baseline assessments and receiving at least a partial dose of PANZYGA.

Patients with a confirmed diagnosis of chronic ITP, without evidence of active major bleeding, may be enrolled in the study. Study procedures will only begin after written informed consent (from parent or guardian) and assent (from the patient, as age appropriate per Institutional Review Board [IRB] requirements) have been obtained. Patients who meet all of the inclusion and none of the exclusion criteria may receive the first infusion of PANZYGA within 2 days after Baseline investigations have been completed.

Each patient will be administered PANZYGA by intravenous infusion at a dose of 1 g/kg body weight PANZYGA on Day 1 and optionally another dose of 1 g/kg PANZYGA on Day 3; body-weight dependent doses will be based on each patient's weight collected at Baseline. Total PANZYGA doses will be 1 g/kg for patients receiving only 1 dose on Day 1 and 2g/kg for those receiving the optional Day 3 dose. Prior to the Day 3 infusion, Investigators will assess each patient's preinfusion platelet count, hematocrit, and hemoglobin. Patients whose platelet count shows evidence of response as indicated by the platelet count at least doubling from Baseline count AND is $>50x10^9$/L, the Day 3 infusion will not be administered. If the Baseline platelet count has doubled but is $\leq 50x10^9$/L, the Day 3 infusion will be administered. If any parameters indicate a clinically relevant change such that, in the Investigator's opinion, it is not safe to administer the second infusion, the patient should be withdrawn from study treatment; however, the patient will be followed for safety through Day 32.

Study interventions and procedures will be performed at predefined timepoints (see Section 6.1 and the Flow Chart of Assessments [Table 1]) including (but are not limited to): blood draws for safety evaluations, vital signs, body weight, physical examinations, AE monitoring, and changes in concomitant medication use. Patients will have clinic visits on Days 1, 3, 5, 8, 15, and 22. They will return to the clinic for a final safety follow-up evaluation at Day 32/End of Study (EOS) Visit.

PANZYGA infusions may be stopped or interrupted at any time if, in the Investigator's opinion, it is not safe to continue or is not in the patient's best interest. Patients who have received a partial dose of PANZYGA should be followed for safety evaluations through Day 32/EOS.

The study is planned to begin screening procedures Q2/Q3 2019 at up to 8 sites in the USA, with recruitment lasting approximately 30 months, and is anticipated to complete in Q1 2022. The study duration for a single patient will be approximately 39 days, including up to a 1-week Screening period.

3.3 Discussion of Study Design and Choice of Control Group(s)

3.3.1 Study Design

This study was designed to meet the US FDA's requirements under the PREA (21 USC 355c) for a post-approval study of PANZYGA in the pediatric population. US FDA is requiring a pediatric study for the treatment of ITP to evaluate PANZYGA for the treatment of ITP in patients ages ≥1 year to <18 years. All of the US FDA's recommendations have been incorporated into the protocol.

This study design is also in line with study protocols evaluating NGAM in adults, with the frequency of blood draws and number of visits reduced to accommodate a pediatric population. Because of the limited number of patients that will be enrolled in this study, along with the increased blood volume and additional site visits that would be required to meet the full recommendations in the European Medicines Agency (EMA) Guideline for confirmatory visits and blood draws, the secondary efficacy endpoints were selected to allow efficacy evaluations in this patient population.

3.3.2 Control Group(s)

A placebo control group will not be included in this post-approval study. An active control group is not considered relevant, as the objective of this study is to evaluate the efficacy and safety of PANZYGA in the pediatric population, not to compare the efficacy and safety of PANZYGA versus another IGIV treatment.

3.3.3 Study Parameters

The primary therapeutic target for ITP treatment is an increase in the platelet count. Therefore, the primary endpoint chosen for the study, namely the response rate (ie, the proportion of patients with an increase in platelets at least once to $\geq 50 \times 10^9$/L within 7 days after the first infusion), is appropriate to adequately describe the efficacy of treatment of PANZYGA in the pediatric population.

To assess the efficacy of PANZYGA in correcting the platelet count, this response rate has been chosen as the primary endpoint. There are several definitions of response published in guidelines and commonly used for the evaluation of ITP treatment; however, an increase in platelets to $\geq 50 \times 10^9$/L is the most established definition of response [7] and as such has been chosen for this post-marketing approval study.

The secondary efficacy endpoints chosen are in accordance with the primary endpoint, in order to further characterize the effect on the increase in platelet count.

The safety assessments, including AE, vital signs, laboratory results, and physical examination are appropriate and commonly used parameters to monitor the of IGIV treatment during a clinical study.

4 STUDY POPULATION

4.1 Population Base

At least 20 female or male patients ≥1 year to <18 years old with chronic ITP will be eligible for this study.

4.1.1 Inclusion Criteria

Patients who meet all of the following criteria are eligible for the study:

1. Females and males aged from ≥1 year to <18 years old
2. Confirmed diagnosis of Chronic Immune Thrombocytopenia (ITP) according to American Society of Hematology (ASH 2011) guidelines
3. Platelets count <$30x10^9$/L at the Baseline Visit
4. Voluntarily given written informed consent (provided by patient's parent or legal guardian) and assent (provided by patient)
5. Females of childbearing potential have been using at least 1 acceptable form of birth control for a minimum of 30 days (or a minimum of 3 months for hormonal contraceptives) prior to the Screening visit, and must agree to use at least 1 acceptable method of contraception for 30 days after the last dose of PANZYGA. Acceptable methods include: intrauterine device (IUD), hormonal contraception, male or female condom, spermicide gel, diaphragm, sponge, or cervical cap. Abstinence is not considered an acceptable method of birth control.
6. Parent or legal guardian must agree and be willing to assist the participant attend study visits, and to follow all protocol requirements and instructions of the study doctor

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria are not eligible for the study:

1. Thrombocytopenia secondary to other diseases (such as Acquired Immunodeficiency Syndrome [AIDS] or systemic lupus erythematosus [SLE]), drug-related thrombocytopenia, or congenital thrombocytopenia
2. Administration of intravenous immunoglobulin (IGIV) or anti-D immunoglobulin within 3 weeks before enrollment
3. Administration of thrombopoietin receptor agonists when the dose has NOT been stable within 3 weeks before enrollment and a dosage change is planned before Day 32
4. Administration of oral immunosuppressants when the dose has NOT been stable during the preceding 2 months (2 weeks for long-term corticosteroid therapy) and a dosage change is planned before

Day 32 (Note: topical agents and inhaled corticosteroid therapy use is permitted)

5. Administration of long-term anti-prolific agents or attenuated androgen therapy when the dose has NOT been stable during the preceding 2 months and no dosage change is planned until Day 32
6. Nonresponsive to previous treatment with IGIV or anti-D immunoglobulin
7. Evidence of an active major bleeding episode at Screening
8. Splenectomy in the previous 4 weeks or planned splenectomy throughout the study period
9. Evans syndrome (experiencing active disease with 2 out of 3 of the following: autoimmune thrombocytopenia, autoimmune hemolytic anemia, and/or autoimmune neutropenia)
10. Known or suspected human immunodeficiency virus (HIV), hepatitis B virus (HBV), and/or hepatitis C virus (HCV) infections
11. Emergency surgery in the previous 4 weeks
12. Severe liver and/or kidney disease (alanine aminotransferase [ALT] >3x upper limit of normal (ULN), aspartate aminotransferase [AST] >3x upper limit of normal (ULN), and/or creatinine >120 µmol/L)
13. History of severe hypersensitivity to blood or plasma derived products, or any component of the PANZYGA
14. Known immunoglobulin A (IgA) deficiency and antibodies against IgA
15. History of, or suspected, alcohol or drug abuse in the previous year
16. Females who are pregnant or nursing
17. Unable or unwilling to comply with the study protocol
18. Receipt of any other investigational medicinal product within 3 months before study entry
19. Risk factors* for thromboembolic events in whom the risks outweigh the potential benefit of PANZYGA treatment.
20. Any other condition(s), that in the Investigator's opinion, make it undesirable for the patient to participate in the study or may interfere with protocol compliance.

* Risk factors include, but are not limited to: obesity, advanced age, hypertension, diabetes, a history of atherosclerosis/vascular disease or thrombotic events, hyperlipidemia, multiple cardiovascular risk factors, acquired or inherited thrombophilic disorders, prolonged periods of immobilization, severe hypovolemia, central venous catheterization, active malignancy and/or known or suspected hyperviscosity.

4.2 Prior and Concomitant Therapy

Details on medications taken within the previous 3 months prior to the Baseline Visit and any concomitant medications taken during the study must be recorded in the electronic case report form (eCRF).

Use of the following medications are forbidden during the study as specified below (Table 2):

Table 2: Prohibited Medications

Medication	Time Window
IGIV	prohibited for 3 weeks prior to Baseline Visit through Day 32
anti-D immunoglobulin	prohibited for 3 weeks prior to Baseline Visit through Day 32
oral immunosuppressants	prohibited during Screening Period through Day 32 **unless** patients have been receiving a stable dose for 2 months (2 weeks for long-term corticosteroid therapies) prior to Screening Visit
thrombopoietin receptor agonists	prohibited during Screening Period through Day 32 **unless** patients have been receiving stable dose for 3 months prior to Screening Visit
long-term anti-prolific agents or attenuated androgen therapy	prohibited during Screening Period through Day 32 **unless** patients have been on a stable dose for 2 months prior to Screening Visit
any other blood or plasma-derived product*	prohibited during Screening Period through Day 32
receipt of any other investigational product	prohibited within 3 months prior to Baseline Visit through Day 32

* Patients who are non-responders or requiring emergent ITP treatment (other than PANZYGA specified in this protocol) will be followed for safety and complete all assessments through Day 32.

Trade names of drugs corresponding to the categories provided in Table 2 will be provided in a Study Manual.

4.3 Withdrawal and Replacement of Patients

4.3.1 Premature Patient Withdrawal

Patients have the right to withdraw from the study at any time for any reason, without the need to justify their decision; parents or legal guardians also have the right to withdraw a patient on the patient's behalf. The Investigator also has the right to withdraw patients in case of AEs, poor compliance, or other reasons. Because an excessive rate of withdrawals can render the study noninterpretable, any unnecessary withdrawal of patients should be avoided.

For any withdrawals after study entry, the Investigator will obtain all the required details and document the reason(s) for discontinuation. If the reason for withdrawal of a patient is an AE, the main specific event or laboratory test will be recorded, and the Investigator will make thorough efforts to clearly document the outcome. Patients should return to the study site and have all safety evaluations, including safety laboratory tests, completed as specified at the Day 32 visit (See Section 6.1.6).

4.3.2 Patient Replacement Policy

Patients withdrawn from the study will not be replaced. Under no circumstances will patients who enroll in the study be permitted to re-enroll after study completion. Patients who fail during the Screening Period (also referred to as Screen Failures) may be re-screened upon written approval from the Sponsor.

4.4 Assignment of Patients to Treatment Groups

This is an open-label non-randomized study. All patients will receive PANZYGA.

4.5 Relevant Protocol Deviations

In case of any major protocol deviation, the Investigator and Octapharma will decide on the further participation of the patient in this study after having discussed all relevant aspects.

A list of all included patients with all deviations from the intended study procedures and other criteria that may affect the patient's data validity for statistical analysis will be prepared upon clinical completion of the study. This will also be discussed by a panel consisting of the clinical study manager, a medical expert of the Sponsor, the data manager and the study statistician. This panel will decide upon the membership of the patient in the Full Analysis Set (FAS), Per Protocol (PP) Set 1 (PP2), PP Set 2 (PP2), and Safety Analysis Set for statistical analysis.

4.6 Subsequent Therapy

If a patient withdraws from the study or is withdrawn by the Investigator by their parent/legal guardian, he/she will receive treatment by the Investigator or personal physician according to institutional standard of care.

5 INVESTIGATIONAL MEDICINAL PRODUCT

5.1 Characterization of Investigational Product

Name of Medicinal Product: PANZYGA

Active ingredient of PANZYGA: Immune globulin human-ifas

Table 3: Qualitative and Quantitative Composition of PANZYGA

Name of Ingredient	Amount
Total protein	9.0 – 11.0 g/100 mL
Protein composition	≥95% Ig (≥96% Ig)*
IgG content	86 – 110 mg/mL
Glycine	15.0 – 19.5 mg/mL (17.3 mg/mL)*
Water for Injection	*ad* 1mL

*Depending on regulatory requirements

PANZYGA is a solvent/detergent (S/D)-treated, sterile preparation of highly purified immunoglobulin G (IgG) derived from large pools of human plasma. PANZYGA is a solution for infusion to be administered intravenously.

This preparation contains approximately 100 mg of protein per mL (10%), of which not less than 96% is normal human immunoglobulin G. PANZYGA contains not more than 3% aggregates, not less than 90% monomers and dimers, and not more than 3% fragments. On average, the product contains 100 µg/mL of IgA, and lower amounts of IgM.

PANZYGA contains only trace amounts of sodium, and the pH is between 4.5 and 5.0. The osmolality is in the range of 240 to 310 mosmol/kg.

The manufacturing process for PANZYGA isolates IgG without additional chemical or enzymatic modification, and the Fc portion is maintained intact. PANZYGA contains the IgG antibody activities present in the donor population. IgG subclasses are fully represented with the following approximate percentages of total IgG: IgG1 is 65%, IgG2 is 28%, IgG3 is 3% and IgG4 is 4%.

PANZYGA contains a broad spectrum of IgG antibodies against bacterial and viral agents that are capable of opsonization and neutralization of microbes and toxins. PANZYGA contains glycine (15.0 to 19.5 mg/mL), but no preservatives or sucrose.

All units of human plasma used in the manufacture of PANZYGA are provided by FDA-approved blood and plasma establishments, and are tested by FDA-licensed serological tests for HBsAg, antibodies to HCV and HIV and Nucleic Acid Test (NAT) for HCV and HIV-1 and found to be non-reactive (negative).

5.2 Packaging and Labelling

PANZYGA for investigational use only will be labeled according to US FDA regulations. Details of the labeling will be included in the Pharmacy Manual.

The batch number(s) used will be recorded in the study documentation and EDC.

5.3 Conditions for Storage and Use

PANZYGA must be stored and transported light-protected at +2°C (36°F) to +8°C (46°F) and must be brought to room temperature before use.

Storage temperature must be maintained at +2°C (36°F) to +8°C (46°F) and will be monitored for the duration of the study by reviewing the temperature logs.

PANZYGA must not be frozen prior to use.

PANZYGA must not be used after its expiry date.

PANZYGA must not be mixed with other medicinal products.

Each PANZYGA bottle is for single use only.

Authorized personnel at the individual study sites will ensure that PANZYGA is stored in appropriate conditions in a secure refrigerator with restricted access and in compliance with national regulations.

5.4 Dose and Dosing Schedule

PANZYGA will be administered by intravenous infusion. Patients should be adequately hydrated prior to infusion.

Patients will receive a dose of 1 g/kg body weight PANZYGA given on Day 1 and optionally another dose of 1 g/kg PANZYGA given on Day 3; body-weight dependent doses will be based on each patient's weight collected at Baseline. Total PANZYGA doses will be 1 g/kg for patients receiving only 1 dose on Day 1 and 2 g/kg for those receiving the optional Day 3 dose. If the Day 3 platelet count shows evidence of response as indicated by the platelet count at least doubling from Baseline count AND is $>50x10^9$/L, the Day 3 infusion will not be administered. If the Baseline platelet count has doubled but is $\leq 50x10^9$/L, the Day 3 infusion will be administered.

PANZYGA will be delivered by intravenous infusion according to the recommended flow rates:

- Initial infusion rate of 0.01 mL/kg/min (60 mg/kg/hr) for the first 30 minutes
- If tolerated, increase to 0.02 mL/kg/min (120 mg/kg/hr) for the second 30 minutes
- If tolerated, increase to 0.04 mL/kg/min (240 mg/kg/hr) for the third 30 minutes
- If tolerated, increase to 0.08 mL/kg/min (480 mg/kg/hr) for the remainder of the infusion.

Infusion rates should not exceed 0.08 mL/kg/min and should not exceed 8.0 mL/min.

If an adverse event (AE) occurs during infusion, the infusion rate should be reduced to half the rate at which the event occurred, or the infusion should be interrupted until symptoms subside. The infusion may then be resumed at an infusion rate tolerated by the patient. The infusion rate may be gradually increased as tolerated by the patient.

5.5 Preparation and Method of Administration

All patients will be infused at the study site under the surveillance of authorized study site staff.

After calculating the volume required for the dose using the patient's Baseline body weight (see Section 5.4), the appropriate number of vials will be removed from the refrigerator. Vials of different sizes may be combined to reach the required amount of IgG. The exact dose will be administered, and the empty and partially used vials will be retained by the site for drug accountability and dose verification.

PANZYGA vials must be allowed to warm to room or body temperature before infusion. After PANZYGA vials have been brought to room or body temperature, they should be inspected visually for particulate matter and discoloration prior to administration. The solution should be clear or slightly opalescent. DO NOT USE IF TURBID, DISCOLORATION IS OBSERVED, AND/OR FLOATING PARTICLES ARE PRESENT. Solutions that are cloudy or vials that have a deposit must not be used and must be discarded according to local policy.

Aseptic technique must be used throughout the entire procedure.

The contents of bottles must be pooled under aseptic conditions into sterile infusion bags and administered immediately after pooling. Only polyvinyl chloride (PVC)-free, diethylhexylphthalate (DEHP)-free and latex–free, infusion bags can be used. Once pooled, a label will be applied on the infusion bag. Detailed instructions of this process and an example label will be included in the Pharmacy Manual.

PANZYGA will be infused into a vein using standard infusion supplies provided by the individual site. Standard procedures should be followed to prime the infusion line with a priming solution (eg, normal saline). At the end of each infusion, the infusion line will be flushed with normal saline solution.

Additional information regarding PANZYGA preparation and infusion procedures will be provided in a pharmacy manual.

Please refer to special warnings and precautions for use provided in the PANZYGA Investigator Brochure.

5.6 Blinding, Emergency Envelopes, and Breaking the Study Blind

Not applicable.

5.7 Treatment Compliance

5.7.1 Drug Dispensing and Accountability

The Sponsor or designee will provide and deliver all PANZYGA to participating Investigators. A Drug Inventory and Dispensing Log will be kept current by the Investigator, detailing the dates and quantities of PANZYGA received, dispensed to each patient, and the quantity remaining at the study site.

The Drug Inventory and Dispensing Log will be available to the monitor to verify drug accountability during the study. The study monitor will inventory all empty and partially used vials of PANZYGA and will cross-check this inventory versus the patient source documentation (records), eCRF, and the Drug Inventory and Dispensing Log.

Unused and partially used vials may be destroyed at the study site or returned to the Sponsor for destruction according to institutional practice. Vials may be destroyed only after drug accountability has been verified and fully reconciled by the monitor and after the Sponsor has granted written approval of destruction.

Additional information regarding PANZYGA drug accountability procedures will be provided in a pharmacy manual.

5.7.2 Assessment of Treatment Compliance

All patients will be infused at the study site under the surveillance of authorized study personnel. Infusion details will be documented together with the batch number(s) in the source data and eCRF.

6 STUDY CONDUCT

Procedures performed at each study visit are presented in the Flow Chart of Assessments (see Table 1). Time windows and tolerances are provided in Table 4.

6.1 Observations by Visit

6.1.1 Baseline Visit/Screening Period

The following assessments will be performed during the Screening Period. The Screening Period can last up to 1 week (to accommodate patient schedules and the informed consent/assent process); however, all Baseline evaluations should be completed within 2 days before the first administration of PANZYGA.

- Obtaining voluntarily given, written (signed and dated) informed consent and assent (as age appropriate)
- Inclusion and exclusion criteria
- Demographic and baseline characteristics
- Medical and surgical history (previous 1 year)
- Splenectomy history
- Physical examination
- Vital signs
- Body weight
- Blood samples for serum chemistry, hematology, and hemolysis analytes
- Blood or urine pregnancy test (females of childbearing potential, only)
- Blood samples for viral markers
- Documentation of prior medications (previous 3 months)

6.1.2 Day 1

Day 1 should take place within 2 days after Baseline evaluations have been completed. If the Baseline and Day 1 Visits occur on the same day, the Baseline investigations do not need to be repeated. If the Baseline evaluations are completed more than 2 days before Day 1, the platelet count must be repeated and evaluated by the Investigator prior to initiating the first infusion.

Before the administration/infusion of PANZYGA, patient eligibility will be re-evaluated. The following assessments will be performed before PANZYGA infusion:

- Confirmation of inclusion and exclusion criteria
- Physical examination
- Vital signs
- Blood samples for serum chemistry, hematology, and hemolysis analytes

The following activities will be performed during or after PANZYGA infusion:

- PANZYGA infusion

- Vital signs (at the start of the infusion, 15 minutes (±15 minutes) after each infusion rate change, and approximately 30 minutes after the end of the infusion)
- Monitoring for AEs
- Documentation of concomitant medication use

6.1.3 Day 3

The following assessments will be performed before PANZYGA infusion:

- Physical examination
- Vital signs
- Blood samples for serum chemistry, hematology, and hemolysis analytes

  NOTE: platelet, hemoglobin and hematocrit results must be available and reviewed by the Investigator prior to initiating the Day 3 infusion

The Investigator will assess each patient's Day 3 preinfusion platelet count, hematocrit, and hemoglobin. If the Day 3 platelet count shows evidence of clinical response, as indicated by the platelet count at least doubling from Baseline count AND is >50x10^9/L, the Day 3 infusion will not be administered. If the Baseline platelet count has doubled but is ≤50x10^9/L, the Day 3 infusion will be administered. In the event that the Day 3 infusion is not administered, all other Day 3 assessments will still be completed. If any of these hematology parameters indicate a clinically relevant change such that, in the Investigator's opinion, it is not safe to administer the second infusion the patient should be withdrawn from study treatment but will be followed for safety through Day 32.

The following activities will be performed during or after PANZYGA infusion:

- PANZYGA infusion
- Vital signs (at the start of the infusion, 15 minutes (±15 minutes) after each infusion rate change, and approximately 30 minutes after the end of the infusion)
- Monitoring for AEs
- Documentation of concomitant medication use

6.1.4 Day 5 and Day 8 (± 1 day)

The following assessments will be performed at Day 5 and Day 8:

- Physical examination
- Blood samples for serum chemistry, hematology, and hemolysis analytes
- Monitoring for AEs
- Documentation of concomitant medication use

6.1.5 Day 15 and Day 22 (± 3 days)

The following assessments will be performed at Day 15 and Day 22:

- Physical examination
- Blood samples for hematology analytes

- Monitoring for AEs
- Documentation of concomitant medication use

6.1.6 Day 32 (End of Study Visit) (± 5 days)

Patients will return to the study site on Day 32 for final safety assessments/EOS Visit. Patients who were withdrawn early from the study should return to the study site for a final safety assessment. The following assessments will be performed:

- Physical examination
- Vital signs
- Blood samples for serum chemistry, hematology, and hemolysis analytes
- Documentation of concomitant medication use

After Day 32, the clinical study is considered completed for the patient. No further study-related assessments will be performed, unless safety concerns (eg, ongoing AEs) require follow-up.

6.1.7 Visit Windows Used in this Study, including Tolerances

In this study, the following time windows and tolerances apply (Table 4):

Table 4: Visit Windows Used in this Study

Time point	Tolerance
Screening Period	7 days prior to Day 1
Final Baseline Evaluations	-2 days before Day 1
Day 1	none
Day 3	none
Day 5	±1 day
Day 8	±1 days
Day 15 and Day 22	±3 days
Day 32	± 5 days

6.2 Duration of Study

6.2.1 Planned Duration for an Individual Patient

The duration of the entire study for each patient will be approximately 39 days, including a 7-day Screening Period.

6.2.2 Planned Duration for the Study as a Whole

The study will be considered completed when all patients have completed the Day 32 EOS Visit.

The estimated start of the study (enrollment of first patient) is Q2/Q3 2019, and the estimated end of the study (last visit of last patient) is Q1 2022.

6.2.3 Premature Termination of the Study

Both the responsible Investigators and the Sponsor reserve the right to terminate the study at any time. Should this be necessary, study close-out procedures will be arranged on an individual site basis after review and consultation by both parties. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the patients' interests.

Furthermore, the Investigator should promptly inform the IRB and provide a detailed written explanation. Pertinent regulatory authorities and IRBs will be informed in accordance with applicable regulatory requirements.

6.2.3.1 Early Termination of the Entire Clinical Study

At any time, the study as a whole will be terminated prematurely if:

- New toxicological or pharmacological findings or safety reports invalidate the earlier positive benefit-risk-assessment for the pediatric population
- Any other reason rendering the continuation of the study impossible for the Sponsor

6.2.3.2 Early Termination at an Individual Study Site

At any time, the study can be terminated at an individual study site if:

- The site cannot comply with the requirements of the protocol
- The site cannot comply with GCP or other regulatory standards
- The site does not meet the required recruitment rate

Should the study be prematurely terminated, all study materials, including PANZYGA, must be returned to the Sponsor.

7 ASSESSMENTS AND METHODS

7.1 Demographic and Baseline Information

Demographic and baseline information will be recorded during the Screening Period:

7.1.1 Demographic and Baseline characteristics

The demographic and baseline characteristics are sex, age, race and ethnic origin, height, and weight.

7.1.2 Medical and Surgical history

The medical history will be collected for the previous year and will be obtained by interviewing the patient. Records of past diseases and treatments (eg, hospital discharge letters) will be obtained for the study files, if available. The onset date of ITP will be recorded.

Surgical history will include the date of splenectomy (if applicable) and any other surgical procedures in the previous year.

7.1.3 Viral Marker Tests

At the Screening Visit, blood samples for viral markers (HIV, HCV, HBV NAT) will be collected and tested at the local laboratory according to the site's standard procedures, to rule out secondary infections that may cause ITP. Infusions may begin before the results are back if the Investigator is not aware of, and the patient isn't exhibiting clinical signs of, any viral infection.

7.1.4 Prior and Concomitant Medication Use

Prior medication use will be obtained by interview and review of patient charts (if available).

Concomitant medication use, defined as medications with a start date and time after the start of the Day 1 infusion, will be collected throughout the study. The start date and time of medication use will be collected on Day 1 and throughout the study.

7.2 Efficacy Assessments

All efficacy assessments will be based on platelet counts performed throughout the study.

Platelet counts will be performed at Baseline (within 2 days prior to the first PANZYGA infusion), at Day 1 and Day 3 prior to planned PANZYGA infusions, and then at all remaining study visits (Days 5, 8, 15, 22, and 32).

7.3 Safety Assessments

7.3.1 Assessments for Safety Evaluations

The following assessments will be performed to evaluate the safety of PANZYGA in the pediatric population:

- AEs and Serious Adverse Events (SAEs)
- Clinical laboratory tests
- Vital signs
- Physical examinations
- Pregnancies

7.3.2 Adverse Events

7.3.2.1 Definitions

- **Adverse event (AE):** An AE is any untoward medical occurrence in a study /patient receiving an investigational medicinal product (IMP) and which 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 an IMP, whether or not related to the IMP.
- **Adverse drug reaction (ADR):** An ADR is any noxious and unintended response to an IMP related to any dose. The phrase 'response to an IMP' means that a causal relationship between the IMP and an AE carries at least a reasonable possibility (ie, the relationship cannot be ruled out).
- **Other significant AEs:** Any marked laboratory abnormalities or any AEs that lead to an intervention, including withdrawal of drug treatment, dose reduction, or significant additional concomitant therapy.
- **Treatment-emergent AE (TEAE):** Any AE that newly appeared, increased in frequency, or worsened in severity following the time of the first IMP infusion until the end of the safety follow-up period.
- **Infusional AE:** Any AE that occurs from the time of infusion and within the 72 hour period after end of infusion.
- **Withdrawal due to AE/ADR:** AE/ADR leading to discontinuation of treatment with IMP. Any such events will be followed up by the Investigator until the event is resolved or until the medical condition of the patient is stable. All follow-up information collected will be made available to the Sponsor.

7.3.2.2 Collection of AEs

The condition of the patient will be monitored throughout the study. At each visit, whether scheduled or unscheduled, AEs will be elicited using a standard nonleading question such as "How have you been since the last visit/during the previous study period?" In addition, the Investigator will check the patient diaries (if applicable) for any documented event.

Any AE or ADR which occurs during the study will be noted in detail on the appropriate pages of the eCRF. If the patient reports several signs or symptoms representing a single syndrome or diagnosis, the diagnosis should be recorded in the eCRF. The Investigator will grade the severity of all AEs or ADRs (mild, moderate, or severe), the seriousness (non-serious or serious), and the causality as defined in Section 7.3.2.3, Section 7.3.3, and Section 7.3.2.4, respectively. The Sponsor is responsible for assessing the expectedness of each ADR (expected or unexpected) as defined in Section 7.3.2.5.

In the event of clinically significant abnormal laboratory findings, the tests will be confirmed and the patient followed up until the laboratory values have returned to normal and/or an adequate explanation for the abnormality has become available.

Diseases, signs and symptoms, and/or laboratory abnormalities already present before the first administration of IMP will not be considered AEs unless an exacerbation in intensity or frequency (worsening) occurs.

The Investigator will provide detailed information about any abnormalities and about the nature of and reasons for any action taken as well as any other observations or comments that may be useful for the interpretation and understanding of an AE or ADR.

7.3.2.3 Severity of AEs

The intensity/severity of AEs will be graded as follows:

- **Mild:** an AE, usually transient, which causes discomfort but does not interfere with the patient's routine activities
- **Moderate:** an AE which is sufficiently discomforting to interfere with the patient's routine activities
- **Severe:** an AE which is incapacitating and prevents the pursuit of the patient's routine activities

The grading of an AE is up to the medical judgement of the Investigator and will be decided on a case-by-case basis.

7.3.2.4 Causality of AEs

The relationship of AEs to the administered IMP will be assessed by the Investigator:

- **Probable:** reports including good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable. A reaction that follows a reasonable temporal sequence from administration of the IMP; or that follows a known or expected response pattern to the suspected medicine; or that is confirmed by stopping or reducing the dosage of the medicine and that could not reasonably be explained by known characteristics of the patient's clinical state.
- **Possible:** reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible and not unlikely,

although the connection is uncertain or doubtful, for example because of missing data or insufficient evidence. A reaction that follows a reasonable temporal sequence from administration of the IMP; that follows a known or expected response pattern to the suspected medicine; but that could readily have been produced by a number of other factors.

- **Unlikely:** reports not following a reasonable temporal sequence from IMP administration. An event which may have been produced by the patient's clinical state or by environmental factors or other therapies administered.
- **Not related (unrelated):** events for which sufficient information exists to conclude that the etiology is unrelated to the IMP.
- **Unclassified:** reports which for one reason or another are not assessable.

7.3.2.5 Classification of ADRs by Expectedness

ADRs will be classified by the Sponsor as either expected or unexpected:

- **Expected:** an ADR that is listed in the current edition of the Investigator's Brochure or other reference safety information.
- **Unexpected:** an ADR that is not listed in the current edition of the Investigator's Brochure or other reference safety information, or that differs because of greater severity or greater specificity.

7.3.2.6 Outcome of AEs

The outcome of all reported AEs will be documented as follows:

1. Recovered, resolved
2. Recovering, resolving
3. Not recovered, not resolved
4. Recovered, resolved with sequelae
5. Fatal
6. Unknown

NOTE: A patient's **death** per se is not an event, but an outcome. The event which resulted in the patient's death must be fully documented and reported, even in case the death occurs within 4 weeks after IMP treatment end and regardless of whether or not it is considered treatment-related.

7.3.2.7 Action(s) taken

AEs requiring action or therapy must be treated with recognized standards of medical care to protect the health and well-being of the patient. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment in an emergency situation.

The action taken by the Investigator must be documented:

a) General actions taken in the event of an AE

- None
- Medication (other than IMP) or other (eg, physical) therapy started

- Test performed
- Other (to be specified)

b) IMP-related actions taken in the event of an AE

- None
- Product withdrawn
- Dose reduced
- Dose increased

The Investigator will follow up on each AE until it has resolved or until the medical condition of the patient has stabilized. Any relevant follow-up information will be reported to the Sponsor.

7.3.3 Serious Adverse Events

An **SAE** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (see below)
- requires hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is another important medical event

NOTE: The term 'life-threatening' refers to an event in which the patient was, in the view of the reporting Investigator, at immediate risk of death at the time of the event; it does not refer to an event which may hypothetically have caused death had it been more severe.

In deciding whether an AE/ADR is serious, medical judgment should be exercised. Thus, important AEs/ADRs that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definitions above should also be considered serious.

In addition, although not classified under the seriousness criteria, all suspected transmissions of an infectious agent should be reported as SAE. A suspected virus transmission means that virus antigen has been detected in the patient. A passive transmission of antibodies alone does not constitute a suspected virus transmission.

7.3.4 SAE Reporting Timelines

All SAEs, whether or not they are suspected to be related to study treatment, are to be reported immediately by telephone, fax, or email to the Clinical Project Manager or designee with the contact detailed provided to each site in the Investigator Site Binder. The contact details will also be communicated at the study initiation visit.

In addition, within 24 hours after recognition of the event, an Octapharma Serious Adverse Event Report must be completed and submitted to:

Octapharma's Corporate Drug Safety Unit
OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235, 1100 Vienna, Austria
Fax: [redacted]
E-mail: [redacted]

24 hours emergency telephone numbers:

[redacted] **or**
[redacted]

Waivers the from SAE Reporting Requirement

Waivers from the SAE reporting requirement include surgeries that are elective or were planned before study entry or prolongations of existing hospitalizations for economic or social, but not medical, reasons. Such surgeries or prolongations of hospitalizations should not be considered SAEs.

7.3.5 Laboratory Tests

Clinical laboratory parameters will be investigated during the study at the time points specified in the Flow Chart of Assessments (Table 1).

All of the study-specific laboratory tests will be performed at the local laboratories for each study site. The laboratory test and sample collection timing are specified below (Table 5).

Table 5: Laboratory Tests and Time Points

Test	Timing
Hematology (complete blood count, WBC differential, hematocrit, hemoglobin, platelet counts, reticulocytes)	During Screening (Baseline evaluation), at Days 1, 3, 5, 8, 15, 22, and at Day 32/EOS
Hemolysis (total, direct, and indirect bilirubin)	During Screening (Baseline evaluation), at Days 1, 3, 5, 8, 22, and at Day 32/EOS
Serum chemistry (ALT, AST, creatinine, Na, Ca, K, BUN, LDH)	During Screening (Baseline evaluation), Days 1, 3, 22, and at Day 32/EOS
Blood or Urine pregnancy test (females of childbearing potential)	During Screening (Baseline evaluation) and Day 32/EOS
Virology: HIV, HCV, HBV NAT	During Screening (Baseline evaluation, see Section 7.1.3)

Investigational sites will follow all site and local laboratory standard operating procedures for sample collection and handling and will provide the sponsor with normal reference ranges and laboratory certification certificates.

The methods of determination and normal ranges for each parameter from each local laboratory will be provided in the clinical study report.

7.3.6 Vital Signs

Vital signs will be collected at the time points specified in the Flow Chart of Assessments (Table 1) are blood pressure, body temperature, pulse rate, and respiratory rate.

On Day 1 and Day 3, vital sign measurements will be recorded before the start of the infusion, 15 minutes (±15 minutes) after every infusion rate change, and approximately 30 minutes after the end of the infusion.

7.3.7 Physical Examination including Height and Body Weight.

Physical examinations will be performed at the visits specified in the Flow Chart of Assessments (Table 1).

Both height and weight will be measured at Baseline.

7.3.8 Other Relevant Safety Information

a) Post-study related safety reports

Any SAE which occurs during the study (ie, within 4 weeks after the last PANZYGA administration, which for most patients will be up to and including Day 32) will be reported by the Investigator to the Sponsor. Proactive monitoring for post-study SAEs is not required.

In case a post-study SAE is identified, the Investigator should complete an SAE form and also state the relation to the clinical study in the report.

Deaths occurring during the study (ie, within 4 weeks after the last PANZYGA administration, which for most patients will be up to and including Day 32) should also be reported, regardless of whether or not they are considered treatment-related.

b) Pregnancies

Every effort will be made to avoid a pregnancy during the use of an IMP. Pregnancies occurring during the study (fetal exposure to PANZYGA) need to be reported.

In case of pregnancy during the study, the Investigator should complete the Pregnancy Notification Form and send or fax it to the Clinical Project Manager or designee (Section 7.3.4).

Follow-up information on the outcome of both mother and fetus will be requested by a Sponsor representative.

c) Overdose, interaction, medication error and lack of efficacy

The following safety relevant information should be reported as an AE or, if the reaction fulfills one of the criteria for seriousness, as SAE.

d) Drug overdose

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol and higher than the known therapeutic dose

that is of clinical relevance. The reaction must be clearly identified as an overdose.

e) Drug interaction

A drug interaction is a situation in which a substance or medicinal product affects the activity of an IMP, ie, increases or decreases its effects, or produces an effect that none of the products would exhibit on its own. The reaction must be clearly identified as a drug interaction.

f) Medication error

A medication error involves the inadvertent administration or unintended use of a medicinal product which may be caused by the naming, presentation of pharmaceutical form/packaging, or instructions for use/labelling. The reaction must be clearly identified as a medication error.

g) Lack of efficacy

Lack of efficacy is suspected when the therapeutic result is not as expected. One example of lack of efficacy could be platelets not increasing following the correct administration of IVIG.

7.4 Other Assessments

7.5 Appropriateness of Measurements

For efficacy evaluations, platelet counts provide a direct measure of the response to IGIV treatment in ITP patients and has been widely used for this purpose in many clinical trials of similar nature. The test is performed routinely at each hospital and is considered to be a reliable and robust parameter.

The definition of response used for the primary endpoint is the most established procedure to obtain a dichotomy of success/failure that can be used to calculate the response rate. It is also acceptable to US FDA and was used as the primary efficacy endpoint in their approval of PANZYGA in the treatment of chronic ITP in adults and is thus expected to best facilitate their review of the efficacy of PANZYGA in this pediatric population.

Monitoring AEs, vital signs, laboratory safety tests, and physical examinations are standard procedures used to evaluate the safety of investigational products in clinical studies.

8 DATA HANDLING AND RECORD KEEPING

8.1 Documentation of Data

8.1.1 Source Data and Records

Source data are defined as all information related to clinical findings, observations, or other activities in the study; written down in original records or certified copies of original records; or electronic medical records; allowing reconstruction and evaluation of the clinical study.

The Investigator will maintain adequate source records (eg, case histories or patient files for each patient enrolled). Source records should be preserved for the maximum period of time required by local regulations.

For each patient enrolled, the Investigator will indicate in the source record(s) that the patient is participating in this study.

All data entered in the eCRF must be supported by source data in the patient records.

The Investigator will permit study-related monitoring, audit(s), IEC/IRB review(s), and regulatory inspection(s), by providing direct access to the source data/records.

The Investigator may authorize site staff (eg, sub-Investigators, research nurses) to enter study data into the eCRF. This must be documented in the Delegation of Authority Log signed by the Investigator.

8.1.2 Electronic Case Report Forms

For each patient enrolled, an eCRF will be completed within the Electronic Data Capture (EDC) system and approved by the Investigator or an authorized sub-Investigator.

Study site staff (eg, research nurse, study coordinator, Investigator) will be responsible for entering patient data into the validated EDC system. All study site personnel will be trained on the EDC system and study-specific eCRFs prior to receiving access to the live database for data entry.

The study site will be provided with the approved eCRF Completion Guidelines to assist in data entry and data issues/questions. The study site will be notified once the eCRF is active to begin data entry. Additional site training may be provided as refreshers throughout the study, if needed. All persons allowed to enter or change eCRF data must be listed in the Delegation of Authority Log.

8.1.3 Changes to Electronic Case Report Form Data

Monitors will perform source data verification (SDV) as defined for the study.

If any errors or discrepancies in the eCRFs are found during data entry or review, discrepancies will be generated programmatically within the EDC system, and 'manual' queries will be generated by either a monitor or Data Management.

Discrepancies and queries can only be corrected by the Investigator(s) or other authorized site personnel. An audit trail documents all changes to the data over the entire study period. If the reason for a change is not obvious, a comment must be supplied in the query's response, stating the reason for the change, prior to closing. The study monitor should provide guidance to Investigator(s) and the Investigator(s)' designated representatives on making such corrections.

Once queries have been resolved by the site staff, the resolutions are assessed by Data Management. If the query response provided confirms the data as correct, the discrepancy will be closed. If the response does not adequately address the question raised, a new query will be issued for further clarification.

Manual checks will be performed, and electronic data check programs run, throughout the study until the data is clean and the database is ready for lock. All discrepancies will be resolved prior to database lock. There will be a final run of the programmed checks to ensure all discrepancies are closed out, SDV will be confirmed as complete by the monitor, and all eCRFs will be approved by the Investigator prior to database lock.

8.2 Information to Investigators

An IB will be handed out to the Investigator before the start of the study. The IB contains all information in the Sponsor's possession necessary for the Investigator to be fully and accurately informed about the safety of the IMP under evaluation and the respective benefit-risk ratio.

The IB will be updated by the Sponsor at regular intervals and whenever relevant new information concerning PANZYGA becomes available.

All participating investigators will be informed about relevant study procedures, about the methods for rating relevant study outcomes, and how to enter data into the eCRF in order to reduce discrepancies. At the study initiation visit, the eCRF will be explained to all study site staff entitled to document data in the eCRF.

The Investigator will be kept informed of important data that relate to the safe use of PANZYGA as the study proceeds.

8.3 Responsibilities

The Principal Investigator is accountable for the conduct of the clinical study. Responsibilities may be delegated to appropriately qualified persons.

A Delegation of Authority Log will be filled in and signed by the Principal Investigator. In accordance with this authority log, study site staff (eg, sub-Investigators, research nurses) are authorized to perform tasks relating to the study.

8.4 Investigator's Site File

At each study site, the Investigator is responsible for maintaining all records to enable the conduct of the study to be fully documented. Essential documents as required by GCP guidelines and regulations (eg, copies of the protocol, study approval letters, all original informed consent and assent forms, site electronic

versions of all eCRFs, drug dispensing and accountability logs, correspondence pertaining to the study) should be filed accurately and kept by the Investigator for the maximum period of time required by local regulations.

The Investigator is responsible for maintaining a confidential patient identification code list, which provides the unique link between named source records and eCRF data for the Sponsor. The Investigator must arrange for the retention of this confidential list for the maximum period of time required by local regulations.

No study document should be destroyed without prior written agreement between the Investigator and the Sponsor. Should the Investigator elect to assign the study documents to another party, or move them to another location, the Sponsor must be notified in writing.

8.5 Provision of Additional Information

On request, the Investigator will supply the Sponsor with additional data relating to the study, or copies of relevant source records, ensuring that the patient's confidentiality is maintained. This is particularly important when source documents are illegible or when errors in data transcription are encountered.

In the event of particular issues or governmental queries, it is also necessary to have access to the complete study records, provided that the patient's confidentiality is protected in accordance with applicable regulations.

8.6 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be established by the Sponsor. The IDMC will be composed of recognized experts in the fields of hematology and/or critical care who are not actively recruiting patients.

The IDMC will review relevant data periodically during the study and will give advice on the continuation, modification, or termination of the study. A written study-specific procedure will define in detail the composition, responsibilities, and procedures of the IDMC.

9 STATISTICAL METHODS AND SAMPLE SIZE

Statistical analysis will be delegated under an agreement of transfer of responsibilities to an external contract research organization (CRO). All Octapharma procedures and policies must be met by this CRO. Discrepancies or exceptions will be approved by the Sponsor's Manager of Biometrics.

9.1 Determination of Sample Size

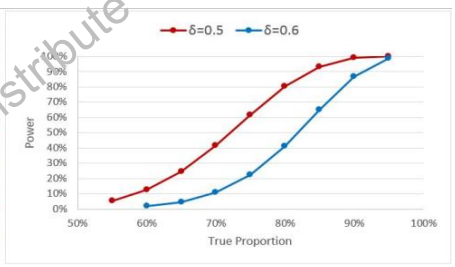
At least 20 patients who meet all eligibility criteria will be enrolled in the study.

The purpose of this study is to evaluate the efficacy and safety of PANZYGA in pediatric patients with chronic ITP; the chosen number of 20 patients to be enrolled is not derived from statistical considerations of power but driven by feasibility constraints with respect to finding pediatric ITP patient eligible and willing to participate in this study.

We expect the true proportion of responders to be comparable to results from similar studies in adult patients, as there is no published data or expert statement that would indicate otherwise. Looking at possible outcome scenarios, 20 evaluable patients give the following picture from a statistical point of view:

Power Considerations for 20 Evaluable Patients:

Responders		Exact 95% Confidence Limits		Hypothetical power to show that the true response rate is above δ (1-sided, α=0.025), given that it is in fact equal to the observed proportion	
Number	Proportion	Lower	Upper	δ=0.5	δ=0.6
11	55%	31,5%	76,9%	5,5%	
12	60%	36,1%	80,9%	12,6%	2%
13	65%	40,8%	84,6%	24,5%	4,4%
14	70%	45,7%	88,1%	41,6%	10,7%
15	75%	50,9%	91,3%	61,7%	22,5%
16	80%	56,3%	94,3%	80,4%	41,1%
17	85%	62,1%	96,8%	93,3%	64,8%
18	90%	68,3%	98,8%	98,9%	86,7%
19	95%	75,1%	99,9%	100,0%	98,4%
20	100%	83,2%	100,0%		



Even though the chosen number of 20 pediatric patients is thus not sufficient 'to power' the study, it will still allow the Sponsor to gather enough clinical evidence to obtain a sound and meaningful medical assessment of the efficacy and safety of PANZYGA in pediatric patients with chronic ITP.

9.2 Statistical Analysis

A formal statistical analysis plan describing all details of the analyses to be performed will be prepared by the study statistician and approved by the Sponsor prior to the start of the statistical analysis.

No confirmatory statistical analysis will be performed; the results of this study will be presented at the descriptive level only.

In general, and if not detailed otherwise in the Statistical Analysis Plan (SAP), all statistical presentations will be fit to the nature and type of the individual data items:

- Binary data (whether or not an event has occurred): counts and proportions
- Count data (the frequency of an event in a set time period): rate (count per unit time)

- Continuous data (measurements on a continuous scale, including quasi-continuous variables): arithmetic mean, standard deviation, median, lower and upper quartile, minimum, maximum
- Scales data (Ordinal and Non-ordinal): absolute and relative frequencies
- Time-to-event data (how long it takes to observe the outcome of interest, e.g. the initial treatment response): time to event or last evaluation (censored data in case subjects are lost to follow-up) and event rate. Such parameters may also be presented as Kaplan-Meier plots of the product-limit survival function estimates.

9.2.1 Populations for Analysis

The following populations will be considered for the statistical analysis:

- Safety Analysis Set (SAF): All patients who received at least part of 1 infusion of PANZYGA.
- Full Analysis Set (FAS): All patients in the SAF who satisfy all major eligibility criteria and for whom any post-baseline data is available. This is the set of eligible patients with treatment effects measured, according to the intention-to-treat (ITT) principle.
- Per-Protocol Set I (PP1): All patients in the FAS, excluding those with significant protocol deviations before the primary efficacy assessment on Day 8 is completed, and which may have an impact on the evaluation of the primary endpoint.
- Per-Protocol Set II (PP2): All patients in the FAS, excluding those with significant protocol violations potentially affecting the (secondary) efficacy evaluations.

Only protocol deviations with the potential to significantly affect the study results or to invalidate the interpretation of the data obtained will lead to exclusion of patients from the PP sets. The inclusion of each patient in the respective analysis populations will be determined before database lock in a data review meeting by a panel consisting of a medical expert from the Sponsor, the clinical study manager, the data manager, and the study statistician.

The analysis of safety will be based on the SAF.

The evaluation of the primary objective will be performed for the FAS (ITT analysis) and for the PP1 set (PP analysis) to assess the robustness of the results. The primary analysis will be the ITT analysis.

For secondary objectives ITT and PP2 analyses will be carried out; again the ITT analysis is considered the primary analysis and will be presented first in the report.

9.2.2 Efficacy Analysis Plan

The primary and secondary efficacy parameters will be determined on the basis of the patient's platelet concentration, listed individually, and presented descriptively.

The primary endpoint parameter 'response' is defined as an increase in platelet count at least once to ≥50x10^9/L within 7 days after the first infusion, ie, by Day 8 (increase must occur at least once on any day up to and including Day 8).

The number and proportion of responders will be presented, together with the associated exact 95% confidence intervals.

The time to reach the desired increase in platelet count as well as the duration of response and the maximum platelet levels will be presented in listings and summarized in statistical tables.

Individual profiles of platelet count over time will be presented as Trellis plots.

9.2.3 Safety Analysis Plan

The safety analysis will comprise descriptive statistics, tabulations, and listings of all TEAEs, safety laboratory results, vital signs, and physical examination findings. All reported AEs will be coded according to the Medical Dictionary for Regulatory Activities) MedDRA.

An AE is defined as treatment-emergent if first onset or worsening is after start of the first infusion of PANZYGA. Only TEAEs are accounted for in the analysis.

AEs will be record at the start of the fist infusion of PANZYGA. AEs that occur between informed consent/assent and the start of the first PANZYGA infusion will be recorded under Medical History.

Incidences of treatment-emergent AEs will be given as the number and percentage of patients who experienced any or a particular AE, including serious and drug-related AEs.

The summary tables for AEs will be given by system organ class and preferred term. Additionally, AEs will be summarized by severity and relationship to study treatment. In addition to the tables presenting incidences including all AEs, incidences will be determined for the subset of SAEs and drug-related AEs.

Incidences of infusional AEs will be given as the number and percentage of patients who experienced any or a particular infusional AE, including serious and drug-related AEs.

The summary tables for infusional AEs will be given by system organ class and preferred term. Additionally, infusional AEs will be summarized by severity and relationship to study treatment. In addition to the tables presenting incidences including all infusional AEs, incidences will be determined for the subset of SAEs and drug-related AEs.

Narratives will be prepared describing each death, other SAEs, and other significant AEs that are judged to be of special interest because of clinical importance.

For each routine laboratory parameter at each visit the actual result, the change from baseline, the out-of-range flag and the assessment of clinical relevance will be summarized descriptively.

Vital signs include systolic and diastolic blood pressure, pulse rate, body temperature and the respiratory rate; descriptive tables on the sampling statistics

of these parameters at each time point will be provided for the values as well as for their changes to baseline.

9.2.4 Handling of Missing Data

No replacement of missing data values is planned, but only observed results (and platelet counts) will be included in the analyses.

9.3 Randomization, Stratification, and Code Release

This is an open-label non-randomized study; therefore, no randomization code list or procedure for code release are required. Patients will not be stratified by age group.

9.4 Interim Analysis

No interim analysis is planned.

10 ETHICAL/REGULATORY, LEGAL AND ADMINISTRATIVE ASPECTS

10.1 Ethical/Regulatory Framework

This study will be conducted in accordance with the ethical principles laid down in the Declaration of Helsinki. The study protocol and any subsequent amendment(s) will be submitted to an IEC/ IRB and to the Regulatory Authority. The study will be conducted in compliance with the protocol, GCP guidelines, and applicable regulatory requirements.

The regulatory application or submission for regulatory approval will be made by the Sponsor or designated third party (eg, CRO) as required by national law.

10.2 Approval of Study Documents

The study protocol, a sample of the patient information and informed consent form, assent form, any other materials provided to the patient and their parent/legal guardian, and further requested information will be submitted by the Sponsor or the Investigator to the appropriate IEC/IRB and the Regulatory Authority. The study must be approved by the IEC/IRB and the Regulatory Authority before any IMP may be shipped to the study sites and any patient is exposed to a study-related procedure.

The Sponsor, the Investigator, and any third party (eg, CRO) involved in obtaining approval must inform each other in writing that all ethical and legal requirements have been met before the first patient is enrolled in the study.

10.3 Patient Information and Informed Consent

The Investigator will obtain freely given written consent from each the patient after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspect of the study which is relevant to the patient's decision to participate. The informed consent form must be signed, with name and date and time noted by the patient, before the patient is exposed to any study-related procedure, including screening tests for eligibility.

For patients not qualified to give legal consent, written consent must be obtained from the legal parent/guardian. If children are old enough to understand the risks and benefits of the study, they should also be informed and provide their written consent using an assent form.

The Investigator will explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, without any consequences for their further care and without the need to justify. The Investigator will complete the informed consent section of the CRF for each patient enrolled.

Each patient (and parent/legal guardian, as appropriate) will be informed that his/her medical (source) records may be reviewed by the study monitor, a quality assurance auditor, or a health authority inspector, in accordance with applicable regulations, and that these persons are bound by confidentiality obligations.

10.4 Protocol Amendments

Any prospective change to the protocol will be agreed between the Investigator (Co-ordinating Investigator in multi-center studies) and the Sponsor prior to its implementation. Any such amendments will be submitted to the any competent IEC/IRB and/or competent authority responsible as required by applicable regulations.

IEC/IRB approval will, at a minimum, be requested for any change to this protocol which could affect the safety of the patients, the objective/design of the study, any increase in dosage or duration of exposure to the IMP, an increase in the number of patients treated, the addition of a new test or procedure, or the dropping of a test intended to monitor safety.

10.5 Confidentiality of Patient Data

The Investigator will ensure that the patient's confidentiality is preserved. On eCRFs or any other documents submitted to the Sponsor, the patients will not be identified by their names, but by a unique patient identifier. Documents not intended for submission to the Sponsor, ie, the confidential patient identification code list, original consent and assent forms, and source records, will be maintained by the Investigator in strict confidence.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Periodic Monitoring

The monitor will contact and visit the Investigator periodically to review all study-related source data/records, verify the adherence to the protocol and the completeness, correctness and accuracy of all CRF entries compared to source data. The Investigator will cooperate with the monitor to ensure that any discrepancies identified are resolved.

For this study, the first monitoring visit shall take place shortly after the inclusion of the first patient. Thereafter, monitoring frequency will depend on study progress and in accordance with the study clinical monitoring plan.

The monitor must be given direct access to source documents (original documents, data, and records). Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the clinical study. Source data will be available for all data in the eCRFs, including all laboratory results.

11.2 Audit and Inspection

The Investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the Sponsor, or to IEC/IRB/regulatory inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and welfare of the patients have been adequately protected, and that all data relevant for the assessment of safety and efficacy of PANZYGA have been reported to the Sponsor.

12 REPORTING AND PUBLICATION

12.1 Clinical Study Report

A clinical study report (in accordance with relevant guidelines and the Sponsor's Standard Operating Procedures [SOPs]) will be prepared by the Sponsor after completion of the study. The Co-ordinating Investigator will approve the final study report after review.

12.2 Publication Policy

The results of this study may be published or presented at scientific meetings.

If the Investigator wants to publish or present study results, the Investigator agrees to inform the Sponsor and to submit all manuscripts or abstracts to the Sponsor before submission to an editorial board or scientific review committee. This will allow the Sponsor to protect proprietary information and to provide comments based on information that may not yet be available to the Investigator.

In accordance with standard editorial and ethical practice, the Sponsor will support publication of multi-center studies only in their entirety and not as individual center data. Authorship will be determined by mutual agreement.

13 LIABILITIES AND INSURANCE

In order to cover any potential damage or injury occurring to a patient in association with PANZYGA or participation in the study, the Sponsor will contract insurance in accordance with local regulations.

The Investigator is responsible for dispensing PANZYGA according to this protocol and for its secure storage and safe handling throughout the study.

14 REFERENCES

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15 APPENDICES

Not applicable.

PROTOCOL AMENDMENT #1

STUDY NUMBER: NGAM-10

STUDY TITLE: Post-Marketing Study to Evaluate the Efficacy and Safety of PANZYGA in Pediatric Patients with Chronic Immune Thrombocytopenia (ITP)

SPONSOR: Octapharma USA
121 River Street, 12th Floor
Hoboken, NJ 07030

TEST PRODUCT: PANZYGA

IND / BLA NUMBERS: IND 14121 / BLA 125587

APPROVED BY: [redacted]
Octapharma Pharmazeutika ProduktionsgmbH
Oberlaaerstr. 235, A-1100 Vienna, Austria

PROTOCOL:	**DATE:**
Final Version 01	30 Jan 2019
Protocol Amendment #1	21 May 2019
Final Version 02	21 May 2019

Rationale for the Amendment:

FDA reviewed Study Protocol No. NGAM-10 Version 01 and provided 7 comments to the Sponsor in a communication dated 16-May-2019. The rationale for Amendment 01 of Protocol NGAM-10 is to address these 7 comments.

In addition, an error was identified in the Flow Chart of Assessments regarding the requirement for hematology / hemolysis and serum chemistry assessments at Day 5, 8, 15 and Day 22 with Sections 6.1.4 and 6.1.5 of the protocol; Amendment 1 reconciles this inconstancy.

The following changes made throughout the protocol were considered significant and are documented in the red-line version of the protocol:

MODIFICATION 1: Expedited Safety Reporting Requirements

The protocol includes the expedited safety reporting of SAEs of the Investigator to the Sponsor in Section 7.3.4. FDA requested that the protocol also include the plan for Sponsor expedited safety reporting to FDA.

Previous requirement: Protocol was silent on Sponsor expedited safety reporting requirements to FDA.

Amended Requirement: A plan for Sponsor expedited safety reporting to FDA was added, along with additional Investigator SAE reporting requirements, as specified in 21 CFR 312.32. The following text was added to Protocol Section 7.3.4:

The Investigator must update the Octapharma Serious Adverse Event Report as soon as any additional information becomes available. The Investigator must also report SAEs to the IRB/IEC as required by local and national laws. The Investigator must maintain documentation of all communications to and from the IRB/IEC.

In accordance with 21 CFR 312.32 and local authorities, the

Sponsor will submit to the FDA unexpected adverse reactions within 15 calendar days. Unexpected fatal or life-threatening adverse reactions will be submitted within 7 calendar days.

MODIFICATION 2: Infusion-Related Adverse Events

Instructions for handling infusion-related adverse events were modified such that in the event of Grade 2 or higher infusion-related reactions the PANZYGA infusion would be stopped; the infusions may be resumed at a lower rate after the symptoms subside. This change will align the management of infusion related reactions with the PANZYGA label (See Protocol Section 5.4) and Study Outline.

Previous requirement:

If an adverse event (AE) occurs during infusion, the infusion rate should be reduced to half the rate at which the event occurred, or the infusion should be

interrupted until symptoms subside. The infusion may then be resumed at an infusion rate tolerated by the patient. The infusion rate may be gradually increased as tolerated by the patient.

Amended Requirement:

If a Grade 2 (moderate) or higher infusion-related adverse event (AE) occurs during infusion, the Panzyga infusion will be stopped. After infusion-related symptoms subside, the infusion may be resumed at a lower rate. The infusion rate may be gradually increased as tolerated by the patient.

If a *Grade 1 (mild) infusion-related* AE occurs during infusion, the infusion rate should be reduced to half the rate at which the event occurred, or the infusion should be interrupted until symptoms subside. The infusion may then be resumed at an infusion rate tolerated by the patient. The infusion rate may be gradually increased as tolerated by the patient.

MODIFICATION 3: Managing Hypersensitivity Reactions

FDA requested that, to enhance the safety of participating patients, the protocol be amended to provide instructions that study sites have access to epinephrine in the event of severe hypersensitivity reaction, as specified in the PANZYGA label) and to include details regarding management of hypersensitivity reactions to Panzyga (See Protocol Section 7.3.2.8).

Previous requirement: Protocol was silent on epinephrine access and handling hypersensitivity reactions.

Amended Requirement: A new section - Section 7.3.2.8: Managing Hypersensitivity Reactions – was added to the protocol.

Section 7.3.2.8 Managing Hypersensitivity Reactions

Severe hypersensitivity reactions may occur during PANZYGA infusions. In the case of any subject exhibiting clinical signs of severe acute hypersensitivity reactions to PANZYGA, the PANZYGA infusion must be immediately stopped. Each site must have Epinephrine readily available and follow their institution's standard procedure for Epinephrine administration and monitoring. After the hypersensitivity reaction subsides, the infusion may be resumed at a lower rate if allowed per the site Epinephrine administration and monitoring procedures, and per Investigator discretion.

MODIFICATION 4: Pre-medication Use Prior to PANZYGA Infusions

The protocol did not specify whether or not pre-medication use was allowed prior to PANZYGA infusions. FDA requested that the protocol be amended to specifically state that patients with a history of hypersensitivity to IGIV may receive pre-medication with H-1 blockers or antipyretics. This change was incorporated throughout the body of the protocol.

Previous requirement: Protocol was silent on pre-medication use prior to PANZYGA infusions.

Amended requirement: A section was added to the protocol (Section 4.2.1: Allowed Pre-medications) to state that patients with a history of hypersensitivity to IGIV may receive premedication with H-1 blockers or antipyretics. In addition, the protocol was amended to include site instructions at each study visit to document any pre-medications that were administered with previous IGIV treatment (Section 6.1.1: Baseline Visit/Screening Period), and to instruct sites to administer pre-medications, as appropriate (Section 6.1.2: Day 1 and Section 6.1.3: Day 3), and to provide site instructions to collect any pre-medication use as a prior medication (Section 7.1.4: Prior and Concomitant Medication Use)

Section 4.2.1 Allowed Pre-medications

Use of H-1 blockers or antipyretics are allowed for patients who have history of hypersensitivity to IGIV treatment; this may minimize the severity of possible infusion-related reactions in patients already predisposed to hypersensitivity reactions. All pre-medications administered prior to PANZYGA administration must be recorded in the eCRF.

Section 6.1.1 Baseline Visit/Screening Period

- *Documentation of prior medications (previous 3 months), including administration of pre-medication(s) as appropriate (see Section 4.2.1)*

Section 6.1.2 Day 1

- *Administration of pre-medication(s) as appropriate (see Section 4.2.1)*

Section 6.1.3 Day 3

- *Administration of pre-medication(s) as appropriate (see Section 4.2.1)*

Section 7.1.4 Prior and Concomitant Medication Use

Prior medication use will be obtained by interview and review of patient charts (if available). Patients will be queried specifically for use of H-1 blockers or antipyretics as pre-medications prior to previous IGIV treatments

MODIFICATION 5: Vital Sign Assessment Times After PANZYGA Infusions

FDA requested additional vital sign assessments after the start of the PANZYGA infusion, specifically to add vital signs assessments prior to any infusion rate change and to assess them every hour. This change was incorporated throughout the body of the protocol.

Previous requirement: The following vital assessments were specified in the protocol: Vital signs (at the start of the infusion, 15 minutes (±15 minutes) after each infusion rate change, and approximately 30 minutes after the end of the infusion.

Amended requirement: The following changes were made each of these sections of the protocol:

Study Outline
Flow Chart of Assessments footnote #9
Section 6.1.2 Day 1
Section 6.1.3 Day 3

Vital signs (at the start of the infusion and every 60 minutes (±15 minutes) thereafter until the end of the infusion. In addition, vital sign measurements will be recorded just prior to every infusion rate change (-10 minutes), 15 minutes (+15 minutes) after each infusion rate change, and approximately 30 minutes after the end of the infusion)

MODIFICATION 6: Thrombopoietin Receptor Agonist - Stable Dose

Thrombopoietin receptor agonist use is prohibited during Screening through Day 32 unless patients have been on a stable dose for 3 weeks. An error was identified in Table 2 which stated 3 months (rather than 3 weeks).

Previous requirement:

Table 2: Prohibited Medications

Medication	**Time Window**
thrombopoietin receptor agonists	prohibited during Screening Period through Day 32 **unless** patients have been receiving stable dose for 3 months prior to Screening Visit

Amended requirement:

Table 2: Prohibited Medications

Medication	***Time Window***
thrombopoietin receptor agonists	*prohibited during Screening Period through Day 32 **unless** patients have been receiving stable dose for <u>3 weeks</u> months prior to Screening Visit*

MODIFICATION 7: Long-term Anti-prolific Agents or Attenuated Androgen Therapy – Stable Dose

Long-term anti-prolific agents or attenuated androgen therapy is prohibited during Screening through Day 32 unless patients have been on a stable dose for 2 months and a dosage change was planned before Day 32. Exclusion Criterion #5 stated that patients would be excluded if **no** dosage was planned before Day 32 (indicating a dosage change was required or a patient was excluded). The

language for this exclusion criterion was modified to clarify that no dose change was permitted during the study.

Previous Requirement:

Study Outline Exclusion Criterion #5
Section 4.1.2 Exclusion Criterion #5

Administration of long-term anti-prolific agents or attenuated androgen therapy when the dose has NOT been stable during the preceding 2 months and no dosage change is planned until Day 32

Amended Requirement:

Study Outline Exclusion Criterion #5
Section 4.1.2 Exclusion Criterion #5

Administration of long-term anti-prolific agents or attenuated androgen therapy when the dose has NOT been stable during the preceding 2 months and a dosage change is planned before Day 32

MODIFICATION 8: Place holder for hematology / hemolysis analytes and serum chemistry assessments

Previous Requirement:

Table 1

Hemolysis is required on Screening/Baseline/Day 1,3,5,8,22 and 32

Serum Chemistry is required on Screening/Baseline/Day 1,3 and 32

Amended Requirement:

Table 1

Hemolysis is required on Screening/Baseline/Day 1,3,5,8,15, 22 and 32

Serum Chemistry is required on Screening/Baseline/Day 1,3,5,8 and 32

This is now consistent with Sections 6.1.4 and 6.1.5 in the body of the protocol.

Please see the attached redline version for documentation of these substantive changes.

AGREEMENT: These signatures constitute approval of this protocol amendment and provide the necessary assurance that the study will be conducted according to all stipulations of protocol and amendments.

Authorised person for signing the Study Protocol and Protocol Amendments on behalf of the Sponsor and Sponsor's Medical Expert:

[redacted] **Date:** [redacted]

[redacted]
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CLINICAL STUDY PROTOCOL

NGAM-10

Post-Marketing Study to Evaluate the Efficacy and Safety of PANZYGA in Pediatric Patients with Chronic Immune Thrombocytopenia (ITP)

Investigational Product:	PANZYGA
Indication:	Chronic Immune Thrombocytopenia (ITP)
Study Design:	Prospective, open-label, single-arm, multi-center study
Sponsor:	Octapharma USA 121 River Street, 12th Floor Hoboken, NJ 07030
Study Number:	NGAM-10
IND Number / BLA Number:	IND 14121 / BLA 125587
Development Phase:	Phase 4
Planned Clinical Start:	Q2/Q3 2019
Planned Clinical End:	Q1 2022
Date of Protocol:	21-May-2019
Version:	02

STUDY OUTLINE

Name of Sponsor/Company: Octapharma USA	
Name of Investigational Product: PANZYGA	**Protocol Identification Code:** NGAM-10
Name of Active Ingredient: Immune globulin human-ifas	**Date of Final Protocol:** 21-May-2019

Title of Study:

Post-Marketing Study to Evaluate the Efficacy and Safety of PANZYGA in Pediatric Patients with Chronic Immune Thrombocytopenia (ITP)

Indication:

Chronic Immune Thrombocytopenia (ITP)

Number of Study Centre(s):

Up to 8 sites in the USA

Objectives:

Primary Objective:

The primary objective is to evaluate the efficacy of PANZYGA in increasing the platelet count in pediatric patients with chronic ITP.

Secondary Objectives:

The secondary objectives of this study are to:

- Assess safety of up to 2 g/kg PANZYGA (1 g/kg PANZYGA on Day 1 and an optional dose of 1 g/kg PANZYGA on Day 3) infused in the pediatric population within the scope of the clinical study
- Determine the time to reach a platelet count of $\geq 50 \times 10^9$/L
- Determine duration of time during which the platelet count is maintained at the level $\geq 50 \times 10^9$/L
- Determine the maximum platelet count during the study

Study Design:

This is a prospective, open-label, single-arm, multicenter, Phase 4 study evaluating the efficacy and safety of PANZYGA in pediatric patients with chronic ITP.

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Name of Investigational Product: PANZYGA	**Protocol Identification Code:** NGAM-10
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Number of Patients:

At least 20 patients

Patient Selection Criteria:

Inclusion Criteria:

1. Females and males aged from ≥1 year to <18 years old
2. Confirmed diagnosis of Chronic Immune Thrombocytopenia (ITP) according to American Society of Hematology (ASH) 2011 guidelines
3. Platelets count $<30x10^9$/L at the Baseline Visit
4. Voluntarily given written informed consent (provided by patient's parent or legal guardian) and assent (provided by patient [if age-appropriate per IRB requirements])
5. Females of childbearing potential have been using at least 1 acceptable form of birth control for a minimum of 30 days (or a minimum of 3 months for hormonal contraceptives) prior to the Screening visit, and must agree to use at least 1 acceptable method of contraception for 30 days after the last dose of PANZYGA. Acceptable methods of birth control for this study include: intrauterine device (IUD), hormonal contraception, male or female condom, spermicide gel, diaphragm, sponge, or cervical cap. Abstinence is not considered an acceptable method of birth control.
6. Parent or legal guardian must agree and be willing to assist the participant attend study visits, and to follow all protocol requirements and instructions of the study doctor

Exclusion Criteria:

1. Thrombocytopenia secondary to other diseases (such as Acquired Immunodeficiency Syndrome [AIDS] or systemic lupus erythematosus [SLE]), drug-related thrombocytopenia, or congenital thrombocytopenia
2. Administration of intravenous immunoglobulin (IGIV) or anti-D immunoglobulin within 3 weeks before enrollment
3. Administration of thrombopoietin receptor agonists when the dose has NOT been stable within 3 weeks before enrollment and a dosage change is planned before Day 32
4. Administration of oral immunosuppressants when the dose has NOT been stable during the preceding 2 months (2 weeks for long-term corticosteroid therapy) and a dosage change is planned before Day 32 (Note: topical agents and inhaled corticosteroid therapy use is permitted)
5. Administration of long-term anti-prolific agents or attenuated androgen therapy when the dose has NOT been stable during the preceding 2 months and a dosage change is planned before Day 32
6. Nonresponsive to previous treatment with IGIV or anti-D immunoglobulin
7. Evidence of an active major bleeding episode at Screening
8. Splenectomy in the previous 4 weeks or planned splenectomy throughout the study period
9. Evans syndrome (experiencing active disease with 2 out of 3 of the following: autoimmune thrombocytopenia, autoimmune hemolytic anemia, and/or autoimmune neutropenia)
10. Known or suspected human immunodeficiency virus (HIV), hepatitis B virus (HBV), and/or hepatitis C virus (HCV) infections
11. Emergency surgery in the previous 4 weeks
12. Severe liver and/or kidney disease (alanine aminotransferase [ALT] >3x upper limit of normal (ULN), aspartate aminotransferase [AST] >3x upper limit of normal (ULN), and/or creatinine >120 µmol/L)
13. History of severe hypersensitivity to blood or plasma derived products, or any component of the PANZYGA
14. Known immunoglobulin A (IgA) deficiency and antibodies against IgA
15. History of, or suspected alcohol or drug abuse in the previous year
16. Females who are pregnant or nursing
17. Unable or unwilling to comply with the study protocol
18. Receipt of any other investigational medicinal product within 3 months before study entry
19. Risk factors* for thromboembolic events in whom the risks outweigh the potential benefit of PANZYGA treatment.

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20. Any other condition(s), that in the Investigator's opinion, make it undesirable for the patient to participate in the study or may interfere with protocol compliance.

* Risk factors include, but are not limited to: obesity, advanced age, hypertension, diabetes, a history of atherosclerosis/vascular disease or thrombotic events, hyperlipidemia, multiple cardiovascular risk factors, acquired or inherited thrombophilic disorders, prolonged periods of immobilization, severe hypovolemia, central venous catheterization, active malignancy and/or known or suspected hyperviscosity.

Test Product, Dose, and Mode of Administration:

PANZYGA (Immune Globulin, intravenous, human-ifas). PANZYGA must be stored and transported light-protected at +2°C (36°F) to +8°C (46°F) and must be brought to room temperature before use.

Patients will receive a dose of 1 g/kg body weight PANZYGA given on Day 1 and optionally another dose of 1 g/kg PANZYGA given on Day 3; body-weight dependent doses will be based on each patient's weight collected at Baseline. Total PANZYGA doses will be 1 g/kg for patients receiving only 1 dose on Day 1 and 2 g/kg for those receiving the optional Day 3 dose. Prior to the Day 3 infusion, each patient's preinfusion platelet count will be reviewed by the Investigator. If the Day 3 platelet count shows evidence of response as indicated by the platelet count at least doubling from Baseline count AND is $>50x10^9$/L, the Day 3 infusion **will not be** administered. If the Baseline platelet count has doubled but is $\leq 50x10^9$/L, the Day 3 infusion **will be** administered.

PANZYGA will be delivered by intravenous infusion according to the recommended flow rates:

- Initial infusion rate of 0.01 mL/kg/min (60 mg/kg/hr) for the first 30 minutes
- If tolerated, increase to 0.02 mL/kg/min (120 mg/kg/hr) for the second 30 minutes
- If tolerated, increase to 0.04 mL/kg/min (240 mg/kg/hr) for the third 30 minutes
- If tolerated, increase to 0.08 mL/kg/min (480 mg/kg/hr) for the remainder of the infusion.

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Infusion rates should not exceed 0.08 mL/kg/min and should not exceed 8.0 mL/min. The infusion rate may be gradually increased as tolerated by the patient.

If a Grade 2 or higher (moderate) infusion-related adverse event (AE) occurs during infusion, the Panzyga infusion will be stopped. After infusion-related symptoms subside, the infusion may be resumed at a lower rate. The infusion rate may be gradually increased as tolerated by the patient.

If a Grade 1 (mild) infusion-related AE occurs during infusion, the infusion rate should be reduced to half the rate at which the event occurred, or the infusion should be interrupted until symptoms subside. The infusion may then be resumed at a rate tolerated by the patient.The batch number(s) used will be recorded in the study documentation and electronic data capture (EDC) system.

Duration of Treatment:

Screening Period: 1 week

Treatment Period: up to 3 days

Follow-up Period: 29 days

Reference Therapy, Dose, and Mode of Administration:

Not Applicable

Study Outcome Parameters (Primary and Secondary Endpoints):

Primary Endpoint:

The primary efficacy parameter is defined as an increase in platelet count at least once to ≥50x10^9/L within 7 days after the first infusion, ie, by Day 8 (increase must occur at least once on any day up to and including Day 8). This definition of clinical response will serve as the basis for the primary endpoint, the response rate (ie, the proportion of patients with an elevation of platelet count at least once to ≥50x10^9/L within 7 days [ie, by Day 8] after the first infusion).

Secondary Endpoints:

- Time to reach a platelet count of ≥50x10^9/L
- Duration of platelet response defined as the number of days the platelet count remains above ≥50x10^9/L

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- Maximum platelet count during the study

Safety Parameters:

- AEs
- Vital signs (blood pressure, heart rate, temperature, respiratory rate)
- Physical examination
- Laboratory parameters: hematology (including reticulocytes), hemolysis, platelet count, serum chemistry (including lactase dehydrogenase [LDH]).

Study Procedures:

The study will be conducted in accordance with ICH-GCP and US FDA regulations.

The Flow Chart of Assessments specifies the procedures that will be performed at each study visit.

Baseline Visit

After appropriate information about the study and PANZYGA has been provided and written informed consent/assent has been obtained, patients will be evaluated for study eligibility according to the inclusion/exclusion criteria. These evaluations will include demographics, medical/surgical history, current medications, physical examinations, blood and urine samples, along with other safety and baseline evaluations as specified in the Flow Chart of Assessments.

Infusion Visits (Day 1 and Day 3)

The first PANZYGA infusion must begin no more than 2 days after Baseline evaluations have been completed and eligibility criteria have been confirmed. If Baseline and Day 1 Visits occur on the same day, Day 1 investigations do not need to be repeated. If Baseline evaluations are completed more than 2 days before Day 1, then the platelet count must be repeated and evaluated by the Investigator prior to the first infusion.

Patients who have met all of the inclusion criteria and none of the exclusion criteria will return to the study site for their first PANZYGA infusion. Required assessments will be performed as specified in the Flow Chart of Assessments, including safety evaluations before and after each infusion. Patients will remain

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at the study site during the infusion and for about 30 minutes after the end of each infusion to complete vital sign measurements.

Patients will receive a dose of 1 g/kg body weight PANZYGA on Day 1 and optionally another dose of 1 g/kg PANZYGA on Day 3; body-weight dependent doses will be based on each patient's weight collected at Baseline. Total PANZYGA doses will be 1 g/kg for patients receiving only 1 dose on Day 1 and 2 g/kg for those receiving the optional Day 3 dose.

Prior to the Day 3 infusion, the Investigator will assess each patient's preinfusion platelet count, hematocrit, and hemoglobin. If the Day 3 platelet count shows evidence of response, as indicated by the platelet count at least doubling from Baseline count AND >50x10^9/L, the Day 3 infusion will not be administered. If the Baseline platelet count has doubled but is ≤50x10^9/L, the Day 3 infusion will be administered. If any of these parameters indicate a clinically relevant change such that, in the Investigator's opinion, it is not safe to administer the second infusion the patient should be withdrawn from study treatment but will be followed for safety through Day 32.

Assessment Day 5 though Day 22

Patients will return to the study site as indicated in the Flow Chart of Assessments for continued efficacy and safety evaluations.

Day 32 (End of Study/Early Termination Visit)

Patients will return to the study site on Day 32 for final safety assessments/End of Study (EOS) visit. Patients withdrawn early from the study will be encouraged to return to the study site and complete the EOS assessments.

Statistical Analysis:

The primary endpoint for this study is the proportion of patients with an increase in platelet count to ≥50x10^9/L at least once within 7 days after the first infusion. This proportion will be assessed and presented together with its associated 95% confidence interval to facilitate comparison with results from other studies and published data. Because of the limited number of patients, no formal hypothesis test will be performed; any p-value or confidence interval presented is to be understood in the exploratory sense.

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All data collected will be presented descriptively. The time to reach the desired increase in platelet count as well as the duration of response will be presented in listings and summarized in statistical tables. Individual profiles of platelet count over time will be presented as Trellis plots.

All safety data, including tolerability assessments, abnormal laboratory values, and AEs will also be listed and summarized statistically.

Statistical presentations will be fit to the nature of individual data items and include sample characteristics, frequency counts and rates. Product-limit survival function estimates (Kaplan-Meier Plots), confidence intervals and graphs will be included as appropriate.

The following populations will be considered for the statistical analysis:

- Safety Analysis Set (SAF): All patients who received at least part of one infusion of PANZYGA.
- Full Analysis Set (FAS): All patients in the SAF who satisfy all major eligibility criteria and for whom any post-baseline data is available. This is the set of eligible patients with treatment effects measured, according to the intention-to-treat (ITT) principle.
- Per-Protocol Set I (PP1): All patients in the FAS, excluding those with significant protocol deviations before the primary efficacy assessment on day 8 is completed, and which may have an impact on the evaluation of the primary endpoint.
- Per-Protocol Set II (PP2): All patients in the FAS, excluding those with significant protocol violations potentially affecting the (secondary) efficacy evaluations.

Only protocol deviations with the potential to significantly affect the study results or to invalidate the interpretation of the data obtained will lead to exclusion of patients from the PP sets. The inclusion of each patient in the respective analysis populations will be determined before database lock in a data review meeting by a panel consisting of a medical expert from the Sponsor, the clinical study manager, the data manager, and the study statistician.

A detailed Statistical Analysis Plan (SAP) will be compiled as a separate document.

FLOW CHART OF ASSESSMENTS

Table 1: Flow Chart of Assessments

ASSESSMENTS	Scr / BL[1]	Day 1	Day 3	Day 5	Day 8	Day 15	Day 22	Day 32[12]
Visit Window (Days)	**-7 / -2**	**0**	**0**	**±1**	**±1**	**±3**	**±3**	**±5**
Informed Consent	X							
Inclusion / Exclusion Criteria Review	X	X						
Demographics	X							
Medical and Surgical History[2]	X							
Body Weight	X							
Physical Examination	X[3]	X[3]	X[4]	X[4]	X[4]	X[3]	X[4]	X[3]
Urine or Blood Pregnancy Test (females of child-bearing potential)	X							X
Hematology: CBC with white blood cell (WBC) differential, hematocrit, hemoglobin, platelet counts, reticulocytes	X	X[5,6]	X[5,6,7]	X	X	X	X	X
Hemolysis: total, direct, and indirect bilirubin	X	X	X	X	X	X	X	X
Serum Chemistry: ALT, AST, creatinine, Na, Ca, K, BUN, LDH	X	X	X	X	X			X
Viral markers (HIV, HCV, HBV nucleic acid test [NAT])	X[7]							
PANZYGA INFUSIONS		**X**	**X**[8]					
Vital Signs: heart rate, blood pressure, temperature, respiratory rate	X	X[9]	X[9]				X	X
AE Monitoring[10]		X	X	X	X	X	X	X
Prior and Concomitant Therapy (drug and non-drug)[11]	X	X	X	X	X	X	X	X

Abbreviations: BL = Baseline, Scr = Screening

1) Screening Period is 7 days. Day 1 (first PANZYGA infusion) must occur no more than 2 days after Baseline evaluations have been completed. If the Baseline visit occurs more than 2 days after Baseline evaluations have been completed, the platelet count must be repeated and evaluated by the Investigator before initiation of the Day 1 infusion. If Baseline and Day 1 visits occur on the same day, the Day 1 investigations need not be repeated.
2) Medical History will be collected for the previous year and will include the onset date of ITP. Surgical history will include the date of splenectomy (if applicable), and any other surgical procedures in the previous year.
3) Brief Physical Examination: general appearance, skin, heart, lungs, abdomen, extremities
4) Limited Physical Examination with targeted body systems per Investigator discretion
5) Pre-infusion
6) Platelet count, hematocrit, and hemoglobin results must be available and reviewed by the Investigator prior to start of the infusion
7) HIV/HCV/HBV NAT Test: Infusions may begin before the results are back if the Investigator is not aware of, and the patient isn't exhibiting clinical signs of, any viral infection.
8) If the Day 3 preinfusion platelet count shows evidence of response as indicated by the platelet count at least doubling from Baseline count AND >50x10^9/L, the Day 3 infusion **will not be** administered. If the Baseline platelet count has doubled but is ≤50x10^9/L, the Day 3 infusion **will be** administered.
9) Vital Signs: at the start of the infusion and every 60 minutes (±15 minutes) thereafter until the end of the infusion. In addition, vital sign measurements will be recorded just prior to every infusion rate change (-10 minutes), 15 minutes (+15 minutes) after each infusion rate change, and approximately 30 minutes after the end of the infusion
10) The start date and start time will be collected for any adverse events starting at Day 1 through Day 32/EOS visit
11) Prior medications will be collected for the 3 months. The start date and start time will be collected for any concomitant medications taken on Day 1 through Day 32/EOS visit
12) Day 32 visit will correspond to the Early Termination visit for patients who are withdrawn early from the study

PROTOCOL SIGNATURES

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and applicable regulatory requirements.

[redacted] Signature Date

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LIST OF ABBREVIATIONS

Abbreviation	Description
ADR	Adverse Drug Reaction
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
ASH	American Society of Hematology
AST	Aspartate Aminotransferase
CIDP	Chronic Inflammatory Demyelinating Poly(radiculo)neuropathy
CRO	Contract Research Organisation
DEHP	Diethylhexylphthalate
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOS	End of Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
ifas	4-letter meaningless suffix assigned by FDA at the end of newly approved biologics
IgA	immunoglobulin A
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITP	Immune Thrombocytopenia
ITT	Intention-to-Treat
IUD	Intrauterine device
IGIV	Intravenous Immunoglobulin
LDH	lactase dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MMN	Multifocal Motor Neuropathy
NAT	Nucleic Acid Test
PMR	Post-Marketing Requirement
PREA	Pediatric Research Equity Act
PP	Per-Protocol
PP1	Per-Protocol Set 1

Abbreviation	Description
PP2	Per-Protocol Set II
PVC	Polyvinyl Chloride
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SLE	systemic lupus erythematosus
SOP	Standard Operating Procedure
TEAE	Treatment-emergent Adverse Event
TNBP	tri-n-butyl phosphate
TPO-RA	Thrombopoietin Receptor Agonists
ULN	Upper Limit of Normal
USC	United States Code

1 INTRODUCTION

Since more than five decades immunoglobulins have been used to provide antibodies for the prevention of viral and bacterial diseases (replacement therapy) in immunocompromised patients. Within the last 25 years intravenous immunoglobulin (IGIV) has been proven to be useful in a wide variety of clinical conditions other than replacement therapy of immunocompromised patients, in which IGIV exhibits an immunomodulatory effect. These include Idiopathic Thrombocytopenic (ITP) in children and adults at high risk of bleeding or prior to surgery to correct the platelet count, Kawasaki disease, and Guillain-Barré syndrome (GBS). More recently, single IGIV brands have also been licensed for Multifocal Motor Neuropathy (MMN) and Chronic Inflammatory Demyelinating Poly(radiculo)neuropathy (CIDP). Experimental off-label use of IGIV mostly in other neurological and dermatological indications is widespread.

ITP is an immune-mediated (disorder characterized by increased platelet destruction. The reason for platelet destruction is the development of autoantibodies to platelet-membrane antigens. These antibodies are particularly produced in the spleen which is also the major site of platelet destruction [1]. In patients suffering from ITP, several studies have shown IGIV effective in increasing platelet counts to prevent or control bleeding [2-4] The mechanism of action in ITP is not fully elucidated but includes immunomodulatory effects, particularly the modulation of cytokines, soluble cytokine receptors and cytokine receptor antagonists with anti-inflammatory effects as well as complement modulation.

Broadly, 2 categories of agents are available for the treatment of ITP: 1) those that rapidly and transiently interfere with the process of platelet destruction for management of acute bleeding or bleeding risk (front-line therapies), and 2) those with potential to provide a more durable improvement in the platelet count (second-line therapies). Corticosteroids, IGIV, and anti-D immune globulin remain the mainstay of front-line treatment of acute bleeding symptoms in both adults and children [5]. Although corticosteroids remain the most commonly used ITP therapy, controversy still exists surrounding selection of agent, dosing, and duration of therapy. For treatment with prednisone, it is generally accepted that shorter courses are preferable to chronic therapy. The 2010 International Consensus Report on the investigation and management of primary ITP developed by an international working group address three classes of second-line therapies: splenectomy, rituximab, and the thrombopoietin receptor agonists (TPO-RA). Due to a relative lack of data, their use was recommended only in patients who were refractory to splenectomy and other therapies. Further study results in 2016 demonstrated that TPO-RA agents are being used in children with ITP of varying duration and severity. The response was similar to clinical trials, but the sustainability of response varied. Future studies need to focus on the ideal timing and rationale for these medications in pediatric patients [6].

PANZYGA is a human immunoglobulin solution with 10% protein content for intravenous administration. PANZYGA is made from a pool of at least 1000 donations of human fresh-frozen plasma per batch.

PANZYGA was granted a US approval by the US Food and Drug Administration (FDA) in August 2018. The license in 2 indications (primary humoral

immunodeficiency diseases and chronic immune thrombocytopenia) was granted based on 2 completed studies. The first study in Primary Immune Deficiency included 51 children and adults from ages 2 years to 65 years who were dosed at 200 mg/kg to 800 mg/kg body weight every 3 to 4 weeks for 360 days. The second study in Immune Thrombocytopenia included 40 adults with chronic ITP receiving 2 gm/kg body weight over 2 consecutive days. Of the 36 subjects in the full analysis set, 29 patients (81%: 95% CI: 64% to 92%) responded to PANZYGA with a rise in platelet count to at least $50x10^9$/L within 7 days after the first infusion.

Further information can be found in the Investigator's Brochure (IB).

1.1 Rationale for Conducting the Study

Under the Pediatric Research Equity Act (PREA) (21 United States Code [USC] 355c) all applications for new active ingredients, new indications, new dosage forms, new dosing regimens or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this required is waived, deferred or inapplicable.

This post-marketing requirement (PMR) study was requested by the US FDA after PANZYGA received marketing approval in the United States. The rationale for conducting this PMR study is to investigate the efficacy and safety of PANZYGA in children suffering from primary ITP.

The study will be conducted in compliance with the protocol, International Conference on Harmonisation-Good Clinical Practice (ICH-GCP), US FDA Code of Federal Regulations, and other local regulatory requirements.

1.2 Dose Rationale

According to recent guidelines, IGIV is recommended for patients with platelet counts $<30x10^9$/L in case of severe bleeding and/or mucous membrane bleeding. Standard doses should be studied (0.8 g/kg to1 g/kg on Day 1, which may be repeated once within 3 days, or 0.4 g/kg/day for 2 to 5 days). If other dosage regimens are to be applied for, they should be supported by clinical data. [7,8]. The dose option for this study is within the recommended guidelines.

1.3 Benefit-Risk Statement

The safety profile of IGIV is well characterized and, in general, the same type of adverse reactions may be expected for PANZYGA. No new or unknown safety problems are expected to emerge which are not already described in the Investigator's Brochure.

Data obtained from the clinical trials conducted with PANZYGA in the adult ITP population clearly met the recommended clinical response criteria for efficacy as set out in the relevant FDA and EU guidelines. These data are comparable with available literature data on other commercial IVIGs and formed the basis for marketing authorization in Europe and the US. The safety profile of PANZYGA is satisfactory and the number of infusional AEs are below the levels as

recommended by the FDA for products of this class. Efficacy and safety data with PANZYGA in 3 clinical studies in 51 patients (also including pediatric patients) with primary immunodeficiency (PID) and in 40 patients with immune thrombocytopenia (ITP) are available. Available data are sufficient to expect favorable benefit-risk profile of PANZYGA in the pediatric ITP population. Expected clinical benefit of using PANZYGA in this study is an increase in platelets level to control or prevent bleeding. The main known risks are listed below:

- Thrombosis may occur with immune globulin intravenous (IGIV) products, including PANZYGA. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.
- Renal dysfunction, acute renal failure, osmotic nephropathy, and death may occur with the administration of IGIV products in predisposed patients. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. PANZYGA does not contain sucrose.
- For patients at risk of thrombosis, renal dysfunction, or renal failure, administer PANZYGA at the minimum infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.
- Standard measures are taken to prevent infections resulting from the use of medicinal products prepared from human blood or plasma. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. During the manufacturing process of PANZYGA, significant viral reduction is obtained.

Inclusion and exclusion criteria, recommendations on the rate of infusion, dosage, and monitoring procedures provided in this protocol sufficiently mitigate above mentioned risks and must be adhered to.

No new or unknown safety problems are expected to emerge in pediatric ITP population, which are not listed above or described in the Investigator's Brochure.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objective is to evaluate the efficacy of PANZYGA in increasing the platelet count in pediatric patients with chronic ITP.

2.2 Secondary Objectives

The secondary objectives of this study are to:

- Assess safety of up to 2 g/kg PANZYGA (1 g/kg PANZYGA on Day 1 and an optional dose of 1 g/kg PANZYGA on Day 3) infused in the pediatric population within the scope of the clinical study
- Determine the time to reach a platelet count of $\geq 50 \times 10^9$/L
- Determine duration of time during which the platelet count is maintained at the level $\geq 50 \times 10^9$/L
- Determine the maximum platelet count during the study

3 INVESTIGATIONAL PLAN

3.1 Primary and Secondary Endpoints

3.1.1 Primary Endpoint

The primary efficacy parameter is defined as an increase in platelet count at least once to ≥50x10^9/L within 7 days after the first infusion, ie, by Day 8 (increase must occur at least once on any day up to and including Day 8). This definition of clinical response will serve as the basis for the primary endpoint, the response rate (ie, the proportion of patients with an elevation of platelet count at least once to ≥50x10^9/L within 7 days [ie, Day 8] after the first infusion).

3.1.2 Secondary Endpoints

Secondary endpoints are defined to further evaluate the efficacy and safety of the PANZYGA infused in the pediatric population.

The following parameters will be used to for efficacy assessments:

- Time to reach a platelet count of ≥50x10^9/L
- Duration of platelet response defined as the number of days the platelet count remains above ≥50x10^9/L
- Maximum platelet count during the study

The following parameters will be used for safety assessments:

- AEs
- Vital signs (blood pressure, heart rate, temperature, respiratory rate)
- Physical examination
- Laboratory parameters: hematology (including reticulocytes), hemolysis, platelet count, serum chemistry (including lactase dehydrogenase [LDH]).

3.2 Overall Study Design and Plan

This is a prospective, open-label, single-arm, multicenter, Phase 4 study evaluating the efficacy and safety of the investigational product, PANZYGA, in pediatric patients with chronic ITP.

The study will enroll at least 20 patients ≥1 year to <18 years old and will not be stratified by age group. A patient is considered enrolled into the study after successfully completing all baseline assessments and receiving at least a partial dose of PANZYGA.

Patients with a confirmed diagnosis of chronic ITP, without evidence of active major bleeding, may be enrolled in the study. Study procedures will only begin after written informed consent (from parent or guardian) and assent (from the patient, as age appropriate per Institutional Review Board [IRB] requirements) have been obtained. Patients who meet all of the inclusion and none of the exclusion criteria may receive the first infusion of PANZYGA within 2 days after Baseline investigations have been completed.

Each patient will be administered PANZYGA by intravenous infusion at a dose of 1 g/kg body weight PANZYGA on Day 1 and optionally another dose of 1 g/kg PANZYGA on Day 3; body-weight dependent doses will be based on each patient's weight collected at Baseline. Total PANZYGA doses will be 1 g/kg for patients receiving only 1 dose on Day 1 and 2g/kg for those receiving the optional Day 3 dose. Prior to the Day 3 infusion, Investigators will assess each patient's preinfusion platelet count, hematocrit, and hemoglobin. Patients whose platelet count shows evidence of response as indicated by the platelet count at least doubling from Baseline count AND is $>50x10^9$/L, the Day 3 infusion will not be administered. If the Baseline platelet count has doubled but is $\leq 50x10^9$/L, the Day 3 infusion will be administered. If any parameters indicate a clinically relevant change such that, in the Investigator's opinion, it is not safe to administer the second infusion, the patient should be withdrawn from study treatment; however, the patient will be followed for safety through Day 32.

Study interventions and procedures will be performed at predefined timepoints (see Section 6.1 and the Flow Chart of Assessments [Table 1]) including (but are not limited to): blood draws for safety evaluations, vital signs, body weight, physical examinations, AE monitoring, and changes in concomitant medication use. Patients will have clinic visits on Days 1, 3, 5, 8, 15, and 22. They will return to the clinic for a final safety follow-up evaluation at Day 32/End of Study (EOS) Visit.

PANZYGA infusions may be stopped or interrupted at any time if, in the Investigator's opinion, it is not safe to continue or is not in the patient's best interest. Patients who have received a partial dose of PANZYGA should be followed for safety evaluations through Day 32/EOS.

The study is planned to begin screening procedures Q2/Q3 2019 at up to 8 sites in the USA, with recruitment lasting approximately 30 months, and is anticipated to complete in Q1 2022. The study duration for a single patient will be approximately 39 days, including up to a 1-week Screening period.

3.3 Discussion of Study Design and Choice of Control Group(s)

3.3.1 Study Design

This study was designed to meet the US FDA's requirements under the PREA (21 USC 355c) for a post-approval study of PANZYGA in the pediatric population. US FDA is requiring a pediatric study for the treatment of ITP to evaluate PANZYGA for the treatment of ITP in patients ages ≥1 year to <18 years. All of the US FDA's recommendations have been incorporated into the protocol.

This study design is also in line with study protocols evaluating NGAM in adults, with the frequency of blood draws and number of visits reduced to accommodate a pediatric population. Because of the limited number of patients that will be enrolled in this study, along with the increased blood volume and additional site visits that would be required to meet the full recommendations in the European Medicines Agency (EMA) Guideline for confirmatory visits and blood draws, the secondary efficacy endpoints were selected to allow efficacy evaluations in this patient population.

3.3.2 Control Group(s)

A placebo control group will not be included in this post-approval study. An active control group is not considered relevant, as the objective of this study is to evaluate the efficacy and safety of PANZYGA in the pediatric population, not to compare the efficacy and safety of PANZYGA versus another IGIV treatment.

3.3.3 Study Parameters

The primary therapeutic target for ITP treatment is an increase in the platelet count. Therefore, the primary endpoint chosen for the study, namely the response rate (ie, the proportion of patients with an increase in platelets at least once to $\geq 50 \times 10^9$/L within 7 days after the first infusion), is appropriate to adequately describe the efficacy of treatment of PANZYGA in the pediatric population.

To assess the efficacy of PANZYGA in correcting the platelet count, this response rate has been chosen as the primary endpoint. There are several definitions of response published in guidelines and commonly used for the evaluation of ITP treatment; however, an increase in platelets to $\geq 50 \times 10^9$/L is the most established definition of response [7] and as such has been chosen for this post-marketing approval study.

The secondary efficacy endpoints chosen are in accordance with the primary endpoint, in order to further characterize the effect on the increase in platelet count.

The safety assessments, including AE, vital signs, laboratory results, and physical examination are appropriate and commonly used parameters to monitor the of IGIV treatment during a clinical study.

4 STUDY POPULATION

4.1 Population Base

At least 20 female or male patients ≥1 year to <18 years old with chronic ITP will be eligible for this study.

4.1.1 Inclusion Criteria

Patients who meet all of the following criteria are eligible for the study:

1. Females and males aged from ≥1 year to <18 years old
2. Confirmed diagnosis of Chronic Immune Thrombocytopenia (ITP) according to American Society of Hematology (ASH 2011) guidelines
3. Platelets count <$30x10^9$/L at the Baseline Visit
4. Voluntarily given written informed consent (provided by patient's parent or legal guardian) and assent (provided by patient)
5. Females of childbearing potential have been using at least 1 acceptable form of birth control for a minimum of 30 days (or a minimum of 3 months for hormonal contraceptives) prior to the Screening visit, and must agree to use at least 1 acceptable method of contraception for 30 days after the last dose of PANZYGA. Acceptable methods include: intrauterine device (IUD), hormonal contraception, male or female condom, spermicide gel, diaphragm, sponge, or cervical cap. Abstinence is not considered an acceptable method of birth control.
6. Parent or legal guardian must agree and be willing to assist the participant attend study visits, and to follow all protocol requirements and instructions of the study doctor

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria are not eligible for the study:

1. Thrombocytopenia secondary to other diseases (such as Acquired Immunodeficiency Syndrome [AIDS] or systemic lupus erythematosus [SLE]), drug-related thrombocytopenia, or congenital thrombocytopenia
2. Administration of intravenous immunoglobulin (IGIV) or anti-D immunoglobulin within 3 weeks before enrollment
3. Administration of thrombopoietin receptor agonists when the dose has NOT been stable within 3 weeks before enrollment and a dosage change is planned before Day 32
4. Administration of oral immunosuppressants when the dose has NOT been stable during the preceding 2 months (2 weeks for long-term corticosteroid therapy) and a dosage change is planned before

Day 32 (Note: topical agents and inhaled corticosteroid therapy use is permitted)

5. Administration of long-term anti-prolific agents or attenuated androgen therapy when the dose has NOT been stable during the preceding 2 months and a dosage change is planned before Day 32
6. Nonresponsive to previous treatment with IGIV or anti-D immunoglobulin
7. Evidence of an active major bleeding episode at Screening
8. Splenectomy in the previous 4 weeks or planned splenectomy throughout the study period
9. Evans syndrome (experiencing active disease with 2 out of 3 of the following: autoimmune thrombocytopenia, autoimmune hemolytic anemia, and/or autoimmune neutropenia)
10. Known or suspected human immunodeficiency virus (HIV), hepatitis B virus (HBV), and/or hepatitis C virus (HCV) infections
11. Emergency surgery in the previous 4 weeks
12. Severe liver and/or kidney disease (alanine aminotransferase [ALT] >3x upper limit of normal (ULN), aspartate aminotransferase [AST] >3x upper limit of normal (ULN), and/or creatinine >120 µmol/L)
13. History of severe hypersensitivity to blood or plasma derived products, or any component of the PANZYGA
14. Known immunoglobulin A (IgA) deficiency and antibodies against IgA
15. History of, or suspected, alcohol or drug abuse in the previous year
16. Females who are pregnant or nursing
17. Unable or unwilling to comply with the study protocol
18. Receipt of any other investigational medicinal product within 3 months before study entry
19. Risk factors* for thromboembolic events in whom the risks outweigh the potential benefit of PANZYGA treatment.
20. Any other condition(s), that in the Investigator's opinion, make it undesirable for the patient to participate in the study or may interfere with protocol compliance.

* Risk factors include, but are not limited to: obesity, advanced age, hypertension, diabetes, a history of atherosclerosis/vascular disease or thrombotic events, hyperlipidemia, multiple cardiovascular risk factors, acquired or inherited thrombophilic disorders, prolonged periods of immobilization, severe hypovolemia, central venous catheterization, active malignancy and/or known or suspected hyperviscosity.

4.2 Prior and Concomitant Therapy

Details on medications taken within the previous 3 months prior to the Baseline Visit and any concomitant medications taken during the study must be recorded in the electronic case report form (eCRF).

4.2.1 Allowed Pre-medications

Use of H-1 blockers or antipyretics are allowed for patients who have history of hypersensitivity to IGIV treatment; this may minimize the severity of possible infusion-related reactions in patients already predisposed to hypersensitivity reactions. All pre-medications administered prior to PANZYGA administration must be recorded in the eCRF.

4.2.2 Prohibited Medications

Use of the following medications are forbidden during the study as specified below (Table 2):

Table 2: Prohibited Medications

Medication	Time Window
IGIV	prohibited for 3 weeks prior to Baseline Visit through Day 32
anti-D immunoglobulin	prohibited for 3 weeks prior to Baseline Visit through Day 32
oral immunosuppressants	prohibited during Screening Period through Day 32 **unless** patients have been receiving a stable dose for 2 months (2 weeks for long-term corticosteroid therapies) prior to Screening Visit
thrombopoietin receptor agonists	prohibited during Screening Period through Day 32 **unless** patients have been receiving stable dose for 3 weeks prior to Screening Visit
long-term anti-prolific agents or attenuated androgen therapy	prohibited during Screening Period through Day 32 **unless** patients have been on a stable dose for 2 months prior to Screening Visit
any other blood or plasma-derived product*	prohibited during Screening Period through Day 32
receipt of any other investigational product	prohibited within 3 months prior to Baseline Visit through Day 32

* Patients who are non-responders or requiring emergent ITP treatment (other than PANZYGA specified in this protocol) will be followed for safety and complete all assessments through Day 32.

Trade names of drugs corresponding to the categories provided in Table 2 will be provided in a Study Manual.

4.3 Withdrawal and Replacement of Patients

4.3.1 Premature Patient Withdrawal

Patients have the right to withdraw from the study at any time for any reason, without the need to justify their decision; parents or legal guardians also have the right to withdraw a patient on the patient's behalf. The Investigator also has the right to withdraw patients in case of AEs, poor compliance, or other reasons.

Because an excessive rate of withdrawals can render the study noninterpretable, any unnecessary withdrawal of patients should be avoided.

For any withdrawals after study entry, the Investigator will obtain all the required details and document the reason(s) for discontinuation. If the reason for withdrawal of a patient is an AE, the main specific event or laboratory test will be recorded, and the Investigator will make thorough efforts to clearly document the outcome. Patients should return to the study site and have all safety evaluations, including safety laboratory tests, completed as specified at the Day 32 visit (See Section 6.1.6).

4.3.2 Patient Replacement Policy

Patients withdrawn from the study will not be replaced. Under no circumstances will patients who enroll in the study be permitted to re-enroll after study completion. Patients who fail during the Screening Period (also referred to as Screen Failures) may be re-screened upon written approval from the Sponsor.

4.4 Assignment of Patients to Treatment Groups

This is an open-label non-randomized study. All patients will receive PANZYGA.

4.5 Relevant Protocol Deviations

In case of any major protocol deviation, the Investigator and Octapharma will decide on the further participation of the patient in this study after having discussed all relevant aspects.

A list of all included patients with all deviations from the intended study procedures and other criteria that may affect the patient's data validity for statistical analysis will be prepared upon clinical completion of the study. This will also be discussed by a panel consisting of the clinical study manager, a medical expert of the Sponsor, the data manager and the study statistician. This panel will decide upon the membership of the patient in the Full Analysis Set (FAS), Per Protocol (PP) Set 1 (PP2), PP Set 2 (PP2), and Safety Analysis Set for statistical analysis.

4.6 Subsequent Therapy

If a patient withdraws from the study or is withdrawn by the Investigator by their parent/legal guardian, he/she will receive treatment by the Investigator or personal physician according to institutional standard of care.

5 INVESTIGATIONAL MEDICINAL PRODUCT

5.1 Characterization of Investigational Product

Name of Medicinal Product: PANZYGA

Active ingredient of PANZYGA: Immune globulin human-ifas

Table 3: Qualitative and Quantitative Composition of PANZYGA

Name of Ingredient	Amount
Total protein	9.0 – 11.0 g/100 mL
Protein composition	≥95% Ig (≥96% Ig)*
IgG content	86 – 110 mg/mL
Glycine	15.0 – 19.5 mg/mL (17.3 mg/mL)*
Water for Injection	*ad* 1mL

*Depending on regulatory requirements

PANZYGA is a solvent/detergent (S/D)-treated, sterile preparation of highly purified immunoglobulin G (IgG) derived from large pools of human plasma. PANZYGA is a solution for infusion to be administered intravenously.

This preparation contains approximately 100 mg of protein per mL (10%), of which not less than 96% is normal human immunoglobulin G. PANZYGA contains not more than 3% aggregates, not less than 90% monomers and dimers, and not more than 3% fragments. On average, the product contains 100 µg/mL of IgA, and lower amounts of IgM.

PANZYGA contains only trace amounts of sodium, and the pH is between 4.5 and 5.0. The osmolality is in the range of 240 to 310 mosmol/kg.

The manufacturing process for PANZYGA isolates IgG without additional chemical or enzymatic modification, and the Fc portion is maintained intact. PANZYGA contains the IgG antibody activities present in the donor population. IgG subclasses are fully represented with the following approximate percentages of total IgG: IgG1 is 65%, IgG2 is 28%, IgG3 is 3% and IgG4 is 4%.

PANZYGA contains a broad spectrum of IgG antibodies against bacterial and viral agents that are capable of opsonization and neutralization of microbes and toxins. PANZYGA contains glycine (15.0 to 19.5 mg/mL), but no preservatives or sucrose.

All units of human plasma used in the manufacture of PANZYGA are provided by FDA-approved blood and plasma establishments, and are tested by FDA-licensed serological tests for HBsAg, antibodies to HCV and HIV and Nucleic Acid Test (NAT) for HCV and HIV-1 and found to be non-reactive (negative).

5.2 Packaging and Labelling

PANZYGA for investigational use only will be labeled according to US FDA regulations. Details of the labeling will be included in the Pharmacy Manual.

The batch number(s) used will be recorded in the study documentation and EDC.

5.3 Conditions for Storage and Use

PANZYGA must be stored and transported light-protected at +2°C (36°F) to +8°C (46°F) and must be brought to room temperature before use.

Storage temperature must be maintained at +2°C (36°F) to +8°C (46°F) and will be monitored for the duration of the study by reviewing the temperature logs.

PANZYGA must not be frozen prior to use.

PANZYGA must not be used after its expiry date.

PANZYGA must not be mixed with other medicinal products.

Each PANZYGA bottle is for single use only.

Authorized personnel at the individual study sites will ensure that PANZYGA is stored in appropriate conditions in a secure refrigerator with restricted access and in compliance with national regulations.

5.4 Dose and Dosing Schedule

PANZYGA will be administered by intravenous infusion. Patients should be adequately hydrated prior to infusion.

Patients will receive a dose of 1 g/kg body weight PANZYGA given on Day 1 and optionally another dose of 1 g/kg PANZYGA given on Day 3; body-weight dependent doses will be based on each patient's weight collected at Baseline. Total PANZYGA doses will be 1 g/kg for patients receiving only 1 dose on Day 1 and 2 g/kg for those receiving the optional Day 3 dose. If the Day 3 platelet count shows evidence of response as indicated by the platelet count at least doubling from Baseline count AND is $>50x10^9$/L, the Day 3 infusion will not be administered. If the Baseline platelet count has doubled but is $\leq 50x10^9$/L, the Day 3 infusion will be administered.

PANZYGA will be delivered by intravenous infusion according to the recommended flow rates:

- Initial infusion rate of 0.01 mL/kg/min (60 mg/kg/hr) for the first 30 minutes
- If tolerated, increase to 0.02 mL/kg/min (120 mg/kg/hr) for the second 30 minutes
- If tolerated, increase to 0.04 mL/kg/min (240 mg/kg/hr) for the third 30 minutes
- If tolerated, increase to 0.08 mL/kg/min (480 mg/kg/hr) for the remainder of the infusion.

Infusion rates should not exceed 0.08 mL/kg/min and should not exceed 8.0 mL/min.

If a Grade 2 (moderate) or higher infusion-related adverse event (AE) occurs during infusion, the Panzyga infusion will be stopped. After infusion-related symptoms subside, the infusion may be resumed at a lower rate. The infusion rate may be gradually increased as tolerated by the patient.

If a Grade 1 (mild) infusion-related AE occurs during infusion, the infusion rate should be reduced to half the rate at which the event occurred, or the infusion

should be interrupted until symptoms subside. The infusion may then be resumed at an infusion rate tolerated by the patient. The infusion rate may be gradually increased as tolerated by the patient.

5.5 Preparation and Method of Administration

All patients will be infused at the study site under the surveillance of authorized study site staff.

After calculating the volume required for the dose using the patient's Baseline body weight (see Section 5.4), the appropriate number of vials will be removed from the refrigerator. Vials of different sizes may be combined to reach the required amount of IgG. The exact dose will be administered, and the empty and partially used vials will be retained by the site for drug accountability and dose verification.

PANZYGA vials must be allowed to warm to room or body temperature before infusion. After PANZYGA vials have been brought to room or body temperature, they should be inspected visually for particulate matter and discoloration prior to administration. The solution should be clear or slightly opalescent. DO NOT USE IF TURBID, DISCOLORATION IS OBSERVED, AND/OR FLOATING PARTICLES ARE PRESENT. Solutions that are cloudy or vials that have a deposit must not be used and must be discarded according to local policy.

Aseptic technique must be used throughout the entire procedure.

The contents of bottles must be pooled under aseptic conditions into sterile infusion bags and administered immediately after pooling. Only polyvinyl chloride (PVC)-free, diethylhexylphthalate (DEHP)-free and latex–free, infusion bags can be used. Once pooled, a label will be applied on the infusion bag. Detailed instructions of this process and an example label will be included in the Pharmacy Manual.

PANZYGA will be infused into a vein using standard infusion supplies provided by the individual site. Standard procedures should be followed to prime the infusion line with a priming solution (eg, normal saline). At the end of each infusion, the infusion line will be flushed with normal saline solution.

Additional information regarding PANZYGA preparation and infusion procedures will be provided in a pharmacy manual.

Please refer to special warnings and precautions for use provided in the PANZYGA Investigator Brochure.

5.6 Blinding, Emergency Envelopes, and Breaking the Study Blind

Not applicable.

5.7 Treatment Compliance

5.7.1 Drug Dispensing and Accountability

The Sponsor or designee will provide and deliver all PANZYGA to participating Investigators. A Drug Inventory and Dispensing Log will be kept current by the

Investigator, detailing the dates and quantities of PANZYGA received, dispensed to each patient, and the quantity remaining at the study site.

The Drug Inventory and Dispensing Log will be available to the monitor to verify drug accountability during the study. The study monitor will inventory all empty and partially used vials of PANZYGA and will cross-check this inventory versus the patient source documentation (records), eCRF, and the Drug Inventory and Dispensing Log.

Unused and partially used vials may be destroyed at the study site or returned to the Sponsor for destruction according to institutional practice. Vials may be destroyed only after drug accountability has been verified and fully reconciled by the monitor and after the Sponsor has granted written approval of destruction.

Additional information regarding PANZYGA drug accountability procedures will be provided in a pharmacy manual.

5.7.2 Assessment of Treatment Compliance

All patients will be infused at the study site under the surveillance of authorized study personnel. Infusion details will be documented together with the batch number(s) in the source data and eCRF.

6 STUDY CONDUCT

Procedures performed at each study visit are presented in the Flow Chart of Assessments (see Table 1). Time windows and tolerances are provided in Table 4.

6.1 Observations by Visit

6.1.1 Baseline Visit/Screening Period

The following assessments will be performed during the Screening Period. The Screening Period can last up to 1 week (to accommodate patient schedules and the informed consent/assent process); however, all Baseline evaluations should be completed within 2 days before the first administration of PANZYGA.

- Obtaining voluntarily given, written (signed and dated) informed consent and assent (as age appropriate)
- Inclusion and exclusion criteria
- Demographic and baseline characteristics
- Medical and surgical history (previous 1 year)
- Splenectomy history
- Physical examination
- Vital signs
- Body weight
- Blood samples for serum chemistry, hematology, and hemolysis analytes
- Blood or urine pregnancy test (females of childbearing potential, only)
- Blood samples for viral markers
- Documentation of prior medications (previous 3 months), including administration of pre-medication(s) as appropriate (see Section 4.2.1)

6.1.2 Day 1

Day 1 should take place within 2 days after Baseline evaluations have been completed. If the Baseline and Day 1 Visits occur on the same day, the Baseline investigations do not need to be repeated. If the Baseline evaluations are completed more than 2 days before Day 1, the platelet count must be repeated and evaluated by the Investigator prior to initiating the first infusion.

Before the administration/infusion of PANZYGA, patient eligibility will be re-evaluated. The following assessments/activities will be performed before PANZYGA infusion:

- Confirmation of inclusion and exclusion criteria
- Physical examination
- Vital signs
- Blood samples for serum chemistry, hematology, and hemolysis analytes
- Administration of pre-medication(s) as appropriate (see Section 4.2.1)

The following activities will be performed during or after PANZYGA infusion:

- PANZYGA infusion
- Vital signs (at the start of the infusion and every 60 minutes (±15 minutes) thereafter until the end of the infusion. In addition, vital sign measurements will be recorded just prior to every infusion rate change (-10 minutes), 15 minutes (+15 minutes) after each infusion rate change, and approximately 30 minutes after the end of the infusion)
- Monitoring for AEs
- Documentation of concomitant medication use

6.1.3 Day 3

The following assessments/activities will be performed before PANZYGA infusion:

- Physical examination
- Vital signs
- Blood samples for serum chemistry, hematology, and hemolysis analytes
- **NOTE:** platelet, hemoglobin and hematocrit results must be available and reviewed by the Investigator prior to initiating the Day 3 infusion
- Administration of pre-medication(s) as appropriate (see Section 4.2.1)

The Investigator will assess each patient's Day 3 preinfusion platelet count, hematocrit, and hemoglobin. If the Day 3 platelet count shows evidence of clinical response, as indicated by the platelet count at least doubling from Baseline count AND is >50x10^9/L, the Day 3 infusion will not be administered. If the Baseline platelet count has doubled but is ≤50x10^9/L, the Day 3 infusion will be administered. In the event that the Day 3 infusion is not administered, all other Day 3 assessments will still be completed. If any of these hematology parameters indicate a clinically relevant change such that, in the Investigator's opinion, it is not safe to administer the second infusion the patient should be withdrawn from study treatment but will be followed for safety through Day 32.

The following activities will be performed during or after PANZYGA infusion:

- PANZYGA infusion
- Vital signs (at the start of the infusion and every 60 minutes (±15 minutes) thereafter until the end of the infusion. In addition, vital sign measurements will be recorded just prior to every infusion rate change (-10 minutes), 15 minutes (+15 minutes) after each infusion rate change, and approximately 30 minutes after the end of the infusion)
- Monitoring for AEs
- Documentation of concomitant medication use

6.1.4 Day 5 and Day 8 (± 1 day)

The following assessments will be performed at Day 5 and Day 8:

- Physical examination
- Blood samples for serum chemistry, hematology, and hemolysis analytes
- Monitoring for AEs

- Documentation of concomitant medication use

6.1.5 Day 15 and Day 22 (± 3 days)

The following assessments will be performed at Day 15 and Day 22:

- Physical examination
- Blood samples for hematology and hemolysis analytes
- Monitoring for AEs
- Documentation of concomitant medication use

6.1.6 Day 32 (End of Study Visit) (± 5 days)

Patients will return to the study site on Day 32 for final safety assessments/EOS Visit. Patients who were withdrawn early from the study should return to the study site for a final safety assessment. The following assessments will be performed:

- Physical examination
- Vital signs
- Blood samples for serum chemistry, hematology, and hemolysis analytes
- Documentation of concomitant medication use

After Day 32, the clinical study is considered completed for the patient. No further study-related assessments will be performed, unless safety concerns (eg, ongoing AEs) require follow-up.

6.1.7 Visit Windows Used in this Study, including Tolerances

In this study, the following time windows and tolerances apply (Table 4):

Table 4: Visit Windows Used in this Study

Time point	Tolerance
Screening Period	7 days prior to Day 1
Final Baseline Evaluations	-2 days before Day 1
Day 1	none
Day 3	none
Day 5	±1 day
Day 8	±1 days
Day 15 and Day 22	±3 days
Day 32	± 5 days

6.2 Duration of Study

6.2.1 Planned Duration for an Individual Patient

The duration of the entire study for each patient will be approximately 39 days, including a 7-day Screening Period.

6.2.2 Planned Duration for the Study as a Whole

The study will be considered completed when all patients have completed the Day 32 EOS Visit.

The estimated start of the study (enrollment of first patient) is Q2/Q3 2019, and the estimated end of the study (last visit of last patient) is Q1 2022.

6.2.3 Premature Termination of the Study

Both the responsible Investigators and the Sponsor reserve the right to terminate the study at any time. Should this be necessary, study close-out procedures will be arranged on an individual site basis after review and consultation by both parties. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the patients' interests.

Furthermore, the Investigator should promptly inform the IRB and provide a detailed written explanation. Pertinent regulatory authorities and IRBs will be informed in accordance with applicable regulatory requirements.

6.2.3.1 Early Termination of the Entire Clinical Study

At any time, the study as a whole will be terminated prematurely if:

- New toxicological or pharmacological findings or safety reports invalidate the earlier positive benefit-risk-assessment for the pediatric population
- Any other reason rendering the continuation of the study impossible for the Sponsor

6.2.3.2 Early Termination at an Individual Study Site

At any time, the study can be terminated at an individual study site if:

- The site cannot comply with the requirements of the protocol
- The site cannot comply with GCP or other regulatory standards
- The site does not meet the required recruitment rate

Should the study be prematurely terminated, all study materials, including PANZYGA, must be returned to the Sponsor.

7 ASSESSMENTS AND METHODS

7.1 Demographic and Baseline Information

Demographic and baseline information will be recorded during the Screening Period:

7.1.1 Demographic and Baseline characteristics

The demographic and baseline characteristics are sex, age, race and ethnic origin, height, and weight.

7.1.2 Medical and Surgical history

The medical history will be collected for the previous year and will be obtained by interviewing the patient. Records of past diseases and treatments (eg, hospital discharge letters) will be obtained for the study files, if available. The onset date of ITP will be recorded.

Surgical history will include the date of splenectomy (if applicable) and any other surgical procedures in the previous year.

7.1.3 Viral Marker Tests

At the Screening Visit, blood samples for viral markers (HIV, HCV, HBV NAT) will be collected and tested at the local laboratory according to the site's standard procedures, to rule out secondary infections that may cause ITP. Infusions may begin before the results are back if the Investigator is not aware of, and the patient isn't exhibiting clinical signs of, any viral infection.

7.1.4 Prior and Concomitant Medication Use

Prior medication use will be obtained by interview and review of patient charts (if available). Patients will queried specifically for use of H-1 blockers or antipyretics as pre-medications prior to previous IGIV treatments.

Concomitant medication use, defined as medications with a start date and time after the start of the Day 1 infusion, will be collected throughout the study. The start date and time of medication use will be collected on Day 1 and throughout the study.

7.2 Efficacy Assessments

All efficacy assessments will be based on platelet counts performed throughout the study.

Platelet counts will be performed at Baseline (within 2 days prior to the first PANZYGA infusion), at Day 1 and Day 3 prior to planned PANZYGA infusions, and then at all remaining study visits (Days 5, 8, 15, 22, and 32).

7.3 Safety Assessments

7.3.1 Assessments for Safety Evaluations

The following assessments will be performed to evaluate the safety of PANZYGA in the pediatric population:

- AEs and Serious Adverse Events (SAEs)
- Clinical laboratory tests
- Vital signs
- Physical examinations
- Pregnancies

7.3.2 Adverse Events

7.3.2.1 Definitions

- **Adverse event (AE):** An AE is any untoward medical occurrence in a study /patient receiving an investigational medicinal product (IMP) and which 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 an IMP, whether or not related to the IMP.
- **Adverse drug reaction (ADR):** An ADR is any noxious and unintended response to an IMP related to any dose. The phrase 'response to an IMP' means that a causal relationship between the IMP and an AE carries at least a reasonable possibility (ie, the relationship cannot be ruled out).
- **Other significant AEs:** Any marked laboratory abnormalities or any AEs that lead to an intervention, including withdrawal of drug treatment, dose reduction, or significant additional concomitant therapy.
- **Treatment-emergent AE (TEAE):** Any AE that newly appeared, increased in frequency, or worsened in severity following the time of the first IMP infusion until the end of the safety follow-up period.
- **Infusional AE:** Any AE that occurs from the time of infusion and within the 72 hour period after end of infusion.
- **Withdrawal due to AE/ADR:** AE/ADR leading to discontinuation of treatment with IMP. Any such events will be followed up by the Investigator until the event is resolved or until the medical condition of the patient is stable. All follow-up information collected will be made available to the Sponsor.

7.3.2.2 Collection of AEs

The condition of the patient will be monitored throughout the study. At each visit, whether scheduled or unscheduled, AEs will be elicited using a standard nonleading question such as "How have you been since the last visit/during the previous study period?" In addition, the Investigator will check the patient diaries (if applicable) for any documented event.

Any AE or ADR which occurs during the study will be noted in detail on the appropriate pages of the eCRF. If the patient reports several signs or symptoms representing a single syndrome or diagnosis, the diagnosis should be recorded in the eCRF. The Investigator will grade the severity of all AEs or ADRs (mild, moderate, or severe), the seriousness (non-serious or serious), and the causality as defined in Section 7.3.2.3, Section 7.3.3, and Section 7.3.2.4, respectively. The Sponsor is responsible for assessing the expectedness of each ADR (expected or unexpected) as defined in Section 7.3.2.5.

In the event of clinically significant abnormal laboratory findings, the tests will be confirmed and the patient followed up until the laboratory values have returned to normal and/or an adequate explanation for the abnormality has become available.

Diseases, signs and symptoms, and/or laboratory abnormalities already present before the first administration of IMP will not be considered AEs unless an exacerbation in intensity or frequency (worsening) occurs.

The Investigator will provide detailed information about any abnormalities and about the nature of and reasons for any action taken as well as any other observations or comments that may be useful for the interpretation and understanding of an AE or ADR.

7.3.2.3 Severity of AEs

The intensity/severity of AEs will be graded as follows:

- **Mild:** an AE, usually transient, which causes discomfort but does not interfere with the patient's routine activities
- **Moderate:** an AE which is sufficiently discomforting to interfere with the patient's routine activities
- **Severe:** an AE which is incapacitating and prevents the pursuit of the patient's routine activities

The grading of an AE is up to the medical judgement of the Investigator and will be decided on a case-by-case basis.

7.3.2.4 Causality of AEs

The relationship of AEs to the administered IMP will be assessed by the Investigator:

- **Probable:** reports including good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable. A reaction that follows a reasonable temporal sequence from administration of the IMP; or that follows a known or expected response pattern to the suspected medicine; or that is confirmed by stopping or reducing the dosage of the medicine and that could not reasonably be explained by known characteristics of the patient's clinical state.
- **Possible:** reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible and not unlikely,

although the connection is uncertain or doubtful, for example because of missing data or insufficient evidence. A reaction that follows a reasonable temporal sequence from administration of the IMP; that follows a known or expected response pattern to the suspected medicine; but that could readily have been produced by a number of other factors.

- **Unlikely:** reports not following a reasonable temporal sequence from IMP administration. An event which may have been produced by the patient's clinical state or by environmental factors or other therapies administered.
- **Not related (unrelated):** events for which sufficient information exists to conclude that the etiology is unrelated to the IMP.
- **Unclassified:** reports which for one reason or another are not assessable.

7.3.2.5 Classification of ADRs by Expectedness

ADRs will be classified by the Sponsor as either expected or unexpected:

- **Expected:** an ADR that is listed in the current edition of the Investigator's Brochure or other reference safety information.
- **Unexpected:** an ADR that is not listed in the current edition of the Investigator's Brochure or other reference safety information, or that differs because of greater severity or greater specificity.

7.3.2.6 Outcome of AEs

The outcome of all reported AEs will be documented as follows:

1. Recovered, resolved
2. Recovering, resolving
3. Not recovered, not resolved
4. Recovered, resolved with sequelae
5. Fatal
6. Unknown

NOTE: A patient's **death** per se is not an event, but an outcome. The event which resulted in the patient's death must be fully documented and reported, even in case the death occurs within 4 weeks after IMP treatment end and regardless of whether or not it is considered treatment-related.

7.3.2.7 Action(s) taken

AEs requiring action or therapy must be treated with recognized standards of medical care to protect the health and well-being of the patient. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment in an emergency situation.

The action taken by the Investigator must be documented:

a) General actions taken in the event of an AE

- None
- Medication (other than IMP) or other (eg, physical) therapy started

- Test performed
- Other (to be specified)

b) IMP-related actions taken in the event of an AE

- None
- Product withdrawn
- Dose reduced
- Dose increased

The Investigator will follow up on each AE until it has resolved or until the medical condition of the patient has stabilized. Any relevant follow-up information will be reported to the Sponsor.

7.3.2.8 Managing Hypersensitivity Reactions

Severe hypersensitivity reactions may occur during PANZYGA infusions [9]. In the case of any subject exhibiting clinical signs of severe acute hypersensitivity reactions to PANZYGA, the PANZYGA infusion must be immediately stopped. Each site must have Epinephrine readily available and follow their institution's standard procedure for Epinephrine administration and monitoring. After the hypersensitivity reaction subsides, the infusion may be resumed at a lower rate if allowed per the site Epinephrine administration and monitoring procedures, and per Investigator discretion.

7.3.3 Serious Adverse Events

An **SAE** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (see below)
- requires hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is another important medical event

NOTE: The term 'life-threatening' refers to an event in which the patient was, in the view of the reporting Investigator, at immediate risk of death at the time of the event; it does not refer to an event which may hypothetically have caused death had it been more severe.

In deciding whether an AE/ADR is serious, medical judgment should be exercised. Thus, important AEs/ADRs that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definitions above should also be considered serious.

In addition, although not classified under the seriousness criteria, all suspected transmissions of an infectious agent should be reported as SAE. A suspected virus transmission means that virus antigen has been detected in the patient. A

passive transmission of antibodies alone does not constitute a suspected virus transmission.

7.3.4 SAE Reporting Timelines

All SAEs, whether or not they are suspected to be related to study treatment, are to be reported immediately by telephone, fax, or email to the Clinical Project Manager or designee with the contact detailed provided to each site in the Investigator Site Binder. The contact details will also be communicated at the study initiation visit.

In addition, within 24 hours after recognition of the event, an Octapharma Serious Adverse Event Report must be completed and submitted to:

Octapharma's Corporate Drug Safety Unit
OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235, 1100 Vienna, Austria
Fax: [redacted]
E-mail: [redacted]

24 hours emergency telephone numbers:

[redacted] **or**
[redacted]

The Investigator must update the Octapharma Serious Adverse Event Report as soon as any additional information becomes available. The Investigator must also report SAEs to the IRB/IEC as required by local and national laws. The Investigator must maintain documentation of all communications to and from the IRB/IEC.

In accordance with 21 CFR 312.32 and local authorities, the

Sponsor will submit to the FDA unexpected adverse reactions within 15 calendar days. Unexpected fatal or life-threatening adverse reactions will be submitted within 7 calendar days.

Waivers the from SAE Reporting Requirement

Waivers from the SAE reporting requirement include surgeries that are elective or were planned before study entry or prolongations of existing hospitalizations for economic or social, but not medical, reasons. Such surgeries or prolongations of hospitalizations should not be considered SAEs.

7.3.5 Laboratory Tests

Clinical laboratory parameters will be investigated during the study at the time points specified in the Flow Chart of Assessments (Table 1).

All of the study-specific laboratory tests will be performed at the local laboratories for each study site. The laboratory test and sample collection timing are specified below (Table 5).

Table 5: Laboratory Tests and Time Points

Test	Timing
Hematology (complete blood count, WBC differential, hematocrit, hemoglobin, platelet counts, reticulocytes)	During Screening (Baseline evaluation), at Days 1, 3, 5, 8, 15, 22, and at Day 32/EOS
Hemolysis (total, direct, and indirect bilirubin)	During Screening (Baseline evaluation), at Days 1, 3, 5, 8, 22, and at Day 32/EOS
Serum chemistry (ALT, AST, creatinine, Na, Ca, K, BUN, LDH)	During Screening (Baseline evaluation), Days 1, 3, 22, and at Day 32/EOS
Blood or Urine pregnancy test (females of childbearing potential)	During Screening (Baseline evaluation) and Day 32/EOS
Virology: HIV, HCV, HBV NAT	During Screening (Baseline evaluation, see Section 7.1.3)

Investigational sites will follow all site and local laboratory standard operating procedures for sample collection and handling and will provide the sponsor with normal reference ranges and laboratory certification certificates.

The methods of determination and normal ranges for each parameter from each local laboratory will be provided in the clinical study report.

7.3.6 Vital Signs

Vital signs will be collected at the time points specified in the Flow Chart of Assessments (Table 1) are blood pressure, body temperature, pulse rate, and respiratory rate.

On Day 1 and Day 3, vital sign measurements will be recorded before the start of the infusion and every 60 minutes (±15 minutes) thereafter until the end of the infusion. In addition, vital sign measurements will be recorded just prior to every infusion rate change (-10 minutes), 15 minutes (+15 minutes) after every infusion rate change, and approximately 30 minutes after the end of the infusion.

7.3.7 Physical Examination including Height and Body Weight.

Physical examinations will be performed at the visits specified in the Flow Chart of Assessments (Table 1).

Both height and weight will be measured at Baseline.

7.3.8 Other Relevant Safety Information

a) Post-study related safety reports

Any SAE which occurs during the study (ie, within 4 weeks after the last PANZYGA administration, which for most patients will be up to and including Day 32) will be reported by the Investigator to the Sponsor. Proactive monitoring for post-study SAEs is not required.

In case a post-study SAE is identified, the Investigator should complete an SAE form and also state the relation to the clinical study in the report.

Deaths occurring during the study (ie, within 4 weeks after the last PANZYGA administration, which for most patients will be up to and including Day 32) should

also be reported, regardless of whether or not they are considered treatment-related.

b) Pregnancies

Every effort will be made to avoid a pregnancy during the use of an IMP. Pregnancies occurring during the study (fetal exposure to PANZYGA) need to be reported.

In case of pregnancy during the study, the Investigator should complete the Pregnancy Notification Form and send or fax it to the Clinical Project Manager or designee (Section 7.3.4).

Follow-up information on the outcome of both mother and fetus will be requested by a Sponsor representative.

c) Overdose, interaction, medication error and lack of efficacy

The following safety relevant information should be reported as an AE or, if the reaction fulfills one of the criteria for seriousness, as SAE.

d) Drug overdose

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol and higher than the known therapeutic dose that is of clinical relevance. The reaction must be clearly identified as an overdose.

e) Drug interaction

A drug interaction is a situation in which a substance or medicinal product affects the activity of an IMP, ie, increases or decreases its effects, or produces an effect that none of the products would exhibit on its own. The reaction must be clearly identified as a drug interaction.

f) Medication error

A medication error involves the inadvertent administration or unintended use of a medicinal product which may be caused by the naming, presentation of pharmaceutical form/packaging, or instructions for use/labelling. The reaction must be clearly identified as a medication error.

g) Lack of efficacy

Lack of efficacy is suspected when the therapeutic result is not as expected. One example of lack of efficacy could be platelets not increasing following the correct administration of IVIG.

7.4 Other Assessments

7.5 Appropriateness of Measurements

For efficacy evaluations, platelet counts provide a direct measure of the response to IGIV treatment in ITP patients and has been widely used for this purpose in

many clinical trials of similar nature. The test is performed routinely at each hospital and is considered to be a reliable and robust parameter.

The definition of response used for the primary endpoint is the most established procedure to obtain a dichotomy of success/failure that can be used to calculate the response rate. It is also acceptable to US FDA and was used as the primary efficacy endpoint in their approval of PANZYGA in the treatment of chronic ITP in adults and is thus expected to best facilitate their review of the efficacy of PANZYGA in this pediatric population.

Monitoring AEs, vital signs, laboratory safety tests, and physical examinations are standard procedures used to evaluate the safety of investigational products in clinical studies.

8 DATA HANDLING AND RECORD KEEPING

8.1 Documentation of Data

8.1.1 Source Data and Records

Source data are defined as all information related to clinical findings, observations, or other activities in the study; written down in original records or certified copies of original records; or electronic medical records; allowing reconstruction and evaluation of the clinical study.

The Investigator will maintain adequate source records (eg, case histories or patient files for each patient enrolled). Source records should be preserved for the maximum period of time required by local regulations.

For each patient enrolled, the Investigator will indicate in the source record(s) that the patient is participating in this study.

All data entered in the eCRF must be supported by source data in the patient records.

The Investigator will permit study-related monitoring, audit(s), IEC/IRB review(s), and regulatory inspection(s), by providing direct access to the source data/records.

The Investigator may authorize site staff (eg, sub-Investigators, research nurses) to enter study data into the eCRF. This must be documented in the Delegation of Authority Log signed by the Investigator.

8.1.2 Electronic Case Report Forms

For each patient enrolled, an eCRF will be completed within the Electronic Data Capture (EDC) system and approved by the Investigator or an authorized sub-Investigator.

Study site staff (eg, research nurse, study coordinator, Investigator) will be responsible for entering patient data into the validated EDC system. All study site personnel will be trained on the EDC system and study-specific eCRFs prior to receiving access to the live database for data entry.

The study site will be provided with the approved eCRF Completion Guidelines to assist in data entry and data issues/questions. The study site will be notified once the eCRF is active to begin data entry. Additional site training may be provided as refreshers throughout the study, if needed. All persons allowed to enter or change eCRF data must be listed in the Delegation of Authority Log.

8.1.3 Changes to Electronic Case Report Form Data

Monitors will perform source data verification (SDV) as defined for the study.

If any errors or discrepancies in the eCRFs are found during data entry or review, discrepancies will be generated programmatically within the EDC system, and 'manual' queries will be generated by either a monitor or Data Management.

Discrepancies and queries can only be corrected by the Investigator(s) or other authorized site personnel. An audit trail documents all changes to the data over the entire study period. If the reason for a change is not obvious, a comment must be supplied in the query's response, stating the reason for the change, prior to closing. The study monitor should provide guidance to Investigator(s) and the Investigator(s)' designated representatives on making such corrections.

Once queries have been resolved by the site staff, the resolutions are assessed by Data Management. If the query response provided confirms the data as correct, the discrepancy will be closed. If the response does not adequately address the question raised, a new query will be issued for further clarification.

Manual checks will be performed, and electronic data check programs run, throughout the study until the data is clean and the database is ready for lock. All discrepancies will be resolved prior to database lock. There will be a final run of the programmed checks to ensure all discrepancies are closed out, SDV will be confirmed as complete by the monitor, and all eCRFs will be approved by the Investigator prior to database lock.

8.2 Information to Investigators

An IB will be handed out to the Investigator before the start of the study. The IB contains all information in the Sponsor's possession necessary for the Investigator to be fully and accurately informed about the safety of the IMP under evaluation and the respective benefit-risk ratio.

The IB will be updated by the Sponsor at regular intervals and whenever relevant new information concerning PANZYGA becomes available.

All participating investigators will be informed about relevant study procedures, about the methods for rating relevant study outcomes, and how to enter data into the eCRF in order to reduce discrepancies. At the study initiation visit, the eCRF will be explained to all study site staff entitled to document data in the eCRF.

The Investigator will be kept informed of important data that relate to the safe use of PANZYGA as the study proceeds.

8.3 Responsibilities

The Principal Investigator is accountable for the conduct of the clinical study. Responsibilities may be delegated to appropriately qualified persons.

A Delegation of Authority Log will be filled in and signed by the Principal Investigator. In accordance with this authority log, study site staff (eg, sub-Investigators, research nurses) are authorized to perform tasks relating to the study.

8.4 Investigator's Site File

At each study site, the Investigator is responsible for maintaining all records to enable the conduct of the study to be fully documented. Essential documents as required by GCP guidelines and regulations (eg, copies of the protocol, study approval letters, all original informed consent and assent forms, site electronic

versions of all eCRFs, drug dispensing and accountability logs, correspondence pertaining to the study) should be filed accurately and kept by the Investigator for the maximum period of time required by local regulations.

The Investigator is responsible for maintaining a confidential patient identification code list, which provides the unique link between named source records and eCRF data for the Sponsor. The Investigator must arrange for the retention of this confidential list for the maximum period of time required by local regulations.

No study document should be destroyed without prior written agreement between the Investigator and the Sponsor. Should the Investigator elect to assign the study documents to another party, or move them to another location, the Sponsor must be notified in writing.

8.5 Provision of Additional Information

On request, the Investigator will supply the Sponsor with additional data relating to the study, or copies of relevant source records, ensuring that the patient's confidentiality is maintained. This is particularly important when source documents are illegible or when errors in data transcription are encountered.

In the event of particular issues or governmental queries, it is also necessary to have access to the complete study records, provided that the patient's confidentiality is protected in accordance with applicable regulations.

8.6 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be established by the Sponsor. The IDMC will be composed of recognized experts in the fields of hematology and/or critical care who are not actively recruiting patients.

The IDMC will review relevant data periodically during the study and will give advice on the continuation, modification, or termination of the study. A written study-specific procedure will define in detail the composition, responsibilities, and procedures of the IDMC.

9 STATISTICAL METHODS AND SAMPLE SIZE

Statistical analysis will be delegated under an agreement of transfer of responsibilities to an external contract research organization (CRO). All Octapharma procedures and policies must be met by this CRO. Discrepancies or exceptions will be approved by the Sponsor's Manager of Biometrics.

9.1 Determination of Sample Size

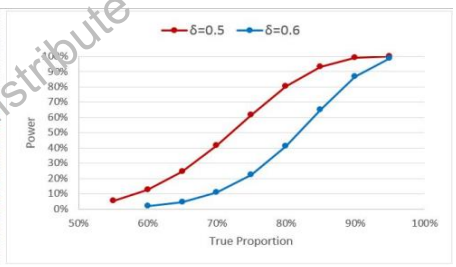
At least 20 patients who meet all eligibility criteria will be enrolled in the study.

The purpose of this study is to evaluate the efficacy and safety of PANZYGA in pediatric patients with chronic ITP; the chosen number of 20 patients to be enrolled is not derived from statistical considerations of power but driven by feasibility constraints with respect to finding pediatric ITP patient eligible and willing to participate in this study.

We expect the true proportion of responders to be comparable to results from similar studies in adult patients, as there is no published data or expert statement that would indicate otherwise. Looking at possible outcome scenarios, 20 evaluable patients give the following picture from a statistical point of view:

Power Considerations for 20 Evaluable Patients:

Responders		Exact 95% Confidence Limits		Hypothetical power to show that the true response rate is above δ (1-sided, α=0.025), given that it is in fact equal to the observed proportion	
Number	Proportion	Lower	Upper	δ=0.5	δ=0.6
11	55%	31,5%	76,9%	5,5%	
12	60%	36,1%	80,9%	12,6%	2%
13	65%	40,8%	84,6%	24,5%	4,4%
14	70%	45,7%	88,1%	41,6%	10,7%
15	75%	50,9%	91,3%	61,7%	22,5%
16	80%	56,3%	94,3%	80,4%	41,1%
17	85%	62,1%	96,8%	93,3%	64,8%
18	90%	68,3%	98,8%	98,9%	86,7%
19	95%	75,1%	99,9%	100,0%	98,4%
20	100%	83,2%	100,0%		



Even though the chosen number of 20 pediatric patients is thus not sufficient 'to power' the study, it will still allow the Sponsor to gather enough clinical evidence to obtain a sound and meaningful medical assessment of the efficacy and safety of PANZYGA in pediatric patients with chronic ITP.

9.2 Statistical Analysis

A formal statistical analysis plan describing all details of the analyses to be performed will be prepared by the study statistician and approved by the Sponsor prior to the start of the statistical analysis.

No confirmatory statistical analysis will be performed; the results of this study will be presented at the descriptive level only.

In general, and if not detailed otherwise in the Statistical Analysis Plan (SAP), all statistical presentations will be fit to the nature and type of the individual data items:

- Binary data (whether or not an event has occurred): counts and proportions
- Count data (the frequency of an event in a set time period): rate (count per unit time)

- Continuous data (measurements on a continuous scale, including quasi-continuous variables): arithmetic mean, standard deviation, median, lower and upper quartile, minimum, maximum
- Scales data (Ordinal and Non-ordinal): absolute and relative frequencies
- Time-to-event data (how long it takes to observe the outcome of interest, e.g. the initial treatment response): time to event or last evaluation (censored data in case subjects are lost to follow-up) and event rate. Such parameters may also be presented as Kaplan-Meier plots of the product-limit survival function estimates.

9.2.1 Populations for Analysis

The following populations will be considered for the statistical analysis:

- Safety Analysis Set (SAF): All patients who received at least part of 1 infusion of PANZYGA.
- Full Analysis Set (FAS): All patients in the SAF who satisfy all major eligibility criteria and for whom any post-baseline data is available. This is the set of eligible patients with treatment effects measured, according to the intention-to-treat (ITT) principle.
- Per-Protocol Set I (PP1): All patients in the FAS, excluding those with significant protocol deviations before the primary efficacy assessment on Day 8 is completed, and which may have an impact on the evaluation of the primary endpoint.
- Per-Protocol Set II (PP2): All patients in the FAS, excluding those with significant protocol violations potentially affecting the (secondary) efficacy evaluations.

Only protocol deviations with the potential to significantly affect the study results or to invalidate the interpretation of the data obtained will lead to exclusion of patients from the PP sets. The inclusion of each patient in the respective analysis populations will be determined before database lock in a data review meeting by a panel consisting of a medical expert from the Sponsor, the clinical study manager, the data manager, and the study statistician.

The analysis of safety will be based on the SAF.

The evaluation of the primary objective will be performed for the FAS (ITT analysis) and for the PP1 set (PP analysis) to assess the robustness of the results. The primary analysis will be the ITT analysis.

For secondary objectives ITT and PP2 analyses will be carried out; again the ITT analysis is considered the primary analysis and will be presented first in the report.

9.2.2 Efficacy Analysis Plan

The primary and secondary efficacy parameters will be determined on the basis of the patient's platelet concentration, listed individually, and presented descriptively.

The primary endpoint parameter 'response' is defined as an increase in platelet count at least once to ≥50x10^9/L within 7 days after the first infusion, ie, by Day 8 (increase must occur at least once on any day up to and including Day 8).

The number and proportion of responders will be presented, together with the associated exact 95% confidence intervals.

The time to reach the desired increase in platelet count as well as the duration of response and the maximum platelet levels will be presented in listings and summarized in statistical tables.

Individual profiles of platelet count over time will be presented as Trellis plots.

9.2.3 Safety Analysis Plan

The safety analysis will comprise descriptive statistics, tabulations, and listings of all TEAEs, safety laboratory results, vital signs, and physical examination findings. All reported AEs will be coded according to the Medical Dictionary for Regulatory Activities) MedDRA.

An AE is defined as treatment-emergent if first onset or worsening is after start of the first infusion of PANZYGA. Only TEAEs are accounted for in the analysis.

AEs will be record at the start of the fist infusion of PANZYGA. AEs that occur between informed consent/assent and the start of the first PANZYGA infusion will be recorded under Medical History.

Incidences of treatment-emergent AEs will be given as the number and percentage of patients who experienced any or a particular AE, including serious and drug-related AEs.

The summary tables for AEs will be given by system organ class and preferred term. Additionally, AEs will be summarized by severity and relationship to study treatment. In addition to the tables presenting incidences including all AEs, incidences will be determined for the subset of SAEs and drug-related AEs.

Incidences of infusional AEs will be given as the number and percentage of patients who experienced any or a particular infusional AE, including serious and drug-related AEs.

The summary tables for infusional AEs will be given by system organ class and preferred term. Additionally, infusional AEs will be summarized by severity and relationship to study treatment. In addition to the tables presenting incidences including all infusional AEs, incidences will be determined for the subset of SAEs and drug-related AEs.

Narratives will be prepared describing each death, other SAEs, and other significant AEs that are judged to be of special interest because of clinical importance.

For each routine laboratory parameter at each visit the actual result, the change from baseline, the out-of-range flag and the assessment of clinical relevance will be summarized descriptively.

Vital signs include systolic and diastolic blood pressure, pulse rate, body temperature and the respiratory rate; descriptive tables on the sampling statistics

of these parameters at each time point will be provided for the values as well as for their changes to baseline.

9.2.4 Handling of Missing Data

No replacement of missing data values is planned, but only observed results (and platelet counts) will be included in the analyses.

9.3 Randomization, Stratification, and Code Release

This is an open-label non-randomized study; therefore, no randomization code list or procedure for code release are required. Patients will not be stratified by age group.

9.4 Interim Analysis

No interim analysis is planned.

10 ETHICAL/REGULATORY, LEGAL AND ADMINISTRATIVE ASPECTS

10.1 Ethical/Regulatory Framework

This study will be conducted in accordance with the ethical principles laid down in the Declaration of Helsinki. The study protocol and any subsequent amendment(s) will be submitted to an IEC/ IRB and to the Regulatory Authority. The study will be conducted in compliance with the protocol, GCP guidelines, and applicable regulatory requirements.

The regulatory application or submission for regulatory approval will be made by the Sponsor or designated third party (eg, CRO) as required by national law.

10.2 Approval of Study Documents

The study protocol, a sample of the patient information and informed consent form, assent form, any other materials provided to the patient and their parent/legal guardian, and further requested information will be submitted by the Sponsor or the Investigator to the appropriate IEC/IRB and the Regulatory Authority. The study must be approved by the IEC/IRB and the Regulatory Authority before any IMP may be shipped to the study sites and any patient is exposed to a study-related procedure.

The Sponsor, the Investigator, and any third party (eg, CRO) involved in obtaining approval must inform each other in writing that all ethical and legal requirements have been met before the first patient is enrolled in the study.

10.3 Patient Information and Informed Consent

The Investigator will obtain freely given written consent from each the patient after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspect of the study which is relevant to the patient's decision to participate. The informed consent form must be signed, with name and date and time noted by the patient, before the patient is exposed to any study-related procedure, including screening tests for eligibility.

For patients not qualified to give legal consent, written consent must be obtained from the legal parent/guardian. If children are old enough to understand the risks and benefits of the study, they should also be informed and provide their written consent using an assent form.

The Investigator will explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, without any consequences for their further care and without the need to justify. The Investigator will complete the informed consent section of the CRF for each patient enrolled.

Each patient (and parent/legal guardian, as appropriate) will be informed that his/her medical (source) records may be reviewed by the study monitor, a quality assurance auditor, or a health authority inspector, in accordance with applicable regulations, and that these persons are bound by confidentiality obligations.

10.4 Protocol Amendments

Any prospective change to the protocol will be agreed between the Investigator (Co-ordinating Investigator in multi-center studies) and the Sponsor prior to its implementation. Any such amendments will be submitted to the any competent IEC/IRB and/or competent authority responsible as required by applicable regulations.

IEC/IRB approval will, at a minimum, be requested for any change to this protocol which could affect the safety of the patients, the objective/design of the study, any increase in dosage or duration of exposure to the IMP, an increase in the number of patients treated, the addition of a new test or procedure, or the dropping of a test intended to monitor safety.

10.5 Confidentiality of Patient Data

The Investigator will ensure that the patient's confidentiality is preserved. On eCRFs or any other documents submitted to the Sponsor, the patients will not be identified by their names, but by a unique patient identifier. Documents not intended for submission to the Sponsor, ie, the confidential patient identification code list, original consent and assent forms, and source records, will be maintained by the Investigator in strict confidence.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Periodic Monitoring

The monitor will contact and visit the Investigator periodically to review all study-related source data/records, verify the adherence to the protocol and the completeness, correctness and accuracy of all CRF entries compared to source data. The Investigator will cooperate with the monitor to ensure that any discrepancies identified are resolved.

For this study, the first monitoring visit shall take place shortly after the inclusion of the first patient. Thereafter, monitoring frequency will depend on study progress and in accordance with the study clinical monitoring plan.

The monitor must be given direct access to source documents (original documents, data, and records). Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the clinical study. Source data will be available for all data in the eCRFs, including all laboratory results.

11.2 Audit and Inspection

The Investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the Sponsor, or to IEC/IRB/regulatory inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and welfare of the patients have been adequately protected, and that all data relevant for the assessment of safety and efficacy of PANZYGA have been reported to the Sponsor.

12 REPORTING AND PUBLICATION

12.1 Clinical Study Report

A clinical study report (in accordance with relevant guidelines and the Sponsor's Standard Operating Procedures [SOPs]) will be prepared by the Sponsor after completion of the study. The Co-ordinating Investigator will approve the final study report after review.

12.2 Publication Policy

The results of this study may be published or presented at scientific meetings.

If the Investigator wants to publish or present study results, the Investigator agrees to inform the Sponsor and to submit all manuscripts or abstracts to the Sponsor before submission to an editorial board or scientific review committee. This will allow the Sponsor to protect proprietary information and to provide comments based on information that may not yet be available to the Investigator.

In accordance with standard editorial and ethical practice, the Sponsor will support publication of multi-center studies only in their entirety and not as individual center data. Authorship will be determined by mutual agreement.

13 LIABILITIES AND INSURANCE

In order to cover any potential damage or injury occurring to a patient in association with PANZYGA or participation in the study, the Sponsor will contract insurance in accordance with local regulations.

The Investigator is responsible for dispensing PANZYGA according to this protocol and for its secure storage and safe handling throughout the study.

14 REFERENCES

1. Diagnosis and treatment of idiopathic thrombocytopenic purpura: recommendations of the American Society of Hematology. The American Society of Hematology ITP Practice Guideline Panel. Ann.Intern.Med. 1997;126:319-326.
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3. Imbach P: Immune thrombocytopenic purpura and intravenous immunoglobulin. Cancer. 1991;68:1422-1425.
4. Newland AC, Burton I, Cavenagh JD, et al: Vigam-S, a solvent/detergent-treated intravenous immunoglobulin, in idiopathic thrombocytopenic purpura. Transfus.Med. 2001;11:37-44.
5. Despotovic JM: Emerging therapies in immune thrombocytopenia. American Society of Hematology. The Hematologist, ASH News and Reports. 2018:15:4;1-7.
6. Neunert C, Despotovic J, Haley K, et. al. Thrombopoietin receptor agonist use in children: data from the pediatric ITP consortium of North America ICON2 study. Pediatric Blood & Cancer. 2016:63(8), 1407-1413. doi:10.1002/pbc.26003
7. European Medicines Agency, Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg). EMA/CHMP/BPWP/94033/2007 rev. 3. Retrieved from: https://www.ema.europa.eu/documents/scientific-guideline/guideline-clinical-investigation-human-normal-immunoglobulin-intravenous-administration-ivig-rev-3_en.pdf
8. American Society of Hematology 2011 Clinical Practice Guideline on the Evaluation and Management of Immune Thrombocytopenia (ITP), Quick Reference Guide.
9. PANZYGA [package insert]. Hoboken, NJ: Octapharma USA Inc; 2018.

15 APPENDICES

Not applicable.

PROTOCOL AMENDMENT #2

STUDY NUMBER: NGAM-10

STUDY TITLE: Post-Marketing Study to Evaluate the Efficacy and Safety of PANZYGA in Pediatric Patients with Chronic Immune Thrombocytopenia (ITP)

SPONSOR: Octapharma USA
121 River Street, 12th Floor
Hoboken, NJ 07030

TEST PRODUCT: PANZYGA

IND / BLA NUMBERS: IND 14121 / BLA 125587

APPROVED BY: [redacted]
Octapharma Pharmazeutika ProduktionsgmbH
Oberlaaerstr. 235, A-1100 Vienna, Austria

PROTOCOL:	DATE:
Final Version 01	30 Jan 2019
Protocol Amendment #1	21 May 2019
Final Version 02	21 May 2019
Protocol Amendment #2	05 Aug 2019
Final Version 03	05 Aug 2019

Rationale for the Amendment:

FDA reviewed Study Protocol No. NGAM-10 Version 02, including Amendment 01 and provided one comment to the Sponsor in a communication dated 01-Aug-2019. The rationale for Amendment 02 to be included in Version 3 of Protocol NGAM-10 is to address that FDA's comment.

In addition, the exclusionary time for a splenectomy has been increased from 4 weeks to 3 months, in order to further enhance patient safety and assure that patients have an adequate recovery time prior to enrolling into this study.

In order to accommodate the pediatric population and improve protocol compliance, the protocol has been amended to allow study visits that do not involve Panzyga infusions and only include safety assessments (including clinical laboratory evaluations) to be conducted locally by the patient's primary care physician or local laboratory services.

Other changes were incorporated throughout the protocol to provide additional instruction to Investigators including allowable time windows for changing infusion rates, vital sign assessments, collection of patient body weight and height, and reconciliation of discrepancies identified between the Flow Chart of Assessments and Section 6.1: Observations by Visit.

The following changes made throughout the protocol were considered significant. All substantive and non-substantive changes (including administrative changes and grammatical, punctuation, or formatting corrections) are documented in the red-line version of the protocol.

MODIFICATION 1: Managing Hypersensitivity Reactions

FDA requested that, to enhance the safety of participating patients, the protocol be amended such that in the event of severe hypersensitivity reactions or anaphylaxis, any further Panzyga administration should be discontinued and not resumed.

Previous requirement:

Section 7.3.2.8: Managing Hypersensitivity Reactions

Severe hypersensitivity reactions may occur during PANZYGA infusions [9]. In the case of any subject exhibiting clinical signs of severe acute hypersensitivity reactions to PANZYGA, the PANZYGA infusion must be immediately stopped. Each site must have Epinephrine readily available and follow their institution's standard procedure for Epinephrine administration and monitoring. After the hypersensitivity reaction subsides, the infusion may be resumed at a lower rate if allowed per the site Epinephrine administration and monitoring procedures, and per Investigator discretion.

Amended Requirement:

Section 7.3.2.8: Managing Hypersensitivity Reactions

Severe hypersensitivity reactions may occur during PANZYGA infusions [9]. In the case of any subject exhibiting clinical signs of severe ~~acute~~ hypersensitivity

reactions to PANZYGA, the PANZYGA infusion must be immediately stopped. Each site must have Epinephrine readily available and follow their institution's standard procedure for Epinephrine administration and monitoring. If a subject developed severe hypersensitivity or anaphylactoid reactions, any further Panzyga administration should be discontinued and not resumed.

MODIFICATION 2: Increasing Exclusionary Time Requirement after Splenectomy

In order to enhance patient safety and assure that patients have an adequate recovery time prior to enrolling into this study, the exclusionary time for a splenectomy has been increased from 4 weeks to 3 months.

Previous requirement:

Study Outline: Exclusion Criterion #8
Section 4.1.2: Exclusion Criterion #8

8) Splenectomy in the previous 4 weeks or planned splenectomy throughout the study period

Amended Requirement:

Study Outline: Exclusion Criterion #8
Section 4.1.2: Exclusion Criterion #8

8) Splenectomy in the previous ~~4 weeks~~ 3 months or planned splenectomy throughout the study period

MODIFICATION 3: Allowable Time Windows for Changing Infusion Rates

The protocol was silent on the allowable time windows for changing infusion rates. Time windows of ±5 minutes have been added in order to provide direction to the Investigators.

Previous requirement:

Study Outline
Section 5.4: Dose and Dosing Schedule

PANZYGA will be delivered by intravenous infusion according to the recommended flow rates:

- Initial infusion rate of 0.01 mL/kg/min (60 mg/kg/hr) for the first 30 minutes
- If tolerated, increase to 0.02 mL/kg/min (120 mg/kg/hr) for the second 30 minutes
- If tolerated, increase to 0.04 mL/kg/min (240 mg/kg/hr) for the third 30 minutes
- If tolerated, increase to 0.08 mL/kg/min (480 mg/kg/hr) for the remainder of the infusion

Amended Requirement:
Study Outline
Section 5.4: Dose and Dosing Schedule
PANZYGA will be delivered by intravenous infusion according to the recommended flow rates:

- *Initial infusion rate of 0.01 mL/kg/min (60 mg/kg/hr) for the first 30 minutes (±5 minutes)*
- *If tolerated, increase to 0.02 mL/kg/min (120 mg/kg/hr) for the second 30 minutes (±5 minutes)*
- *If tolerated, increase to 0.04 mL/kg/min (240 mg/kg/hr) for the third 30 minutes (±5 minutes)*
- *If tolerated, increase to 0.08 mL/kg/min (480 mg/kg/hr) for the remainder of the infusion*

MODIFICATION 4: Allowable Time Window for Vital Sign Assessments Taken at the End of the Infusion

The protocol was silent on the time windows for vital signs taken after the end of the Panzyga infusion. Time windows of +15 minutes have been added in order to provide direction to the Investigators.

Previous requirement:

Table 1 Flow Chart of Assessments Footnote 9

Footnote 9) Vital Signs: at the start of the infusion and every 60 minutes (±15 minutes) thereafter until the end of the infusion. In addition, vital sign measurements will be recorded just prior to every infusion rate change (-10 minutes), 15 minutes (+15 minutes) after each infusion rate change, and approximately 30 minutes after the end of the infusion.

Section 6.1.2: Day 1
Section 6.1.3: Day 3

- Vital signs (at the start of the infusion and every 60 minutes (±15 minutes) thereafter until the end of the infusion. In addition, vital sign measurements will be recorded just prior to every infusion rate change (-10 minutes), 15 minutes (+15 minutes) after each infusion rate change, and approximately 30 minutes after the end of the infusion)

Amended Requirement:

Table 1 Flow Chart of Assessments Footnote 9

Footnote 9) Vital Signs: at the start of the infusion and every 60 minutes (±15 minutes) thereafter until the end of the infusion. In addition, vital sign measurements will be recorded just prior to every infusion rate change (-10 minutes), 15 minutes (+15 minutes) after each infusion rate change, and approximately 30 minutes (+15 minutes) after the end of the infusion

Section 6.1.2: Day 1
Section 6.1.3: Day 3

- *Vital signs (at the start of the infusion and every 60 minutes (±15 minutes) thereafter until the end of the infusion. In addition, vital sign measurements will be recorded just prior to every infusion rate change (-10 minutes), 15 minutes (+15 minutes) after each infusion rate change, and approximately 30 minutes (+15 minutes) after the end of the infusion*

MODIFICATION 5: Clarification of Body Weight and Height Assessments

Section 7.3.7 (Physical Examination including Body Weight and Height) specifies that patient body weight and height are part of the physical examination performed at Baseline. In order to clarify this requirement, specific instructions regarding the measurement of body weight and height have been added elsewhere in the protocol.

Previous requirement:

The Flow Chart of Assessments (Table 1) and the description of assessments performed at the Baseline Visit (Section 6.1.1) specified a physical examination but did not specifically address the collection of height at the Baseline visit.

Amended Requirement:

Table 1: Flow Chart of Assessments and Footnote 3

"Height" was added after Physical Examination in the Flow Chart, and further clarification was added to Footnote 3 indicating that height would only be collected at Baseline, only (see example below extracted from Table 1).

ASSESSMENTS	Screening / Baseline
Physical Examination *and Height*	X[3]

Footnote 3) Brief Physical Examination: general appearance, skin, heart, lungs, abdomen, extremities. Height will only be collected at Baseline.

Section 6.1.1: Baseline Visit/Screening Period

- *Physical examination and height*

MODIFICATION 6: Reconcile Vital Sign Assessments at Day 22

Vital sign assessments are not required at the Day 22 visit and are not included in the assessments listed in Day 22 Visit procedures (Section 6.1.5). The Flow Chart of Assessments (Table 1) included an "X" in the box under the Day 22 assessments.

Amended Requirement:

Table 1: Flow Chart of Assessments

The "X" was removed in table under the Day 22 assessments (see below extracted from Table 1).

ASSESSMENTS	Scr / BL[1]	Day 1	Day 3	Day 5[12]	Day 8[12]	Day 15[12]	Day 22[12]	Day 32[13]
Vital Signs: heart rate, blood pressure, temperature, respiratory rate	*X*	*X*[9]	*X*[9]				~~*X*~~	*X*

MODIFICATION 7: Reconcile Adverse Event Collection and Pregnancy Tests

Both adverse event collection and pregnancy tests are required at the Day 32 visit; these requirements are indicated in the Flow Chart of Assessments (Table 1). However, they are not specified in Section 6.1.6: Day 32 (End of Study Visit) assessments.

Adverse events will be collected from the start of the first infusion on Day 1, as specified in Footnote 10 in the Flow Chart of Assessments (Table 1). Further clarification will be provided to the Investigator in Section 6.1.6: Day 32 (End of Study Visit) and Section 7.3.2.2: Collection of AEs.

Amended Requirement:

Section 6.1.6: Day 32 (End of Study Visit)

- *Physical examination*
- *Vital signs*
- *Blood samples for serum chemistry, hematology, and hemolysis analytes*
- *Blood or urine pregnancy test (females of childbearing potential, only)*
- *Monitoring for AEs*
- *Documentation of concomitant medication use*

Section 7.3.2.2 Collection of AEs

AEs will be collected from the start of the first infusion on Day 1. Any illnesses captured between signing the ICF and the first infusion will be captured under medical history. The condition of the patient will be monitored throughout the study. At each visit, whether scheduled or unscheduled, AEs will be elicited using a standard nonleading question such as "How have you been since the last visit/during the previous study period?" In addition, the Investigator will check the patient diaries (if applicable) for any documented event.

MODIFICATION 8: Reconsent of Patients Who Turn 18 Years Old during Study Participation

The patient population for this study includes infants and children from ≥1 year to <18 years old. It is possible that some patients may turn 18 years old during their participation. Therefore, a note was added to the age-related inclusion criterion that these patients must be re-consented after their 18th birthday.

Amended Requirement:

Study Outline: Inclusion Criterion #1
Section 4.1.1: Inclusion Criterion #1

1) Females and males aged from ≥1 year to <18 years old

***Note:** Patients who turn 18 years old during study participation must be re-consented at their next study visit with an adult informed consent form.*

MODIFICATION 9: Allowing Safety Assessment Visits to be Performed Locally by the Patient's Primary Care Physician and/or Local Laboratory Services

The patient population for this study includes infants and children from ≥1 year to <18 years old. As this is a rare disease being treated at specialty centers, sometimes the patient population may be 2 to 3 hours away from the study center. This could cause difficulty with compliance. In order to accommodate the needs of this population and their parents or guardians and improve compliance with the protocol visit schedule, the clinical sites that will be participating in this study have requested that the protocol allow study visits that do not involve Panzyga infusions to be conducted locally by the patient's primary care physician. Days 5, 8, 15, and 22 include limited physical examinations, adverse event and concomitant medication use documentation, and blood draws for clinical laboratory assessments. Required interactions and communication channels between the local physician and the Principal Investigator (eg, telemedicine or other means of electronic communication) will be outlined in the Investigator Site File.

Previous requirement:

The protocol does not address study visits taking place at locations other than those associated with the Principal Investigator's clinical site.

Amended Requirement:

Table 1: Flow Chart of Assessments

A footnote (new Footnote 12) was added to Day 5, Day 8, Day 15, and Day 22 Visit Days in the flow chart, and the original Footnote 12 was changed to Footnote 13. In addition, it was clarified that limited physical examinations would be performed on Day 3 and Day 15 (see example below extracted from Table 1: Flow Chart of Assessments).

ASSESSMENTS	**Scr / BL[1]**	**Day 1**	**Day 3**	***Day 5[12]***	***Day 8[12]***	***Day 15[12]***	***Day 22[12]***	***Day 32[13] [12]***
Physical Examination and Height	*X[3]*	*X[3]*	*~~X[3]~~X[4]*	*X[4]*	*X[4]*	*~~X[3]~~X[4]*	*X[4]*	*X[3]*

Footnote 3) Brief Physical Examination: general appearance, skin, heart, lungs, abdomen, extremities. Height will only be collected at Baseline.

Footnote 4) Limited Physical Examination with targeted body systems per Investigator discretion.

Footnote 12) Days 5, 8, 15, and 22 visits may be performed locally by patient's primary care physician or a local laboratory service upon agreement with the site Principal Investigator, the IRB, and the Sponsor.

Footnote 13 ~~12~~) Day 32 visit will correspond to the Early Termination visit for patients who are withdrawn early from the study,

Section 6.1.4: Day 5 and Day 8

Day 5 and Day 8 visits and assessments may be performed locally (by patient's primary care physician or local laboratory services) upon agreement with the site Principal Investigator, the IRB, and the Sponsor. Required interactions and communication channels between the primary care physician and the Principal Investigator (eg, telemedicine or other means of electronic communication) will be outlined in the Investigator Site Binder.

Section 6.1.5: Day 15 and Day 22

Day 15 and Day 22 visits and assessments may be performed locally (by patient's primary care physician or local laboratory services*) upon agreement with the site Principal Investigator, the IRB, and the Sponsor. Required interactions and communication channels between the primary care physician and the Principal Investigator (eg, telemedicine or other means of electronic communication) will be outlined in the Investigator Site Binder.*

Section 7.3.5: Laboratory Tests

Investigational sites will follow all site and local laboratory standard operating procedures for sample collection and handling and will provide the ~~s~~Sponsor with normal reference ranges and laboratory certification certificates. Upon agreement with site Principal Investigator, the IRB, and the Sponsor, Days 5, 8, 15, and 22 visits may be performed locally by the patient's primary care physician. Laboratory samples may be collected by a patient's primary care physician or by a local laboratory service (that draws, processes, and reports laboratory results) that is in the proximity of the patient's home; these samples must be analyzed according to the chosen laboratory's standard operating procedures. Normal reference ranges and laboratory certification certificates of any laboratories will also be provided to the Sponsor.

Please see the attached redline version for documentation of these substantive changes, along with minor grammatical, formatting, punctuation, and other non-substantive changes.

AGREEMENT: These signatures constitute approval of this protocol amendment and provide the necessary assurance that the study will be conducted according to all stipulations of protocol and amendments.

Authorised person for signing the Study Protocol and Protocol Amendments on behalf of the Sponsor and Sponsor's Medical Expert:

[redacted] Date: [redacted]

[redacted]
Octapharma Pharmazeutika Produktionsgesellschaft m.b.H.
Oberlaaerstr. 235, A-1100 Vienna, Austria
Tel: [redacted], Fax: [redacted]

[redacted] **of the Amendment:**

[redacted] Date: [redacted]

[redacted]
Octapharma USA, Inc.
121 River Street, Suite 1201
Tel: [redacted], Fax [redacted]

[redacted] Date: [redacted]

[redacted]
Octapharma Pharmazeutika Produktionsgesellschaft m.b.H.
Oberlaaerstr. 235, A-1100 Vienna, Austria
Tel: [redacted], Fax: [redacted]

CLINICAL STUDY PROTOCOL

NGAM-10

Post-Marketing Study to Evaluate the Efficacy and Safety of PANZYGA in Pediatric Patients with Chronic Immune Thrombocytopenia (ITP)

Investigational Product:	PANZYGA
Indication:	Chronic Immune Thrombocytopenia (ITP)
Study Design:	Prospective, open-label, single-arm, multi-center study
Sponsor:	Octapharma USA 121 River Street, 12th Floor Hoboken, NJ 07030
Study Number:	NGAM-10
IND Number / BLA Number:	IND 14121 / BLA 125587
Development Phase:	Phase 4
Planned Clinical Start:	Q3 2019
Planned Clinical End:	Q1 2022
Date of Protocol:	05-Aug-2019
Version:	03 (Incorporating Amendment 2)

STUDY OUTLINE

Name of Sponsor/Company: Octapharma USA	
Name of Investigational Product: PANZYGA	**Protocol Identification Code:** NGAM-10
Name of Active Ingredient: Immune globulin human-ifas	**Date of Final Protocol:** 05-Aug-2019

Title of Study:

Post-Marketing Study to Evaluate the Efficacy and Safety of PANZYGA in Pediatric Patients with Chronic Immune Thrombocytopenia (ITP)

Indication:

Chronic Immune Thrombocytopenia (ITP)

Number of Study Centre(s):

Up to 8 sites in the USA

Objectives:

Primary Objective:

The primary objective is to evaluate the efficacy of PANZYGA in increasing the platelet count in pediatric patients with chronic ITP.

Secondary Objectives:

The secondary objectives of this study are to:

- Assess safety of up to 2 g/kg PANZYGA (1 g/kg PANZYGA on Day 1 and an optional dose of 1 g/kg PANZYGA on Day 3) infused in the pediatric population within the scope of the clinical study
- Determine the time to reach a platelet count of $\geq 50 \times 10^9$/L
- Determine duration of time during which the platelet count is maintained at the level $\geq 50 \times 10^9$/L
- Determine the maximum platelet count during the study

Study Design:

This is a prospective, open-label, single-arm, multicenter, Phase 4 study evaluating the efficacy and safety of PANZYGA in pediatric patients with chronic ITP.

Name of Sponsor/Company: Octapharma USA	
Name of Investigational Product: PANZYGA	**Protocol Identification Code:** NGAM-10
Name of Active Ingredient: Immune globulin human-ifas	**Date of Final Protocol:** 05-Aug-2019

Number of Patients:

At least 20 patients

Patient Selection Criteria:

Inclusion Criteria:

1. Females and males aged from ≥1 year to <18 years old

   Note: Patients who turn 18 years old during study participation must be re-consented at their next study visit with an adult informed consent form.
2. Confirmed diagnosis of Chronic Immune Thrombocytopenia (ITP) according to American Society of Hematology (ASH) 2011 guidelines
3. Platelets count $<30x10^9$/L at the Baseline Visit
4. Voluntarily given written informed consent (provided by patient's parent or legal guardian) and assent (provided by patient [if age-appropriate per IRB requirements])
5. ~~5.~~ Females of childbearing potential who have been using at least 1 acceptable form of birth control for a minimum of 30 days (or a minimum of 3 months for hormonal contraceptives) prior to the Screening visit, and must agree to use at least 1 acceptable method of contraception for 30 days after the last dose of PANZYGA. Acceptable methods of birth control for this study include: intrauterine device (IUD), hormonal contraception, male or female condom, spermicide gel, diaphragm, sponge, or cervical cap. Abstinence is not considered an acceptable method of birth control.
6. Parent or legal guardian must agree and be willing to assist the participant attend study visits, and to follow all protocol requirements and instructions of the study doctor

Exclusion Criteria:

1. Thrombocytopenia secondary to other diseases (such as Acquired Immunodeficiency Syndrome [AIDS] or systemic lupus erythematosus [SLE]), drug-related thrombocytopenia, or congenital thrombocytopenia
2. Administration of intravenous immunoglobulin (IGIV) or anti-D immunoglobulin within 3 weeks before enrollment
3. Administration of thrombopoietin receptor agonists when the dose has NOT been stable within 3 weeks before enrollment and a dosage change is planned before Day 32
4. Administration of oral immunosuppressants when the dose has NOT been stable during the preceding 2 months (2 weeks for long-term corticosteroid therapy) and a dosage change is planned before Day 32 (Note: topical agents and inhaled corticosteroid therapy use is permitted)
5. Administration of long-term anti-prolific agents or attenuated androgen therapy when the dose has NOT been stable during the preceding 2 months and a dosage change is planned before Day 32
6. Nonresponsive to previous treatment with IGIV or anti-D immunoglobulin
7. Evidence of an active major bleeding episode at Screening
8. Splenectomy in the previous 3 months or planned splenectomy throughout the study period
9. Evans syndrome (experiencing active disease with 2 out of 3 of the following: autoimmune thrombocytopenia, autoimmune hemolytic anemia, and/or autoimmune neutropenia)
10. Known or suspected human immunodeficiency virus (HIV), hepatitis B virus (HBV), and/or hepatitis C virus (HCV) infections
11. Emergency surgery in the previous 4 weeks
12. Severe liver and/or kidney disease (alanine aminotransferase [ALT] >3x upper limit of normal (ULN), aspartate aminotransferase [AST] >3x upper limit of normal (ULN), and/or creatinine >120 µmol/L)
13. History of severe hypersensitivity to blood or plasma derived products, or any component of the PANZYGA
14. Known immunoglobulin A (IgA) deficiency and antibodies against IgA
15. History of, or suspected alcohol or drug abuse in the previous year
16. Females who are pregnant or nursing
17. Unable or unwilling to comply with the study protocol
18. Receipt of any other investigational medicinal product within 3 months before study entry
19. Risk factors* for thromboembolic events in whom the risks outweigh the potential benefit of PANZYGA treatment.

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20. Any other condition(s), that in the Investigator's opinion, make it undesirable for the patient to participate in the study or may interfere with protocol compliance.

* Risk factors include, but are not limited to: obesity, advanced age, hypertension, diabetes, a history of atherosclerosis/vascular disease or thrombotic events, hyperlipidemia, multiple cardiovascular risk factors, acquired or inherited thrombophilic disorders, prolonged periods of immobilization, severe hypovolemia, central venous catheterization, active malignancy and/or known or suspected hyperviscosity.

Test Product, Dose, and Mode of Administration:

PANZYGA (Immune Globulin, intravenous, human-ifas). PANZYGA must be stored and transported light-protected at +2°C (36°F) to +8°C (46°F) and must be brought to room temperature before use.

Patients will receive a dose of 1 g/kg body weight PANZYGA given on Day 1 and optionally another dose of 1 g/kg PANZYGA given on Day 3; body-weight dependent doses will be based on each patient's weight collected at Baseline. Total PANZYGA doses will be 1 g/kg for patients receiving only 1 dose on Day 1 and 2 g/kg for those receiving the optional Day 3 dose. Prior to the Day 3 infusion, each patient's preinfusion platelet count will be reviewed by the Investigator. If the Day 3 platelet count shows evidence of response as indicated by the platelet count at least doubling from Baseline count AND is >50x10^9/L, the Day 3 infusion **will not be** administered. If the Baseline platelet count has doubled but is ≤50x10^9/L, the Day 3 infusion **will be** administered.

PANZYGA will be delivered by intravenous infusion according to the recommended flow rates:

- Initial infusion rate of 0.01 mL/kg/min (60 mg/kg/hr) for the first 30 minutes (±5 minutes)
- If tolerated, increase to 0.02 mL/kg/min (120 mg/kg/hr) for the second 30 minutes (±5 minutes)
- If tolerated, increase to 0.04 mL/kg/min (240 mg/kg/hr) for the third 30 minutes (±5 minutes)
- If tolerated, increase to 0.08 mL/kg/min (480 mg/kg/hr) for the remainder of the infusion.

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Infusion rates should not exceed 0.08 mL/kg/min and should not exceed 8.0 mL/min. The infusion rate may be gradually increased as tolerated by the patient.

If a Grade 2 or higher (moderate) infusion-related adverse event (AE) occurs during infusion, the Panzyga infusion will be stopped. After infusion-related symptoms subside, the infusion may be resumed at a lower rate. The infusion rate may be gradually increased as tolerated by the patient.

If a Grade 1 (mild) infusion-related AE occurs during infusion, the infusion rate should be reduced to half the rate at which the event occurred, or the infusion should be interrupted until symptoms subside. The infusion may then be resumed at a rate tolerated by the patient. The batch number(s) used will be recorded in the study documentation and electronic data capture (EDC) system.

Duration of Treatment:

Screening Period: 1 week

Treatment Period: up to 3 days

Follow-up Period: 29 days

Reference Therapy, Dose, and Mode of Administration:

Not Applicable

Study Outcome Parameters (Primary and Secondary Endpoints):

Primary Endpoint:

The primary efficacy parameter is defined as an increase in platelet count at least once to ≥50x10^9/L within 7 days after the first infusion, ie, by Day 8 (increase must occur at least once on any day up to and including Day 8). This definition of clinical response will serve as the basis for the primary endpoint, the response rate (ie, the proportion of patients with an elevation of platelet count at least once to ≥50x10^9/L within 7 days [ie, by Day 8] after the first infusion).

Secondary Endpoints:

- Time to reach a platelet count of ≥50x10^9/L
- Duration of platelet response defined as the number of days the platelet count remains above ≥50x10^9/L

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- Maximum platelet count during the study

Safety Parameters:

- AEs
- Vital signs (blood pressure, heart rate, temperature, respiratory rate)
- Physical examination
- Laboratory parameters: hematology (including reticulocytes), hemolysis, platelet count, serum chemistry (including lactase dehydrogenase [LDH]).

Study Procedures:

The study will be conducted in accordance with ICH-GCP and US FDA regulations.

The Flow Chart of Assessments specifies the procedures that will be performed at each study visit.

Baseline Visit

After appropriate information about the study and PANZYGA has been provided and written informed consent/assent has been obtained, patients will be evaluated for study eligibility according to the inclusion/exclusion criteria. These evaluations will include demographics, medical/surgical history, current medications, physical examinations, blood and urine samples, along with other safety and baseline evaluations as specified in the Flow Chart of Assessments.

Infusion Visits (Day 1 and Day 3)

The first PANZYGA infusion must begin no more than 2 days after Baseline evaluations have been completed and eligibility criteria have been confirmed. If Baseline and Day 1 Visits occur on the same day, Day 1 investigations do not need to be repeated. If Baseline evaluations are completed more than 2 days before Day 1, then the platelet count must be repeated and evaluated by the Investigator prior to the first infusion.

Patients who have met all of the inclusion criteria and none of the exclusion criteria will return to the study site for their first PANZYGA infusion. Required assessments will be performed as specified in the Flow Chart of Assessments, including safety evaluations before and after each infusion. Patients will remain

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at the study site during the infusion and for about 30 minutes after the end of each infusion to complete vital sign measurements.

Patients will receive a dose of 1 g/kg body weight PANZYGA on Day 1 and optionally another dose of 1 g/kg PANZYGA on Day 3; body-weight dependent doses will be based on each patient's weight collected at Baseline. Total PANZYGA doses will be 1 g/kg for patients receiving only 1 dose on Day 1 and 2 g/kg for those receiving the optional Day 3 dose.

Prior to the Day 3 infusion, the Investigator will assess each patient's preinfusion platelet count, hematocrit, and hemoglobin. If the Day 3 platelet count shows evidence of response, as indicated by the platelet count at least doubling from Baseline count AND >50x10^9/L, the Day 3 infusion will not be administered. If the Baseline platelet count has doubled but is ≤50x10^9/L, the Day 3 infusion will be administered. If any of these parameters indicate a clinically relevant change such that, in the Investigator's opinion, it is not safe to administer the second infusion the patient should be withdrawn from study treatment but will be followed for safety through Day 32.

Assessment Day 5 though Day 22

Patients will return to the study site as indicated in the Flow Chart of Assessments for continued efficacy and safety evaluations.

Day 32 (End of Study/Early Termination Visit)

Patients will return to the study site on Day 32 for final safety assessments/End of Study (EOS) visit. Patients withdrawn early from the study will be encouraged to return to the study site and complete the EOS assessments.

Statistical Analysis:

The primary endpoint for this study is the proportion of patients with an increase in platelet count to ≥50x10^9/L at least once within 7 days after the first infusion. This proportion will be assessed and presented together with its associated 95% confidence interval to facilitate comparison with results from other studies and published data. Because of the limited number of patients, no formal hypothesis test will be performed; any p-value or confidence interval presented is to be understood in the exploratory sense.

All data collected will be presented descriptively. The time to reach the desired increase in platelet count as well as the duration of response will be presented in listings and summarized in statistical tables. Individual profiles of platelet count over time will be presented as Trellis plots.

All safety data, including tolerability assessments, abnormal laboratory values, and AEs will also be listed and summarized statistically.

Statistical presentations will be fit to the nature of individual data items and include sample characteristics, frequency counts and rates. Product-limit survival function estimates (Kaplan-Meier Plots), confidence intervals and graphs will be included as appropriate.

The following populations will be considered for the statistical analysis:

- Safety Analysis Set (SAF): All patients who received at least part of one infusion of PANZYGA.
- Full Analysis Set (FAS): All patients in the SAF who satisfy all major eligibility criteria and for whom any post-baseline data is available. This is the set of eligible patients with treatment effects measured, according to the intention-to-treat (ITT) principle.
- Per-Protocol Set I (PP1): All patients in the FAS, excluding those with significant protocol deviations before the primary efficacy assessment on day 8 is completed, and which may have an impact on the evaluation of the primary endpoint.
- Per-Protocol Set II (PP2): All patients in the FAS, excluding those with significant protocol violations potentially affecting the (secondary) efficacy evaluations.

Only protocol deviations with the potential to significantly affect the study results or to invalidate the interpretation of the data obtained will lead to exclusion of patients from the PP sets. The inclusion of each patient in the respective analysis populations will be determined before database lock in a data review meeting by a panel consisting of a medical expert from the Sponsor, the clinical study manager, the data manager, and the study statistician.

A detailed Statistical Analysis Plan (SAP) will be compiled as a separate document.

FLOW CHART OF ASSESSMENTS

Table 1: Flow Chart of Assessments

ASSESSMENTS	Scr / BL[1]	Day 1	Day 3	Day 5[12]	Day 8[12]	Day 15[12]	Day 22[12]	Day 32[13]
Visit Window (Days)	**-7 / -2**	**0**	**0**	**±1**	**±1**	**±3**	**±3**	**±5**
Informed Consent	X							
Inclusion / Exclusion Criteria Review	X	X						
Demographics	X							
Medical and Surgical History[2]	X							
Body Weight	X							
Physical Examination and Height	X[3]	X[3]	X[3]	X[4]	X[4]	X[4]	X[4]	X[3]
Urine or Blood Pregnancy Test (females of child-bearing potential)	X							X
Hematology: CBC with white blood cell (WBC) differential, hematocrit, hemoglobin, platelet counts, reticulocytes	X	X[5,6]	X[5,6,7]	X	X	X	X	X
Hemolysis: total, direct, and indirect bilirubin	X	X	X	X	X	X	X	X
Serum Chemistry: ALT, AST, creatinine, Na, Ca, K, BUN, LDH	X	X	X	X	X			X
Viral markers (HIV, HCV, HBV nucleic acid test [NAT])	X[7]							
PANZYGA INFUSIONS		**X**	**X**[8]					
Vital Signs: heart rate, blood pressure, temperature, respiratory rate	X	X[9]	X[9]					X
AE Monitoring[10]		X	X	X	X	X	X	X
Prior and Concomitant Therapy (drug and non-drug)[11]	X	X	X	X	X	X	X	X

Abbreviations: BL = Baseline, Scr = Screening

1) Screening Period is 7 days. Day 1 (first PANZYGA infusion) must occur no more than 2 days after Baseline evaluations have been completed. If the Baseline visit occurs more than 2 days after Baseline evaluations have been completed, the platelet count must be repeated and evaluated by the Investigator before initiation of the Day 1 infusion. If Baseline and Day 1 visits occur on the same day, the Day 1 investigations need not be repeated.
2) Medical History will be collected for the previous year and will include the onset date of ITP. Surgical history will include the date of splenectomy (if applicable), and any other surgical procedures in the previous year.
3) Brief Physical Examination: general appearance, skin, heart, lungs, abdomen, extremities. Height will only be collected at Baseline.
4) Limited Physical Examination with targeted body systems per Investigator discretion.
5) Pre-infusion.
6) Platelet count, hematocrit, and hemoglobin results must be available and reviewed by the Investigator prior to start of the infusion.
7) HIV/HCV/HBV NAT Test: Infusions may begin before the results are back if the Investigator is not aware of, and the patient isn't exhibiting clinical signs of, any viral infection.
8) If the Day 3 preinfusion platelet count shows evidence of response as indicated by the platelet count at least doubling from Baseline count AND >50x10^9/L, the Day 3 infusion **will not be** administered. If the Baseline platelet count has doubled but is ≤50x10^9/L, the Day 3 infusion **will be** administered.
9) Vital Signs: at the start of the infusion and every 60 minutes (±15 minutes) thereafter until the end of the infusion. In addition, vital sign measurements will be recorded just prior to every infusion rate change (-10 minutes), 15 minutes (+15 minutes) after each infusion rate change, and approximately 30 minutes (+15 minutes) after the end of the infusion.
10) The start date and start time will be collected for any adverse events starting at Day 1 through Day 32/EOS visit.
11) Prior medications will be collected for the 3 months. The start date and start time will be collected for any concomitant medications taken on Day 1 through Day 32/EOS visit.
12) Days 5, 8, 15, and 22 visits may be performed locally by patient's primary care physician or a local laboratory service upon agreement with the site Principal Investigator, the IRB, and the Sponsor.
13) Day 32 visit will correspond to the Early Termination visit for patients who are withdrawn early from the study.

PROTOCOL SIGNATURES

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and [redacted]

[redacted]

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LIST OF ABBREVIATIONS

Abbreviation	Description
ADR	Adverse Drug Reaction
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
ASH	American Society of Hematology
AST	Aspartate Aminotransferase
CIDP	Chronic Inflammatory Demyelinating Poly(radiculo)neuropathy
CRO	Contract Research Organisation
DEHP	Diethylhexylphthalate
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOS	End of Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
ifas	4-letter meaningless suffix assigned by FDA at the end of newly approved biologics
IgA	immunoglobulin A
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITP	Immune Thrombocytopenia
ITT	Intention-to-Treat
IUD	Intrauterine device
IGIV	Intravenous Immunoglobulin
LDH	lactase dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MMN	Multifocal Motor Neuropathy
NAT	Nucleic Acid Test
PMR	Post-Marketing Requirement
PREA	Pediatric Research Equity Act
PP	Per-Protocol
PP1	Per-Protocol Set 1

Abbreviation	Description
PP2	Per-Protocol Set II
PVC	Polyvinyl Chloride
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SLE	systemic lupus erythematosus
SOP	Standard Operating Procedure
TEAE	Treatment-emergent Adverse Event
TNBP	tri-n-butyl phosphate
TPO-RA	Thrombopoietin Receptor Agonists
ULN	Upper Limit of Normal
USC	United States Code

1 INTRODUCTION

Since more than five decades immunoglobulins have been used to provide antibodies for the prevention of viral and bacterial diseases (replacement therapy) in immunocompromised patients. Within the last 25 years intravenous immunoglobulin (IGIV) has been proven to be useful in a wide variety of clinical conditions other than replacement therapy of immunocompromised patients, in which IGIV exhibits an immunomodulatory effect. These include Idiopathic Thrombocytopenic (ITP) in children and adults at high risk of bleeding or prior to surgery to correct the platelet count, Kawasaki disease, and Guillain-Barré syndrome (GBS). More recently, single IGIV brands have also been licensed for Multifocal Motor Neuropathy (MMN) and Chronic Inflammatory Demyelinating Poly(radiculo)neuropathy (CIDP). Experimental off-label use of IGIV mostly in other neurological and dermatological indications is widespread.

ITP is an immune-mediated (disorder characterized by increased platelet destruction. The reason for platelet destruction is the development of autoantibodies to platelet-membrane antigens. These antibodies are particularly produced in the spleen which is also the major site of platelet destruction [1]. In patients suffering from ITP, several studies have shown IGIV effective in increasing platelet counts to prevent or control bleeding [2-4] The mechanism of action in ITP is not fully elucidated but includes immunomodulatory effects, particularly the modulation of cytokines, soluble cytokine receptors and cytokine receptor antagonists with anti-inflammatory effects as well as complement modulation.

Broadly, 2 categories of agents are available for the treatment of ITP: 1) those that rapidly and transiently interfere with the process of platelet destruction for management of acute bleeding or bleeding risk (front-line therapies), and 2) those with potential to provide a more durable improvement in the platelet count (second-line therapies). Corticosteroids, IGIV, and anti-D immune globulin remain the mainstay of front-line treatment of acute bleeding symptoms in both adults and children [5]. Although corticosteroids remain the most commonly used ITP therapy, controversy still exists surrounding selection of agent, dosing, and duration of therapy. For treatment with prednisone, it is generally accepted that shorter courses are preferable to chronic therapy. The 2010 International Consensus Report on the investigation and management of primary ITP developed by an international working group address three classes of second-line therapies: splenectomy, rituximab, and the thrombopoietin receptor agonists (TPO-RA). Due to a relative lack of data, their use was recommended only in patients who were refractory to splenectomy and other therapies. Further study results in 2016 demonstrated that TPO-RA agents are being used in children with ITP of varying duration and severity. The response was similar to clinical trials, but the sustainability of response varied. Future studies need to focus on the ideal timing and rationale for these medications in pediatric patients [6].

PANZYGA is a human immunoglobulin solution with 10% protein content for intravenous administration. PANZYGA is made from a pool of at least 1000 donations of human fresh-frozen plasma per batch.

PANZYGA was granted a US approval by the US Food and Drug Administration (FDA) in August 2018. The license in 2 indications (primary humoral

immunodeficiency diseases and chronic immune thrombocytopenia) was granted based on 2 completed studies. The first study in Primary Immune Deficiency included 51 children and adults from ages 2 years to 65 years who were dosed at 200 mg/kg to 800 mg/kg body weight every 3 to 4 weeks for 360 days. The second study in Immune Thrombocytopenia included 40 adults with chronic ITP receiving 2 gm/kg body weight over 2 consecutive days. Of the 36 subjects in the full analysis set, 29 patients (81%: 95% CI: 64% to 92%) responded to PANZYGA with a rise in platelet count to at least $50x10^9$/L within 7 days after the first infusion.

Further information can be found in the Investigator's Brochure (IB).

1.1 Rationale for Conducting the Study

Under the Pediatric Research Equity Act (PREA) (21 United States Code [USC] 355c) all applications for new active ingredients, new indications, new dosage forms, new dosing regimens or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this required is waived, deferred or inapplicable.

This post-marketing requirement (PMR) study was requested by the US FDA after PANZYGA received marketing approval in the United States. The rationale for conducting this PMR study is to investigate the efficacy and safety of PANZYGA in children suffering from primary ITP.

The study will be conducted in compliance with the protocol, International Conference on Harmonisation-Good Clinical Practice (ICH-GCP), US FDA Code of Federal Regulations, and other local regulatory requirements.

1.2 Dose Rationale

According to recent guidelines, IGIV is recommended for patients with platelet counts $<30x10^9$/L in case of severe bleeding and/or mucous membrane bleeding. Standard doses should be studied (0.8 g/kg to1 g/kg on Day 1, which may be repeated once within 3 days, or 0.4 g/kg/day for 2 to 5 days). If other dosage regimens are to be applied for, they should be supported by clinical data. [7,8]. The dose option for this study is within the recommended guidelines.

1.3 Benefit-Risk Statement

The safety profile of IGIV is well characterized and, in general, the same type of adverse reactions may be expected for PANZYGA. No new or unknown safety problems are expected to emerge which are not already described in the Investigator's Brochure.

Data obtained from the clinical trials conducted with PANZYGA in the adult ITP population clearly met the recommended clinical response criteria for efficacy as set out in the relevant FDA and EU guidelines. These data are comparable with available literature data on other commercial IVIGs and formed the basis for marketing authorization in Europe and the US. The safety profile of PANZYGA is satisfactory and the number of infusional AEs are below the levels as

recommended by the FDA for products of this class. Efficacy and safety data with PANZYGA in 3 clinical studies in 51 patients (also including pediatric patients) with primary immunodeficiency (PID) and in 40 patients with immune thrombocytopenia (ITP) are available. Available data are sufficient to expect favorable benefit-risk profile of PANZYGA in the pediatric ITP population. Expected clinical benefit of using PANZYGA in this study is an increase in platelets level to control or prevent bleeding. The main known risks are listed below:

- Thrombosis may occur with immune globulin intravenous (IGIV) products, including PANZYGA. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.
- Renal dysfunction, acute renal failure, osmotic nephropathy, and death may occur with the administration of IGIV products in predisposed patients. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. PANZYGA does not contain sucrose.
- For patients at risk of thrombosis, renal dysfunction, or renal failure, administer PANZYGA at the minimum infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.
- Standard measures are taken to prevent infections resulting from the use of medicinal products prepared from human blood or plasma. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. During the manufacturing process of PANZYGA, significant viral reduction is obtained.

Inclusion and exclusion criteria, recommendations on the rate of infusion, dosage, and monitoring procedures provided in this protocol sufficiently mitigate above mentioned risks and must be adhered to.

No new or unknown safety problems are expected to emerge in pediatric ITP population, which are not listed above or described in the Investigator's Brochure.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objective is to evaluate the efficacy of PANZYGA in increasing the platelet count in pediatric patients with chronic ITP.

2.2 Secondary Objectives

The secondary objectives of this study are to:

- Assess safety of up to 2 g/kg PANZYGA (1 g/kg PANZYGA on Day 1 and an optional dose of 1 g/kg PANZYGA on Day 3) infused in the pediatric population within the scope of the clinical study
- Determine the time to reach a platelet count of $\geq 50 \times 10^9$/L
- Determine duration of time during which the platelet count is maintained at the level $\geq 50 \times 10^9$/L
- Determine the maximum platelet count during the study

3 INVESTIGATIONAL PLAN

3.1 Primary and Secondary Endpoints

3.1.1 Primary Endpoint

The primary efficacy parameter is defined as an increase in platelet count at least once to ≥50x10^9/L within 7 days after the first infusion, ie, by Day 8 (increase must occur at least once on any day up to and including Day 8). This definition of clinical response will serve as the basis for the primary endpoint, the response rate (ie, the proportion of patients with an elevation of platelet count at least once to ≥50x10^9/L within 7 days [ie, Day 8] after the first infusion).

3.1.2 Secondary Endpoints

Secondary endpoints are defined to further evaluate the efficacy and safety of the PANZYGA infused in the pediatric population.

The following parameters will be used to for efficacy assessments:

- Time to reach a platelet count of ≥50x10^9/L
- Duration of platelet response defined as the number of days the platelet count remains above ≥50x10^9/L
- Maximum platelet count during the study

The following parameters will be used for safety assessments:

- AEs
- Vital signs (blood pressure, heart rate, temperature, respiratory rate)
- Physical examination
- Laboratory parameters: hematology (including reticulocytes), hemolysis, platelet count, serum chemistry (including lactase dehydrogenase [LDH])

3.2 Overall Study Design and Plan

This is a prospective, open-label, single-arm, multicenter, Phase 4 study evaluating the efficacy and safety of the investigational product, PANZYGA, in pediatric patients with chronic ITP.

The study will enroll at least 20 patients ≥1 year to <18 years old and will not be stratified by age group. A patient is considered enrolled into the study after successfully completing all baseline assessments and receiving at least a partial dose of PANZYGA.

Patients with a confirmed diagnosis of chronic ITP, without evidence of active major bleeding, may be enrolled in the study. Study procedures will only begin after written informed consent (from parent or guardian) and assent (from the patient, as age appropriate per Institutional Review Board [IRB] requirements) have been obtained. Patients who meet all of the inclusion and none of the exclusion criteria may receive the first infusion of PANZYGA within 2 days after Baseline investigations have been completed.

Each patient will be administered PANZYGA by intravenous infusion at a dose of 1 g/kg body weight PANZYGA on Day 1 and optionally another dose of 1 g/kg PANZYGA on Day 3; body-weight dependent doses will be based on each patient's weight collected at Baseline. Total PANZYGA doses will be 1 g/kg for patients receiving only 1 dose on Day 1 and 2g/kg for those receiving the optional Day 3 dose. Prior to the Day 3 infusion, Investigators will assess each patient's preinfusion platelet count, hematocrit, and hemoglobin. Patients whose platelet count shows evidence of response as indicated by the platelet count at least doubling from Baseline count AND is $>50x10^9$/L, the Day 3 infusion will not be administered. If the Baseline platelet count has doubled but is $\leq 50x10^9$/L, the Day 3 infusion will be administered. If any parameters indicate a clinically relevant change such that, in the Investigator's opinion, it is not safe to administer the second infusion, the patient should be withdrawn from study treatment; however, the patient will be followed for safety through Day 32.

Study interventions and procedures will be performed at predefined timepoints (see Section 6.1 and the Flow Chart of Assessments [Table 1]) including (but are not limited to): blood draws for safety evaluations, vital signs, body weight, physical examinations, AE monitoring, and changes in concomitant medication use. Patients will have clinic visits on Days 1, 3, 5, 8, 15, and 22. They will return to the clinic for a final safety follow-up evaluation at Day 32/End of Study (EOS) Visit.

PANZYGA infusions may be stopped or interrupted at any time if, in the Investigator's opinion, it is not safe to continue or is not in the patient's best interest. Patients who have received a partial dose of PANZYGA should be followed for safety evaluations through Day 32/EOS.

The study is planned to begin screening procedures Q3 2019 at up to 8 sites in the USA, with recruitment lasting approximately 30 months, and is anticipated to complete in Q1 2022. The study duration for a single patient will be approximately 39 days, including up to a 1-week Screening period.

3.3 Discussion of Study Design and Choice of Control Group(s)

3.3.1 Study Design

This study was designed to meet the US FDA's requirements under the PREA (21 USC 355c) for a post-approval study of PANZYGA in the pediatric population. US FDA is requiring a pediatric study for the treatment of ITP to evaluate PANZYGA for the treatment of ITP in patients ages ≥1 year to <18 years. All of the US FDA's recommendations have been incorporated into the protocol.

This study design is also in line with study protocols evaluating NGAM in adults, with the frequency of blood draws and number of visits reduced to accommodate a pediatric population. Because of the limited number of patients that will be enrolled in this study, along with the increased blood volume and additional site visits that would be required to meet the full recommendations in the European Medicines Agency (EMA) Guideline for confirmatory visits and blood draws, the secondary efficacy endpoints were selected to allow efficacy evaluations in this patient population.

3.3.2 Control Group(s)

A placebo control group will not be included in this post-approval study. An active control group is not considered relevant, as the objective of this study is to evaluate the efficacy and safety of PANZYGA in the pediatric population, not to compare the efficacy and safety of PANZYGA versus another IGIV treatment.

3.3.3 Study Parameters

The primary therapeutic target for ITP treatment is an increase in the platelet count. Therefore, the primary endpoint chosen for the study, namely the response rate (ie, the proportion of patients with an increase in platelets at least once to $\geq 50 \times 10^9$/L within 7 days after the first infusion), is appropriate to adequately describe the efficacy of treatment of PANZYGA in the pediatric population.

To assess the efficacy of PANZYGA in correcting the platelet count, this response rate has been chosen as the primary endpoint. There are several definitions of response published in guidelines and commonly used for the evaluation of ITP treatment; however, an increase in platelets to $\geq 50 \times 10^9$/L is the most established definition of response [7] and as such has been chosen for this post-marketing approval study.

The secondary efficacy endpoints chosen are in accordance with the primary endpoint, in order to further characterize the effect on the increase in platelet count.

The safety assessments, including AE, vital signs, laboratory results, and physical examination are appropriate and commonly used parameters to monitor the of IGIV treatment during a clinical study.

4 STUDY POPULATION

4.1 Population Base

At least 20 female or male patients ≥1 year to <18 years old with chronic ITP will be eligible for this study.

4.1.1 Inclusion Criteria

Patients who meet all of the following criteria are eligible for the study:

1. Females and males aged from ≥1 year to <18 years old

   Note: Patients who turn 18 years old during study participation must be re-consented at their next study visit with an adult informed consent form.
2. Confirmed diagnosis of Chronic Immune Thrombocytopenia (ITP) according to American Society of Hematology (ASH 2011) guidelines
3. Platelets count <30x10^9/L at the Baseline Visit
4. Voluntarily given written informed consent (provided by patient's parent or legal guardian) and assent (provided by patient)
5. Females of childbearing potential who have been using at least 1 acceptable form of birth control for a minimum of 30 days (or a minimum of 3 months for hormonal contraceptives) prior to the Screening visit, and must agree to use at least 1 acceptable method of contraception for 30 days after the last dose of PANZYGA. Acceptable methods include: intrauterine device (IUD), hormonal contraception, male or female condom, spermicide gel, diaphragm, sponge, or cervical cap. Abstinence is not considered an acceptable method of birth control.
6. Parent or legal guardian must agree and be willing to assist the participant attend study visits, and to follow all protocol requirements and instructions of the study doctor

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria are not eligible for the study:

1. Thrombocytopenia secondary to other diseases (such as Acquired Immunodeficiency Syndrome [AIDS] or systemic lupus erythematosus [SLE]), drug-related thrombocytopenia, or congenital thrombocytopenia
2. Administration of intravenous immunoglobulin (IGIV) or anti-D immunoglobulin within 3 weeks before enrollment
3. Administration of thrombopoietin receptor agonists when the dose has NOT been stable within 3 weeks before enrollment and a dosage change is planned before Day 32

4. Administration of oral immunosuppressants when the dose has NOT been stable during the preceding 2 months (2 weeks for long-term corticosteroid therapy) and a dosage change is planned before Day 32 (Note: topical agents and inhaled corticosteroid therapy use is permitted)
5. Administration of long-term anti-prolific agents or attenuated androgen therapy when the dose has NOT been stable during the preceding 2 months and a dosage change is planned before Day 32
6. Nonresponsive to previous treatment with IGIV or anti-D immunoglobulin
7. Evidence of an active major bleeding episode at Screening
8. Splenectomy in the previous 3 months or planned splenectomy throughout the study period
9. Evans syndrome (experiencing active disease with 2 out of 3 of the following: autoimmune thrombocytopenia, autoimmune hemolytic anemia, and/or autoimmune neutropenia)
10. Known or suspected human immunodeficiency virus (HIV), hepatitis B virus (HBV), and/or hepatitis C virus (HCV) infections
11. Emergency surgery in the previous 4 weeks
12. Severe liver and/or kidney disease (alanine aminotransferase [ALT] >3x upper limit of normal (ULN), aspartate aminotransferase [AST] >3x upper limit of normal (ULN), and/or creatinine >120 µmol/L)
13. History of severe hypersensitivity to blood or plasma derived products, or any component of the PANZYGA
14. Known immunoglobulin A (IgA) deficiency and antibodies against IgA
15. History of, or suspected, alcohol or drug abuse in the previous year
16. Females who are pregnant or nursing
17. Unable or unwilling to comply with the study protocol
18. Receipt of any other investigational medicinal product within 3 months before study entry
19. Risk factors* for thromboembolic events in whom the risks outweigh the potential benefit of PANZYGA treatment.
20. Any other condition(s), that in the Investigator's opinion, make it undesirable for the patient to participate in the study or may interfere with protocol compliance.

* Risk factors include, but are not limited to: obesity, advanced age, hypertension, diabetes, a history of atherosclerosis/vascular disease or thrombotic events, hyperlipidemia, multiple cardiovascular risk factors, acquired or inherited thrombophilic disorders, prolonged periods of immobilization, severe hypovolemia, central venous catheterization, active malignancy and/or known or suspected hyperviscosity.

4.2 Prior and Concomitant Therapy

Details on medications taken within the previous 3 months prior to the Baseline Visit and any concomitant medications taken during the study must be recorded in the electronic case report form (eCRF).

4.2.1 Allowed Pre-medications

Use of H-1 blockers or antipyretics are allowed for patients who have history of hypersensitivity to IGIV treatment; this may minimize the severity of possible infusion-related reactions in patients already predisposed to hypersensitivity reactions. All pre-medications administered prior to PANZYGA administration must be recorded in the eCRF.

4.2.2 Prohibited Medications

Use of the following medications are forbidden during the study as specified below (Table 2):

Table 2: Prohibited Medications

Medication	Time Window
IGIV	prohibited for 3 weeks prior to Baseline Visit through Day 32
anti-D immunoglobulin	prohibited for 3 weeks prior to Baseline Visit through Day 32
oral immunosuppressants	prohibited during Screening Period through Day 32 **unless** patients have been receiving a stable dose for 2 months (2 weeks for long-term corticosteroid therapies) prior to Screening Visit
thrombopoietin receptor agonists	prohibited during Screening Period through Day 32 **unless** patients have been receiving stable dose for 3 weeks prior to Screening Visit
long-term anti-prolific agents or attenuated androgen therapy	prohibited during Screening Period through Day 32 **unless** patients have been on a stable dose for 2 months prior to Screening Visit
any other blood or plasma-derived product*	prohibited during Screening Period through Day 32
receipt of any other investigational product	prohibited within 3 months prior to Baseline Visit through Day 32

* Patients who are non-responders or requiring emergent ITP treatment (other than PANZYGA specified in this protocol) will be followed for safety and complete all assessments through Day 32.

Trade names of drugs corresponding to the categories provided in Table 2 will be provided in the Investigator Site Binder.

4.3 Withdrawal and Replacement of Patients

4.3.1 Premature Patient Withdrawal

Patients have the right to withdraw from the study at any time for any reason, without the need to justify their decision; parents or legal guardians also have the right to withdraw a patient on the patient's behalf. The Investigator also has the right to withdraw patients in case of AEs, poor compliance, or other reasons. Because an excessive rate of withdrawals can render the study noninterpretable, any unnecessary withdrawal of patients should be avoided.

For any withdrawals after study entry, the Investigator will obtain all the required details and document the reason(s) for discontinuation. If the reason for withdrawal of a patient is an AE, the main specific event or laboratory test will be recorded, and the Investigator will make thorough efforts to clearly document the outcome. Patients should return to the study site and have all safety evaluations, including safety laboratory tests, completed as specified at the Day 32 visit (See Section 6.1.6).

4.3.2 Patient Replacement Policy

Patients withdrawn from the study will not be replaced. Under no circumstances will patients who enroll in the study be permitted to re-enroll after study completion. Patients who fail during the Screening Period (also referred to as Screen Failures) may be re-screened upon written approval from the Sponsor.

4.4 Assignment of Patients to Treatment Groups

This is an open-label non-randomized study. All patients will receive PANZYGA.

4.5 Relevant Protocol Deviations

In case of any major protocol deviation, the Investigator and Octapharma will decide on the further participation of the patient in this study after having discussed all relevant aspects.

A list of all included patients with all deviations from the intended study procedures and other criteria that may affect the patient's data validity for statistical analysis will be prepared upon clinical completion of the study. This will also be discussed by a panel consisting of the clinical study manager, a medical expert of the Sponsor, the data manager and the study statistician. This panel will decide upon the membership of the patient in the Full Analysis Set (FAS), Per Protocol (PP) Set 1 (PP2), PP Set 2 (PP2), and Safety Analysis Set for statistical analysis.

4.6 Subsequent Therapy

If a patient withdraws from the study or is withdrawn by the Investigator by their parent/legal guardian, he/she will receive treatment by the Investigator or personal physician according to institutional standard of care.

5 INVESTIGATIONAL MEDICINAL PRODUCT

5.1 Characterization of Investigational Product

Name of Medicinal Product: PANZYGA

Active ingredient of PANZYGA: Immune globulin human-ifas

Table 3: Qualitative and Quantitative Composition of PANZYGA

Name of Ingredient	Amount
Total protein	9.0 – 11.0 g/100 mL
Protein composition	≥95% Ig (≥96% Ig)*
IgG content	86 – 110 mg/mL
Glycine	15.0 – 19.5 mg/mL (17.3 mg/mL)*
Water for Injection	*ad* 1mL

*Depending on regulatory requirements

PANZYGA is a solvent/detergent (S/D)-treated, sterile preparation of highly purified immunoglobulin G (IgG) derived from large pools of human plasma. PANZYGA is a solution for infusion to be administered intravenously.

This preparation contains approximately 100 mg of protein per mL (10%), of which not less than 96% is normal human immunoglobulin G. PANZYGA contains not more than 3% aggregates, not less than 90% monomers and dimers, and not more than 3% fragments. On average, the product contains 100 µg/mL of IgA, and lower amounts of IgM.

PANZYGA contains only trace amounts of sodium, and the pH is between 4.5 and 5.0. The osmolality is in the range of 240 to 310 mosmol/kg.

The manufacturing process for PANZYGA isolates IgG without additional chemical or enzymatic modification, and the Fc portion is maintained intact. PANZYGA contains the IgG antibody activities present in the donor population. IgG subclasses are fully represented with the following approximate percentages of total IgG: IgG1 is 65%, IgG2 is 28%, IgG3 is 3% and IgG4 is 4%.

PANZYGA contains a broad spectrum of IgG antibodies against bacterial and viral agents that are capable of opsonization and neutralization of microbes and toxins. PANZYGA contains glycine (15.0 to 19.5 mg/mL), but no preservatives or sucrose.

All units of human plasma used in the manufacture of PANZYGA are provided by FDA-approved blood and plasma establishments, and are tested by FDA-licensed serological tests for HBsAg, antibodies to HCV and HIV and Nucleic Acid Test (NAT) for HCV and HIV-1 and found to be non-reactive (negative).

5.2 Packaging and Labelling

PANZYGA for investigational use only will be labeled according to US FDA regulations. Details of the labeling will be included in the Pharmacy Manual.

The batch number(s) used will be recorded in the study documentation and EDC.

5.3 Conditions for Storage and Use

PANZYGA must be stored and transported light-protected at +2°C (36°F) to +8°C (46°F) and must be brought to room temperature before use.

Storage temperature must be maintained at +2°C (36°F) to +8°C (46°F) and will be monitored for the duration of the study by reviewing the temperature logs.

PANZYGA must not be frozen prior to use.

PANZYGA must not be used after its expiry date.

PANZYGA must not be mixed with other medicinal products.

Each PANZYGA bottle is for single use only.

Authorized personnel at the individual study sites will ensure that PANZYGA is stored in appropriate conditions in a secure refrigerator with restricted access and in compliance with national regulations.

5.4 Dose and Dosing Schedule

PANZYGA will be administered by intravenous infusion. Patients should be adequately hydrated prior to infusion.

Patients will receive a dose of 1 g/kg body weight PANZYGA given on Day 1 and optionally another dose of 1 g/kg PANZYGA given on Day 3; body-weight dependent doses will be based on each patient's weight collected at Baseline. Total PANZYGA doses will be 1 g/kg for patients receiving only 1 dose on Day 1 and 2 g/kg for those receiving the optional Day 3 dose. If the Day 3 platelet count shows evidence of response as indicated by the platelet count at least doubling from Baseline count AND is $>50x10^9$/L, the Day 3 infusion will not be administered. If the Baseline platelet count has doubled but is $\leq 50x10^9$/L, the Day 3 infusion will be administered.

PANZYGA will be delivered by intravenous infusion according to the recommended flow rates:

- Initial infusion rate of 0.01 mL/kg/min (60 mg/kg/hr) for the first 30 minutes (±5 minutes)
- If tolerated, increase to 0.02 mL/kg/min (120 mg/kg/hr) for the second 30 minutes (±5 minutes)
- If tolerated, increase to 0.04 mL/kg/min (240 mg/kg/hr) for the third 30 minutes (±5 minutes)
- If tolerated, increase to 0.08 mL/kg/min (480 mg/kg/hr) for the remainder of the infusion

Infusion rates should not exceed 0.08 mL/kg/min and should not exceed 8.0 mL/min.

If a Grade 2 (moderate) or higher infusion-related adverse event (AE) occurs during infusion, the Panzyga infusion will be stopped. After infusion-related symptoms subside, the infusion may be resumed at a lower rate. The infusion rate may be gradually increased as tolerated by the patient.

If a Grade 1 (mild) infusion-related AE occurs during infusion, the infusion rate should be reduced to half the rate at which the event occurred, or the infusion should be interrupted until symptoms subside. The infusion may then be resumed at an infusion rate tolerated by the patient. The infusion rate may be gradually increased as tolerated by the patient.

5.5 Preparation and Method of Administration

All patients will be infused at the study site under the surveillance of authorized study site staff.

After calculating the volume required for the dose using the patient's Baseline body weight (see Section 5.4), the appropriate number of vials will be removed from the refrigerator. Vials of different sizes may be combined to reach the required amount of IgG. The exact dose will be administered, and the empty and partially used vials will be retained by the site for drug accountability and dose verification.

PANZYGA vials must be allowed to warm to room or body temperature before infusion. After PANZYGA vials have been brought to room or body temperature, they should be inspected visually for particulate matter and discoloration prior to administration. The solution should be clear or slightly opalescent. DO NOT USE IF TURBID, DISCOLORATION IS OBSERVED, AND/OR FLOATING PARTICLES ARE PRESENT. Solutions that are cloudy or vials that have a deposit must not be used and must be discarded according to local policy.

Aseptic technique must be used throughout the entire procedure.

The contents of bottles must be pooled under aseptic conditions into sterile infusion bags and administered immediately after pooling. Only polyvinyl chloride (PVC)-free, diethylhexylphthalate (DEHP)-free and latex–free, infusion bags can be used. Once pooled, a label will be applied on the infusion bag. Detailed instructions of this process and an example label will be included in the Pharmacy Manual.

PANZYGA will be infused into a vein using standard infusion supplies provided by the individual site. Standard procedures should be followed to prime the infusion line with a priming solution (eg, normal saline). At the end of each infusion, the infusion line will be flushed with normal saline solution.

Additional information regarding PANZYGA preparation and infusion procedures will be provided in a pharmacy manual.

Please refer to special warnings and precautions for use provided in the PANZYGA Investigator Brochure.

5.6 Blinding, Emergency Envelopes, and Breaking the Study Blind

Not applicable.

5.7 Treatment Compliance

5.7.1 Drug Dispensing and Accountability

The Sponsor or designee will provide and deliver all PANZYGA to participating Investigators. A Drug Inventory and Dispensing Log will be kept current by the Investigator, detailing the dates and quantities of PANZYGA received, dispensed to each patient, and the quantity remaining at the study site.

The Drug Inventory and Dispensing Log will be available to the monitor to verify drug accountability during the study. The study monitor will inventory all empty and partially used vials of PANZYGA and will cross-check this inventory versus the patient source documentation (records), eCRF, and the Drug Inventory and Dispensing Log.

Unused and partially used vials may be destroyed at the study site or returned to the Sponsor for destruction according to institutional practice. Vials may be destroyed only after drug accountability has been verified and fully reconciled by the monitor and after the Sponsor has granted written approval of destruction.

Additional information regarding PANZYGA drug accountability procedures will be provided in a pharmacy manual.

5.7.2 Assessment of Treatment Compliance

All patients will be infused at the study site under the surveillance of authorized study personnel. Infusion details will be documented together with the batch number(s) in the source data and eCRF.

6 STUDY CONDUCT

Procedures performed at each study visit are presented in the Flow Chart of Assessments (see Table 1). Time windows and tolerances are provided in Table 4.

6.1 Observations by Visit

6.1.1 Baseline Visit/Screening Period

The following assessments will be performed during the Screening Period. The Screening Period can last up to 1 week (to accommodate patient schedules and the informed consent/assent process); however, all Baseline evaluations should be completed within 2 days before the first administration of PANZYGA.

- Obtaining voluntarily given, written (signed and dated) informed consent and assent (as age appropriate)
- Inclusion and exclusion criteria
- Demographic and baseline characteristics
- Medical and surgical history (previous 1 year)
- Splenectomy history
- Physical examination and height
- Vital signs
- Body weight
- Blood samples for serum chemistry, hematology, and hemolysis analytes
- Blood or urine pregnancy test (females of childbearing potential, only)
- Blood samples for viral markers
- Documentation of prior medications (previous 3 months), including administration of pre-medication(s) as appropriate (see Section 4.2.1)

6.1.2 Day 1

Day 1 should take place within 2 days after Baseline evaluations have been completed. If the Baseline and Day 1 Visits occur on the same day, the Baseline investigations do not need to be repeated. If the Baseline evaluations are completed more than 2 days before Day 1, the platelet count must be repeated and evaluated by the Investigator prior to initiating the first infusion.

Before the administration/infusion of PANZYGA, patient eligibility will be re-evaluated. The following assessments/activities will be performed before PANZYGA infusion:

- Confirmation of inclusion and exclusion criteria
- Physical examination
- Vital signs
- Blood samples for serum chemistry, hematology, and hemolysis analytes
- Administration of pre-medication(s) as appropriate (see Section 4.2.1)

The following activities will be performed during or after PANZYGA infusion:

- PANZYGA infusion
- Vital signs (at the start of the infusion and every 60 minutes (±15 minutes) thereafter until the end of the infusion. In addition, vital sign measurements will be recorded just prior to every infusion rate change (-10 minutes), 15 minutes (+15 minutes) after each infusion rate change, and approximately 30 minutes (+15 minutes) after the end of the infusion
- Monitoring for AEs
- Documentation of concomitant medication use

6.1.3 Day 3

The following assessments/activities will be performed before PANZYGA infusion:

- Physical examination
- Vital signs
- Blood samples for serum chemistry, hematology, and hemolysis analytes
- **NOTE:** platelet, hemoglobin and hematocrit results must be available and reviewed by the Investigator prior to initiating the Day 3 infusion
- Administration of pre-medication(s) as appropriate (see Section 4.2.1)

The Investigator will assess each patient's Day 3 preinfusion platelet count, hematocrit, and hemoglobin. If the Day 3 platelet count shows evidence of clinical response, as indicated by the platelet count at least doubling from Baseline count AND is >50x10^9/L, the Day 3 infusion will not be administered. If the Baseline platelet count has doubled but is ≤50x10^9/L, the Day 3 infusion will be administered. In the event that the Day 3 infusion is not administered, all other Day 3 assessments will still be completed. If any of these hematology parameters indicate a clinically relevant change such that, in the Investigator's opinion, it is not safe to administer the second infusion the patient should be withdrawn from study treatment but will be followed for safety through Day 32.

The following activities will be performed during or after PANZYGA infusion:

- PANZYGA infusion
- Vital signs (at the start of the infusion and every 60 minutes (±15 minutes) thereafter until the end of the infusion. In addition, vital sign measurements will be recorded just prior to every infusion rate change (-10 minutes), 15 minutes (+15 minutes) after each infusion rate change, and approximately 30 minutes (+15 minutes) after the end of the infusion
- Monitoring for AEs
- Documentation of concomitant medication use

6.1.4 Day 5 and Day 8 (± 1 day)

Day 5 and Day 8 visits and assessments may be performed locally (by patient's primary care physician or local laboratory services) upon agreement with the site Principal Investigator, the IRB, and the Sponsor. Required interactions and communication channels between the primary care physician and the Principal

Investigator (eg, telemedicine or other means of electronic communication) will be outlined in the Investigator Site Binder.

The following assessments will be performed at Day 5 and Day 8:

- Physical examination
- Blood samples for serum chemistry, hematology, and hemolysis analytes
- Monitoring for AEs
- Documentation of concomitant medication use

6.1.5 Day 15 and Day 22 (± 3 days)

Day 15 and Day 22 visits and assessments may be performed locally (by patient's primary care physician or local laboratory services) upon agreement with the site Principal Investigator, the IRB, and the Sponsor. Required interactions and communication channels between the primary care physician and the Principal Investigator (eg, telemedicine or other means of electronic communication) will be outlined in the Investigator Site Binder.

The following assessments will be performed at Day 15 and Day 22:

- Physical examination
- Blood samples for hematology and hemolysis analytes
- Monitoring for AEs
- Documentation of concomitant medication use

6.1.6 Day 32 (End of Study Visit) (± 5 days)

Patients will return to the study site on Day 32 for final safety assessments/EOS Visit. Patients who were withdrawn early from the study should return to the study site for a final safety assessment. The following assessments will be performed:

- Physical examination
- Vital signs
- Blood samples for serum chemistry, hematology, and hemolysis analytes
- Blood or urine pregnancy test (females of childbearing potential, only)
- Monitoring for AEs
- Documentation of concomitant medication use

After Day 32, the clinical study is considered completed for the patient. No further study-related assessments will be performed, unless safety concerns (eg, ongoing AEs) require follow-up.

6.1.7 Visit Windows Used in this Study, including Tolerances

In this study, the following time windows and tolerances apply (Table 4):

Table 4: Visit Windows Used in this Study

Time point	Tolerance
Screening Period	7 days prior to Day 1
Final Baseline Evaluations	-2 days before Day 1

Time point	Tolerance
Day 1	none
Day 3	none
Day 5	±1 day
Day 8	±1 days
Day 15 and Day 22	±3 days
Day 32	± 5 days

6.2 Duration of Study

6.2.1 Planned Duration for an Individual Patient

The duration of the entire study for each patient will be approximately 39 days, including a 7-day Screening Period.

6.2.2 Planned Duration for the Study as a Whole

The study will be considered completed when all patients have completed the Day 32 EOS Visit.

The estimated start of the study (enrollment of first patient) is Q3 2019, and the estimated end of the study (last visit of last patient) is Q1 2022.

6.2.3 Premature Termination of the Study

Both the responsible Investigators and the Sponsor reserve the right to terminate the study at any time. Should this be necessary, study close-out procedures will be arranged on an individual site basis after review and consultation by both parties. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the patients' interests.

Furthermore, the Investigator should promptly inform the IRB and provide a detailed written explanation. Pertinent regulatory authorities and IRBs will be informed in accordance with applicable regulatory requirements.

6.2.3.1 Early Termination of the Entire Clinical Study

At any time, the study as a whole will be terminated prematurely if:

- New toxicological or pharmacological findings or safety reports invalidate the earlier positive benefit-risk-assessment for the pediatric population
- Any other reason rendering the continuation of the study impossible for the Sponsor

6.2.3.2 Early Termination at an Individual Study Site

At any time, the study can be terminated at an individual study site if:

- The site cannot comply with the requirements of the protocol
- The site cannot comply with GCP or other regulatory standards

- The site does not meet the required recruitment rate

Should the study be prematurely terminated, all study materials, including PANZYGA, must be returned to the Sponsor.

7 ASSESSMENTS AND METHODS

7.1 Demographic and Baseline Information

Demographic and baseline information will be recorded during the Screening Period:

7.1.1 Demographic and Baseline characteristics

The demographic and baseline characteristics are sex, age, race and ethnic origin, height, and weight.

7.1.2 Medical and Surgical history

The medical history will be collected for the previous year and will be obtained by interviewing the patient. Records of past diseases and treatments (eg, hospital discharge letters) will be obtained for the study files, if available. The onset date of ITP will be recorded.

Surgical history will include the date of splenectomy (if applicable) and any other surgical procedures in the previous year.

7.1.3 Viral Marker Tests

At the Screening Visit, blood samples for viral markers (HIV, HCV, HBV NAT) will be collected and tested at the local laboratory according to the site's standard procedures, to rule out secondary infections that may cause ITP. Infusions may begin before the results are back if the Investigator is not aware of, and the patient isn't exhibiting clinical signs of, any viral infection.

7.1.4 Prior and Concomitant Medication Use

Prior medication use will be obtained by interview and review of patient charts (if available). Patients will be queried specifically for use of H-1 blockers or antipyretics as pre-medications prior to previous IGIV treatments.

Concomitant medication use, defined as medications with a start date and time after the start of the Day 1 infusion, will be collected throughout the study. The start date and time of medication use will be collected on Day 1 and throughout the study.

7.2 Efficacy Assessments

All efficacy assessments will be based on platelet counts performed throughout the study.

Platelet counts will be performed at Baseline (within 2 days prior to the first PANZYGA infusion), at Day 1 and Day 3 prior to planned PANZYGA infusions, and then at all remaining study visits (Days 5, 8, 15, 22, and 32).

7.3 Safety Assessments

7.3.1 Assessments for Safety Evaluations

The following assessments will be performed to evaluate the safety of PANZYGA in the pediatric population:

- AEs and Serious Adverse Events (SAEs)
- Clinical laboratory tests
- Vital signs
- Physical examinations
- Pregnancies

7.3.2 Adverse Events

7.3.2.1 Definitions

- **Adverse event (AE):** An AE is any untoward medical occurrence in a study /patient receiving an investigational medicinal product (IMP) and which 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 an IMP, whether or not related to the IMP.
- **Adverse drug reaction (ADR):** An ADR is any noxious and unintended response to an IMP related to any dose. The phrase 'response to an IMP' means that a causal relationship between the IMP and an AE carries at least a reasonable possibility (ie, the relationship cannot be ruled out).
- **Other significant AEs:** Any marked laboratory abnormalities or any AEs that lead to an intervention, including withdrawal of drug treatment, dose reduction, or significant additional concomitant therapy.
- **Treatment-emergent AE (TEAE):** Any AE that newly appeared, increased in frequency, or worsened in severity following the time of the first IMP infusion until the end of the safety follow-up period.
- **Infusional AE:** Any AE that occurs from the time of infusion and within the 72 hour period after end of infusion.
- **Withdrawal due to AE/ADR:** AE/ADR leading to discontinuation of treatment with IMP. Any such events will be followed up by the Investigator until the event is resolved or until the medical condition of the patient is stable. All follow-up information collected will be made available to the Sponsor.

7.3.2.2 Collection of AEs

AEs will be collected from the start of the first infusion on Day 1. Any illnesses captured between signing the ICF and the first infusion will be captured under medical history. The condition of the patient will be monitored throughout the study. At each visit, whether scheduled or unscheduled, AEs will be elicited using a standard nonleading question such as "How have you been since the last

visit/during the previous study period?" In addition, the Investigator will check the patient diaries (if applicable) for any documented event.

Any AE or ADR which occurs during the study will be noted in detail on the appropriate pages of the eCRF. If the patient reports several signs or symptoms representing a single syndrome or diagnosis, the diagnosis should be recorded in the eCRF. The Investigator will grade the severity of all AEs or ADRs (mild, moderate, or severe), the seriousness (non-serious or serious), and the causality as defined in Section 7.3.2.3, Section 7.3.3, and Section 7.3.2.4, respectively. The Sponsor is responsible for assessing the expectedness of each ADR (expected or unexpected) as defined in Section 7.3.2.5.

In the event of clinically significant abnormal laboratory findings, the tests will be confirmed and the patient followed until the laboratory values have returned to normal and/or an adequate explanation for the abnormality has become available.

Diseases, signs and symptoms, and/or laboratory abnormalities already present before the first administration of IMP will not be considered AEs unless an exacerbation in intensity or frequency (worsening) occurs.

The Investigator will provide detailed information about any abnormalities and about the nature of and reasons for any action taken as well as any other observations or comments that may be useful for the interpretation and understanding of an AE or ADR.

7.3.2.3 Severity of AEs

The intensity/severity of AEs will be graded as follows:

- **Mild:** an AE, usually transient, which causes discomfort but does not interfere with the patient's routine activities
- **Moderate:** an AE which is sufficiently discomforting to interfere with the patient's routine activities
- **Severe:** an AE which is incapacitating and prevents the pursuit of the patient's routine activities

The grading of an AE is up to the medical judgement of the Investigator and will be decided on a case-by-case basis.

7.3.2.4 Causality of AEs

The relationship of AEs to the administered IMP will be assessed by the Investigator:

- **Probable:** reports including good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable. A reaction that follows a reasonable temporal sequence from administration of the IMP; or that follows a known or expected response pattern to the suspected medicine; or that is confirmed by stopping or reducing the dosage of the medicine and that could not reasonably be explained by known characteristics of the patient's clinical state.

- **Possible:** reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example because of missing data or insufficient evidence. A reaction that follows a reasonable temporal sequence from administration of the IMP; that follows a known or expected response pattern to the suspected medicine; but that could readily have been produced by a number of other factors.
- **Unlikely:** reports not following a reasonable temporal sequence from IMP administration. An event which may have been produced by the patient's clinical state or by environmental factors or other therapies administered.
- **Not related (unrelated):** events for which sufficient information exists to conclude that the etiology is unrelated to the IMP.
- **Unclassified:** reports which for one reason or another are not assessable.

7.3.2.5 Classification of ADRs by Expectedness

ADRs will be classified by the Sponsor as either expected or unexpected:

- **Expected:** an ADR that is listed in the current edition of the Investigator's Brochure or other reference safety information.
- **Unexpected:** an ADR that is not listed in the current edition of the Investigator's Brochure or other reference safety information, or that differs because of greater severity or greater specificity.

7.3.2.6 Outcome of AEs

The outcome of all reported AEs will be documented as follows:

1. Recovered, resolved
2. Recovering, resolving
3. Not recovered, not resolved
4. Recovered, resolved with sequelae
5. Fatal
6. Unknown

NOTE: A patient's **death** per se is not an event, but an outcome. The event which resulted in the patient's death must be fully documented and reported, even in case the death occurs within 4 weeks after IMP treatment end and regardless of whether or not it is considered treatment-related.

7.3.2.7 Action(s) taken

AEs requiring action or therapy must be treated with recognized standards of medical care to protect the health and well-being of the patient. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment in an emergency situation.

The action taken by the Investigator must be documented:

a) General actions taken in the event of an AE

- None
- Medication (other than IMP) or other (eg, physical) therapy started
- Test performed
- Other (to be specified)

b) IMP-related actions taken in the event of an AE

- None
- Product withdrawn
- Dose reduced
- Dose increased

The Investigator will follow up on each AE until it has resolved or until the medical condition of the patient has stabilized. Any relevant follow-up information will be reported to the Sponsor.

7.3.2.8 Managing Hypersensitivity Reactions

Severe hypersensitivity reactions may occur during PANZYGA infusions [9]. In the case of any subject exhibiting clinical signs of severe hypersensitivity reactions to PANZYGA, the PANZYGA infusion must be immediately stopped. Each site must have Epinephrine readily available and follow their institution's standard procedure for Epinephrine administration and monitoring. If a subject develops severe hypersensitivity or anaphylactoid reactions, any further Panzyga administration should be discontinued and not resumed.

7.3.3 Serious Adverse Events

An **SAE** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (see below)
- requires hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is another important medical event

NOTE: The term 'life-threatening' refers to an event in which the patient was, in the view of the reporting Investigator, at immediate risk of death at the time of the event; it does not refer to an event which may hypothetically have caused death had it been more severe.

In deciding whether an AE/ADR is serious, medical judgment should be exercised. Thus, important AEs/ADRs that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definitions above should also be considered serious.

In addition, although not classified under the seriousness criteria, all suspected transmissions of an infectious agent should be reported as SAE. A suspected virus transmission means that virus antigen has been detected in the patient. A passive transmission of antibodies alone does not constitute a suspected virus transmission.

7.3.4 SAE Reporting Timelines

All SAEs, whether or not they are suspected to be related to study treatment, are to be reported immediately by telephone, fax, or email to the Clinical Project Manager or designee with the contact detailed provided to each site in the Investigator Site Binder. The contact details will also be communicated at the study initiation visit.

In addition, within 24 hours after recognition of the event, an Octapharma Serious Adverse Event Report must be completed and submitted to:

Octapharma's Corporate Drug Safety Unit
OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235, 1100 Vienna, Austria
Fax: [redacted]
E-mail: [redacted]

24 hours emergency telephone numbers:

[redacted] **or**
[redacted]

The Investigator must update the Octapharma Serious Adverse Event Report as soon as any additional information becomes available. The Investigator must also report SAEs to the IRB/IEC as required by local and national laws. The Investigator must maintain documentation of all communications to and from the IRB/IEC.

In accordance with 21 CFR 312.32 and local authorities, the Sponsor will submit to the FDA unexpected adverse reactions within 15 calendar days. Unexpected fatal or life-threatening adverse reactions will be submitted within 7 calendar days.

Waivers the from SAE Reporting Requirement

Waivers from the SAE reporting requirement include surgeries that are elective or were planned before study entry or prolongations of existing hospitalizations for economic or social, but not medical, reasons. Such surgeries or prolongations of hospitalizations should not be considered SAEs.

7.3.5 Laboratory Tests

Clinical laboratory parameters will be investigated during the study at the time points specified in the Flow Chart of Assessments (Table 1).

All of the study-specific laboratory tests will be performed at the local laboratories for each study site. The laboratory test and sample collection timing are specified below (Table 5).

Table 5: Laboratory Tests and Time Points

Test	Timing
Hematology (complete blood count, WBC differential, hematocrit, hemoglobin, platelet counts, reticulocytes)	During Screening (Baseline evaluation), at Days 1, 3, 5, 8, 15, 22, and at Day 32/EOS
Hemolysis (total, direct, and indirect bilirubin)	During Screening (Baseline evaluation), at Days 1, 3, 5, 8, 22, and at Day 32/EOS
Serum chemistry (ALT, AST, creatinine, Na, Ca, K, BUN, LDH)	During Screening (Baseline evaluation), Days 1, 3, 22, and at Day 32/EOS
Blood or Urine pregnancy test (females of childbearing potential)	During Screening (Baseline evaluation) and Day 32/EOS
Virology: HIV, HCV, HBV NAT	During Screening (Baseline evaluation, see Section 7.1.3)

Investigational sites will follow all site and local laboratory standard operating procedures for sample collection and handling and will provide the Sponsor with normal reference ranges and laboratory certification certificates. Upon agreement with site Principal Investigator, the IRB, and the Sponsor, Days 5, 8, 15, and 22 visits may be performed locally by the patient's primary care physician. Laboratory samples may be collected by a patient's primary care physician or by a local laboratory service (that draws, processes, and reports laboratory results) that is in the proximity of the patient's home; these samples must be analyzed according to the chosen laboratory's standard operating procedures. Normal reference ranges and laboratory certification certificates of any laboratories will also be provided to the Sponsor.

The methods of determination and normal ranges for each parameter from each local laboratory will be provided in the clinical study report.

7.3.6 Vital Signs

Vital signs will be collected at the time points specified in the Flow Chart of Assessments (Table 1) are blood pressure, body temperature, pulse rate, and respiratory rate.

On Day 1 and Day 3, vital sign measurements will be recorded before the start of the infusion and every 60 minutes (±15 minutes) thereafter until the end of the infusion. In addition, vital sign measurements will be recorded just prior to every infusion rate change (-10 minutes), 15 minutes (+15 minutes) after every infusion rate change, and approximately 30 minutes (+15 minutes) after the end of the infusion.

7.3.7 Physical Examination including Height and Body Weight.

Physical examinations will be performed at the visits specified in the Flow Chart of Assessments (Table 1).

Both height and weight will be measured at Baseline.

7.3.8 Other Relevant Safety Information

a) Post-study related safety reports

Any SAE which occurs during the study (ie, within 4 weeks after the last PANZYGA administration, which for most patients will be up to and including Day 32) will be reported by the Investigator to the Sponsor. Proactive monitoring for post-study SAEs is not required.

In case a post-study SAE is identified, the Investigator should complete an SAE form and also state the relation to the clinical study in the report.

Deaths occurring during the study (ie, within 4 weeks after the last PANZYGA administration, which for most patients will be up to and including Day 32) should also be reported, regardless of whether or not they are considered treatment-related.

b) Pregnancies

Every effort will be made to avoid a pregnancy during the use of an IMP. Pregnancies occurring during the study (fetal exposure to PANZYGA) need to be reported.

In case of pregnancy during the study, the Investigator should complete the Pregnancy Notification Form and send or fax it to the Clinical Project Manager or designee (Section 7.3.4).

Follow-up information on the outcome of both mother and fetus will be requested by a Sponsor representative.

c) Overdose, interaction, medication error and lack of efficacy

The following safety relevant information should be reported as an AE or, if the reaction fulfills one of the criteria for seriousness, as SAE.

d) Drug overdose

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol and higher than the known therapeutic dose that is of clinical relevance. The reaction must be clearly identified as an overdose.

e) Drug interaction

A drug interaction is a situation in which a substance or medicinal product affects the activity of an IMP, ie, increases or decreases its effects, or produces an effect that none of the products would exhibit on its own. The reaction must be clearly identified as a drug interaction.

f) Medication error

A medication error involves the inadvertent administration or unintended use of a medicinal product which may be caused by the naming, presentation of pharmaceutical form/packaging, or instructions for use/labelling. The reaction must be clearly identified as a medication error.

g) Lack of efficacy

Lack of efficacy is suspected when the therapeutic result is not as expected. One example of lack of efficacy could be platelets not increasing following the correct administration of IVIG.

7.4 Other Assessments

7.5 Appropriateness of Measurements

For efficacy evaluations, platelet counts provide a direct measure of the response to IGIV treatment in ITP patients and has been widely used for this purpose in many clinical trials of similar nature. The test is performed routinely at each hospital and is considered to be a reliable and robust parameter.

The definition of response used for the primary endpoint is the most established procedure to obtain a dichotomy of success/failure that can be used to calculate the response rate. It is also acceptable to US FDA and was used as the primary efficacy endpoint in their approval of PANZYGA in the treatment of chronic ITP in adults and is thus expected to best facilitate their review of the efficacy of PANZYGA in this pediatric population.

Monitoring AEs, vital signs, laboratory safety tests, and physical examinations are standard procedures used to evaluate the safety of investigational products in clinical studies.

8 DATA HANDLING AND RECORD KEEPING

8.1 Documentation of Data

8.1.1 Source Data and Records

Source data are defined as all information related to clinical findings, observations, or other activities in the study; written down in original records or certified copies of original records; or electronic medical records; allowing reconstruction and evaluation of the clinical study.

The Investigator will maintain adequate source records (eg, case histories or patient files for each patient enrolled). Source records should be preserved for the maximum period of time required by local regulations.

For each patient enrolled, the Investigator will indicate in the source record(s) that the patient is participating in this study.

All data entered in the eCRF must be supported by source data in the patient records.

The Investigator will permit study-related monitoring, audit(s), IEC/IRB review(s), and regulatory inspection(s), by providing direct access to the source data/records.

The Investigator may authorize site staff (eg, sub-Investigators, research nurses) to enter study data into the eCRF. This must be documented in the Delegation of Authority Log signed by the Investigator.

8.1.2 Electronic Case Report Forms

For each patient enrolled, an eCRF will be completed within the Electronic Data Capture (EDC) system and approved by the Investigator or an authorized sub-Investigator.

Study site staff (eg, research nurse, study coordinator, Investigator) will be responsible for entering patient data into the validated EDC system. All study site personnel will be trained on the EDC system and study-specific eCRFs prior to receiving access to the live database for data entry.

The study site will be provided with the approved eCRF Completion Guidelines to assist in data entry and data issues/questions. The study site will be notified once the eCRF is active to begin data entry. Additional site training may be provided as refreshers throughout the study, if needed. All persons allowed to enter or change eCRF data must be listed in the Delegation of Authority Log.

8.1.3 Changes to Electronic Case Report Form Data

Monitors will perform source data verification (SDV) as defined for the study.

If any errors or discrepancies in the eCRFs are found during data entry or review, discrepancies will be generated programmatically within the EDC system, and 'manual' queries will be generated by either a monitor or Data Management.

Discrepancies and queries can only be corrected by the Investigator(s) or other authorized site personnel. An audit trail documents all changes to the data over the entire study period. If the reason for a change is not obvious, a comment must be supplied in the query's response, stating the reason for the change, prior to closing. The study monitor should provide guidance to Investigator(s) and the Investigator(s)' designated representatives on making such corrections.

Once queries have been resolved by the site staff, the resolutions are assessed by Data Management. If the query response provided confirms the data as correct, the discrepancy will be closed. If the response does not adequately address the question raised, a new query will be issued for further clarification.

Manual checks will be performed, and electronic data check programs run, throughout the study until the data is clean and the database is ready for lock. All discrepancies will be resolved prior to database lock. There will be a final run of the programmed checks to ensure all discrepancies are closed out, SDV will be confirmed as complete by the monitor, and all eCRFs will be approved by the Investigator prior to database lock.

8.2 Information to Investigators

An IB will be handed out to the Investigator before the start of the study. The IB contains all information in the Sponsor's possession necessary for the Investigator to be fully and accurately informed about the safety of the IMP under evaluation and the respective benefit-risk ratio.

The IB will be updated by the Sponsor at regular intervals and whenever relevant new information concerning PANZYGA becomes available.

All participating investigators will be informed about relevant study procedures, about the methods for rating relevant study outcomes, and how to enter data into the eCRF in order to reduce discrepancies. At the study initiation visit, the eCRF will be explained to all study site staff entitled to document data in the eCRF.

The Investigator will be kept informed of important data that relate to the safe use of PANZYGA as the study proceeds.

8.3 Responsibilities

The Principal Investigator is accountable for the conduct of the clinical study. Responsibilities may be delegated to appropriately qualified persons.

A Delegation of Authority Log will be filled in and signed by the Principal Investigator. In accordance with this authority log, study site staff (eg, sub-Investigators, research nurses) are authorized to perform tasks relating to the study.

8.4 Investigator's Site File

At each study site, the Investigator is responsible for maintaining all records to enable the conduct of the study to be fully documented. Essential documents as required by GCP guidelines and regulations (eg, copies of the protocol, study approval letters, all original informed consent and assent forms, site electronic

versions of all eCRFs, drug dispensing and accountability logs, correspondence pertaining to the study) should be filed accurately and kept by the Investigator for the maximum period of time required by local regulations.

The Investigator is responsible for maintaining a confidential patient identification code list, which provides the unique link between named source records and eCRF data for the Sponsor. The Investigator must arrange for the retention of this confidential list for the maximum period of time required by local regulations.

No study document should be destroyed without prior written agreement between the Investigator and the Sponsor. Should the Investigator elect to assign the study documents to another party, or move them to another location, the Sponsor must be notified in writing.

8.5 Provision of Additional Information

On request, the Investigator will supply the Sponsor with additional data relating to the study, or copies of relevant source records, ensuring that the patient's confidentiality is maintained. This is particularly important when source documents are illegible or when errors in data transcription are encountered.

In the event of particular issues or governmental queries, it is also necessary to have access to the complete study records, provided that the patient's confidentiality is protected in accordance with applicable regulations.

8.6 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be established by the Sponsor. The IDMC will be composed of recognized experts in the fields of hematology and/or critical care who are not actively recruiting patients.

The IDMC will review relevant data periodically during the study and will give advice on the continuation, modification, or termination of the study. A written study-specific procedure will define in detail the composition, responsibilities, and procedures of the IDMC.

9 STATISTICAL METHODS AND SAMPLE SIZE

Statistical analysis will be delegated under an agreement of transfer of responsibilities to an external contract research organization (CRO). All Octapharma procedures and policies must be met by this CRO. Discrepancies or exceptions will be approved by the Sponsor's Manager of Biometrics.

9.1 Determination of Sample Size

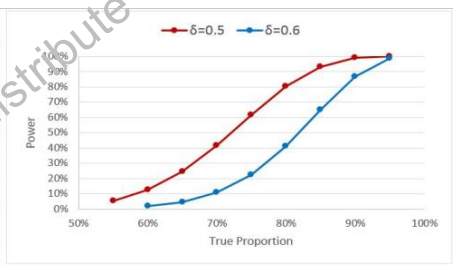
At least 20 patients who meet all eligibility criteria will be enrolled in the study.

The purpose of this study is to evaluate the efficacy and safety of PANZYGA in pediatric patients with chronic ITP; the chosen number of 20 patients to be enrolled is not derived from statistical considerations of power but driven by feasibility constraints with respect to finding pediatric ITP patient eligible and willing to participate in this study.

We expect the true proportion of responders to be comparable to results from similar studies in adult patients, as there is no published data or expert statement that would indicate otherwise. Looking at possible outcome scenarios, 20 evaluable patients give the following picture from a statistical point of view:

Power Considerations for 20 Evaluable Patients:

Responders		Exact 95% Confidence Limits		Hypothetical power to show that the true response rate is above δ (1-sided, α=0.025), given that it is in fact equal to the observed proportion	
Number	Proportion	Lower	Upper	δ=0.5	δ=0.6
11	55%	31,5%	76,9%	5,5%	
12	60%	36,1%	80,9%	12,6%	2%
13	65%	40,8%	84,6%	24,5%	4,4%
14	70%	45,7%	88,1%	41,6%	10,7%
15	75%	50,9%	91,3%	61,7%	22,5%
16	80%	56,3%	94,3%	80,4%	41,1%
17	85%	62,1%	96,8%	93,3%	64,8%
18	90%	68,3%	98,8%	98,9%	86,7%
19	95%	75,1%	99,9%	100,0%	98,4%
20	100%	83,2%	100,0%		



Even though the chosen number of 20 pediatric patients is thus not sufficient 'to power' the study, it will still allow the Sponsor to gather enough clinical evidence to obtain a sound and meaningful medical assessment of the efficacy and safety of PANZYGA in pediatric patients with chronic ITP.

9.2 Statistical Analysis

A formal statistical analysis plan describing all details of the analyses to be performed will be prepared by the study statistician and approved by the Sponsor prior to the start of the statistical analysis.

No confirmatory statistical analysis will be performed; the results of this study will be presented at the descriptive level only.

In general, and if not detailed otherwise in the Statistical Analysis Plan (SAP), all statistical presentations will be fit to the nature and type of the individual data items:

- Binary data (whether or not an event has occurred): counts and proportions
- Count data (the frequency of an event in a set time period): rate (count per unit time)

- Continuous data (measurements on a continuous scale, including quasi-continuous variables): arithmetic mean, standard deviation, median, lower and upper quartile, minimum, maximum
- Scales data (Ordinal and Non-ordinal): absolute and relative frequencies
- Time-to-event data (how long it takes to observe the outcome of interest, e.g. the initial treatment response): time to event or last evaluation (censored data in case subjects are lost to follow-up) and event rate. Such parameters may also be presented as Kaplan-Meier plots of the product-limit survival function estimates.

9.2.1 Populations for Analysis

The following populations will be considered for the statistical analysis:

- Safety Analysis Set (SAF): All patients who received at least part of 1 infusion of PANZYGA.
- Full Analysis Set (FAS): All patients in the SAF who satisfy all major eligibility criteria and for whom any post-baseline data is available. This is the set of eligible patients with treatment effects measured, according to the intention-to-treat (ITT) principle.
- Per-Protocol Set I (PP1): All patients in the FAS, excluding those with significant protocol deviations before the primary efficacy assessment on Day 8 is completed, and which may have an impact on the evaluation of the primary endpoint.
- Per-Protocol Set II (PP2): All patients in the FAS, excluding those with significant protocol violations potentially affecting the (secondary) efficacy evaluations.

Only protocol deviations with the potential to significantly affect the study results or to invalidate the interpretation of the data obtained will lead to exclusion of patients from the PP sets. The inclusion of each patient in the respective analysis populations will be determined before database lock in a data review meeting by a panel consisting of a medical expert from the Sponsor, the clinical study manager, the data manager, and the study statistician.

The analysis of safety will be based on the SAF.

The evaluation of the primary objective will be performed for the FAS (ITT analysis) and for the PP1 set (PP analysis) to assess the robustness of the results. The primary analysis will be the ITT analysis.

For secondary objectives ITT and PP2 analyses will be carried out; again the ITT analysis is considered the primary analysis and will be presented first in the report.

9.2.2 Efficacy Analysis Plan

The primary and secondary efficacy parameters will be determined on the basis of the patient's platelet concentration, listed individually, and presented descriptively.

The primary endpoint parameter 'response' is defined as an increase in platelet count at least once to ≥50x10^9/L within 7 days after the first infusion, ie, by Day 8 (increase must occur at least once on any day up to and including Day 8).

The number and proportion of responders will be presented, together with the associated exact 95% confidence intervals.

The time to reach the desired increase in platelet count as well as the duration of response and the maximum platelet levels will be presented in listings and summarized in statistical tables.

Individual profiles of platelet count over time will be presented as Trellis plots.

9.2.3 Safety Analysis Plan

The safety analysis will comprise descriptive statistics, tabulations, and listings of all TEAEs, safety laboratory results, vital signs, and physical examination findings. All reported AEs will be coded according to the Medical Dictionary for Regulatory Activities) MedDRA.

An AE is defined as treatment-emergent if first onset or worsening is after start of the first infusion of PANZYGA. Only TEAEs are accounted for in the analysis.

AEs will be record at the start of the fist infusion of PANZYGA. AEs that occur between informed consent/assent and the start of the first PANZYGA infusion will be recorded under Medical History.

Incidences of treatment-emergent AEs will be given as the number and percentage of patients who experienced any or a particular AE, including serious and drug-related AEs.

The summary tables for AEs will be given by system organ class and preferred term. Additionally, AEs will be summarized by severity and relationship to study treatment. In addition to the tables presenting incidences including all AEs, incidences will be determined for the subset of SAEs and drug-related AEs.

Incidences of infusional AEs will be given as the number and percentage of patients who experienced any or a particular infusional AE, including serious and drug-related AEs.

The summary tables for infusional AEs will be given by system organ class and preferred term. Additionally, infusional AEs will be summarized by severity and relationship to study treatment. In addition to the tables presenting incidences including all infusional AEs, incidences will be determined for the subset of SAEs and drug-related AEs.

Narratives will be prepared describing each death, other SAEs, and other significant AEs that are judged to be of special interest because of clinical importance.

For each routine laboratory parameter at each visit the actual result, the change from baseline, the out-of-range flag and the assessment of clinical relevance will be summarized descriptively.

Vital signs include systolic and diastolic blood pressure, pulse rate, body temperature and the respiratory rate; descriptive tables on the sampling statistics

of these parameters at each time point will be provided for the values as well as for their changes to baseline.

9.2.4 Handling of Missing Data

No replacement of missing data values is planned, but only observed results (and platelet counts) will be included in the analyses.

9.3 Randomization, Stratification, and Code Release

This is an open-label non-randomized study; therefore, no randomization code list or procedure for code release are required. Patients will not be stratified by age group.

9.4 Interim Analysis

No interim analysis is planned.

10 ETHICAL/REGULATORY, LEGAL AND ADMINISTRATIVE ASPECTS

10.1 Ethical/Regulatory Framework

This study will be conducted in accordance with the ethical principles laid down in the Declaration of Helsinki. The study protocol and any subsequent amendment(s) will be submitted to an IEC/ IRB and to the Regulatory Authority. The study will be conducted in compliance with the protocol, GCP guidelines, and applicable regulatory requirements.

The regulatory application or submission for regulatory approval will be made by the Sponsor or designated third party (eg, CRO) as required by national law.

10.2 Approval of Study Documents

The study protocol, a sample of the patient information and informed consent form, assent form, any other materials provided to the patient and their parent/legal guardian, and further requested information will be submitted by the Sponsor or the Investigator to the appropriate IEC/IRB and the Regulatory Authority. The study must be approved by the IEC/IRB and the Regulatory Authority before any IMP may be shipped to the study sites and any patient is exposed to a study-related procedure.

The Sponsor, the Investigator, and any third party (eg, CRO) involved in obtaining approval must inform each other in writing that all ethical and legal requirements have been met before the first patient is enrolled in the study.

10.3 Patient Information and Informed Consent

The Investigator will obtain freely given written consent from each the patient after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspect of the study which is relevant to the patient's decision to participate. The informed consent form must be signed, with name and date and time noted by the patient, before the patient is exposed to any study-related procedure, including screening tests for eligibility.

For patients not qualified to give legal consent, written consent must be obtained from the legal parent/guardian. If children are old enough to understand the risks and benefits of the study, they should also be informed and provide their written consent using an assent form.

The Investigator will explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, without any consequences for their further care and without the need to justify. The Investigator will complete the informed consent section of the CRF for each patient enrolled.

Each patient (and parent/legal guardian, as appropriate) will be informed that his/her medical (source) records may be reviewed by the study monitor, a quality assurance auditor, or a health authority inspector, in accordance with applicable regulations, and that these persons are bound by confidentiality obligations.

10.4 Protocol Amendments

Any prospective change to the protocol will be agreed between the Investigator (Co-ordinating Investigator in multi-center studies) and the Sponsor prior to its implementation. Any such amendments will be submitted to the any competent IEC/IRB and/or competent authority responsible as required by applicable regulations.

IEC/IRB approval will, at a minimum, be requested for any change to this protocol which could affect the safety of the patients, the objective/design of the study, any increase in dosage or duration of exposure to the IMP, an increase in the number of patients treated, the addition of a new test or procedure, or the dropping of a test intended to monitor safety.

10.5 Confidentiality of Patient Data

The Investigator will ensure that the patient's confidentiality is preserved. On eCRFs or any other documents submitted to the Sponsor, the patients will not be identified by their names, but by a unique patient identifier. Documents not intended for submission to the Sponsor, ie, the confidential patient identification code list, original consent and assent forms, and source records, will be maintained by the Investigator in strict confidence.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Periodic Monitoring

The monitor will contact and visit the Investigator periodically to review all study-related source data/records, verify the adherence to the protocol and the completeness, correctness and accuracy of all CRF entries compared to source data. The Investigator will cooperate with the monitor to ensure that any discrepancies identified are resolved.

For this study, the first monitoring visit shall take place shortly after the inclusion of the first patient. Thereafter, monitoring frequency will depend on study progress and in accordance with the study clinical monitoring plan.

The monitor must be given direct access to source documents (original documents, data, and records). Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the clinical study. Source data will be available for all data in the eCRFs, including all laboratory results.

11.2 Audit and Inspection

The Investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the Sponsor, or to IEC/IRB/regulatory inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and welfare of the patients have been adequately protected, and that all data relevant for the assessment of safety and efficacy of PANZYGA have been reported to the Sponsor.

12 REPORTING AND PUBLICATION

12.1 Clinical Study Report

A clinical study report (in accordance with relevant guidelines and the Sponsor's Standard Operating Procedures [SOPs]) will be prepared by the Sponsor after completion of the study. The Co-ordinating Investigator will approve the final study report after review.

12.2 Publication Policy

The results of this study may be published or presented at scientific meetings.

If the Investigator wants to publish or present study results, the Investigator agrees to inform the Sponsor and to submit all manuscripts or abstracts to the Sponsor before submission to an editorial board or scientific review committee. This will allow the Sponsor to protect proprietary information and to provide comments based on information that may not yet be available to the Investigator.

In accordance with standard editorial and ethical practice, the Sponsor will support publication of multi-center studies only in their entirety and not as individual center data. Authorship will be determined by mutual agreement.

13 LIABILITIES AND INSURANCE

In order to cover any potential damage or injury occurring to a patient in association with PANZYGA or participation in the study, the Sponsor will contract insurance in accordance with local regulations.

The Investigator is responsible for dispensing PANZYGA according to this protocol and for its secure storage and safe handling throughout the study.

14 REFERENCES

1. Diagnosis and treatment of idiopathic thrombocytopenic purpura: recommendations of the American Society of Hematology. The American Society of Hematology ITP Practice Guideline Panel. Ann.Intern.Med. 1997;126:319-326.
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4. Newland AC, Burton I, Cavenagh JD, et al: Vigam-S, a solvent/detergent-treated intravenous immunoglobulin, in idiopathic thrombocytopenic purpura. Transfus.Med. 2001;11:37-44.
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6. Neunert C, Despotovic J, Haley K, et. al. Thrombopoietin receptor agonist use in children: data from the pediatric ITP consortium of North America ICON2 study. Pediatric Blood & Cancer. 2016:63(8), 1407-1413. doi:10.1002/pbc.26003
7. European Medicines Agency, Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg). EMA/CHMP/BPWP/94033/2007 rev. 3. Retrieved from: https://www.ema.europa.eu/documents/scientific-guideline/guideline-clinical-investigation-human-normal-immunoglobulin-intravenous-administration-ivig-rev-3_en.pdf
8. American Society of Hematology 2011 Clinical Practice Guideline on the Evaluation and Management of Immune Thrombocytopenia (ITP), Quick Reference Guide.
9. PANZYGA [package insert]. Hoboken, NJ: Octapharma USA Inc; 2018.

15 APPENDICES

Not applicable.

PROTOCOL AMENDMENT #3

STUDY NUMBER: NGAM-10

STUDY TITLE: Post-Marketing Study to Evaluate the Efficacy and Safety of PANZYGA in Pediatric Patients with Chronic Immune Thrombocytopenia (ITP)

SPONSOR: Octapharma USA, Inc.
117 West Century Road
Paramus, NJ 07652

TEST PRODUCT: PANZYGA

IND / BLA NUMBERS: IND 14121 / BLA 125587

APPROVED BY: [redacted]
Octapharma Pharmazeutika ProduktionsgmbH
Oberlaaerstr. 235, A-1100 Vienna, Austria

PROTOCOL:	DATE:
Final Version 01	30 Jan 2019
Protocol Amendment #1	21 May 2019
Final Version 02	21 May 2019
Protocol Amendment #2	05 Aug 2019
Final Version 03	05 Aug 2019
Protocol Amendment #3	27 Apr 2020
Final Version 04	27 Apr 2020

Rationale for the Amendment:

In March 2020, revised in April 2020, FDA issued a COVID-19 guidance document to "…provide general considerations to assist sponsors in assuring the safety of trial participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity during the COVID-19 pandemic." (Guidance for Industry – FDA Guidance on the Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic. March 2020, rev. April 2020). The protocol has been amended to address considerations specified in the guidance document. The primary change has been to require that sites receive written approval from the Sponsor prior to enrolling patients, thereby confirming that the site has: a COVID-19 policy in place that allows patient enrollment, adequate staff available to treat and follow patients during the pandemic, the ability for the monitor to conduct remote monitoring visits, and evaluated safety risks to the patient of enrolling versus not enrolling in the study. The protocol has also been amended to specify that in the event of any circumstances that may occur, including but not limited to the COVID-19 pandemic, remote monitoring visits would be allowed.

In addition to addressing FDA COVID-19 guidance document recommendations, the following changes made throughout the protocol were considered significant:

- Patients may not be enrolled into the study without first receiving written approval by the Sponsor. Investigators must complete a study-specific form indicating that they have evaluated the risks versus benefits of patient participation during the COVID-19 pandemic and verifying that the facility has procedures in place to ensure patient safety (Section 6.1.2).
- In the event of any circumstances that may occur that prohibit on-site monitoring visits (including but not limited to the COVID-19 pandemic), remote monitoring visits would be allowed (Section 11.1).

In addition to these changes enforced to comply with the FDA COVID-19 guidance document, some other minor changes to clarify sections of the protocol as described:

- The planned study start date was amended from Q3 2019 to Q1 2020 as first patient was enrolled during Q1 2020. The study end date was not changed; therefore, recruitment time period was changed from will now be approximately 30 months to approximately 24 months.
- Inclusion Criterion #2 was modified to reflect the updated ASH Guidelines for Chronic ITP
- Inclusion Criterion #5 was modified to clarify that acceptable forms of contraception must be used throughout the study and that abstinence would be considered an acceptable form of birth control for non-sexually active females.
- Exclusion Criterion #2 was modified to include a time window surrounding the exclusionary administration of intravenous immunoglobulin or anti-D

immunoglobulin prior to the first infusion; it is now within 3 weeks (±3 days) before enrollment.

- Exclusion Criterion #6 was modified to clarify that only patients who have never responded to previous IGIV or anti-D immunoglobulin would be excluded. Patient who have responded, but may have on occasion not responded, can be enrolled.
- Clarified that the Screening/Baseline Visit may take place on the same day as Day 1. If the visits take place on the same day, Day 1 procedures do not need to be repeated prior to PANZYGA infusion.
- The protocol had specified that PANZYGA would not be administered on Day 3 if both of the following occurred: the platelet count doubled from Day 1 AND was >50x10^9/L. Per Investigator input, and in order to simplify the instructions and avoid protocol deviations, the protocol was amended such that only platelet counts would be used as the determining factor of whether or not Panzyga would be administered on Day 3. Whether or not the platelet count doubled from Screening/Baseline would not be taken into consideration.
- Additional instructions were provided to the Investigator regarding the expected body systems evaluated as part of brief versus targeted physical examinations. Brief physical examinations will include examinations of the patient's general appearance, skin, heart, lungs, abdomen, and extremities. Targeted physical examinations will be limited to targeted body systems per Investigator discretion.
- Section 4.2.2 (Prohibited Medication) added that in the event the platelet count has not reached >50x10^9/L by Day 8 prohibited medications would be allowed for patient safety.
- Section 5.5 was amended to delete the word "exact" in front of dosing: "The exact dose will be administered, and the empty and partially used vials will be retained by the site for drug accountability and dose verification." Clinics in the US recommend rounding IVIG doses to the nearest 5 grams in adults and 1 gram in children (which is within 10% of the prescribed dose). Removing "exact" will prevent the generation of protocol deviations for these small dose changes that do not affect subject safety.
- Clarified that sites may use non-PVC-free infusion bags, if PVC-free bags are not available.
- Clarified that sites may use a solution other than normal saline to flush the infusion line, per their routine procedures.
- Clarified that the study site pharmacy may follow their own drug dispensing and accountability procedures, if they are required to do so. Adherence site-specific pharmacy requirements will not be considered a protocol deviation.
- Section 9.2.2 (Efficacy Analysis Plan) was updated to reflect the most current draft Statistical Analysis Plan.

- Inconsistencies identified between protocol sections, along with grammatical, punctuation, and formatting corrections were addressed.
- Updated Sponsor address

Please see the attached redline version for documentation of these substantive changes, along with minor grammatical, formatting, punctuation, and other non-substantive changes.

AGREEMENT: These signatures constitute approval of this protocol amendment and provide the necessary assurance that the study will be conducted according to all stipulations of protocol and amendments.

Authorised person for signing the Study Protocol and Protocol Amendments on behalf of the Sponsor and Sponsor's Medical Expert:

[redacted] Date: [redacted]

[redacted]

Octapharma Pharmazeutika Prod. Ges.m.b.H.
Oberlaaerstr. 235, A-1100 Vienna, Austria
Tel: [redacted], Fax: [redacted]

[redacted] Date: [redacted]

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Octapharma USA, Inc.
117 West Century Road
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octapharma

CLINICAL STUDY PROTOCOL

NGAM-10

Post-Marketing Study to Evaluate the Efficacy and Safety of PANZYGA in Pediatric Patients with Chronic Immune Thrombocytopenia (ITP)

Investigational Product:	PANZYGA
Indication:	Chronic Immune Thrombocytopenia (ITP)
Study Design:	Prospective, open-label, single-arm, multi-center study
Sponsor:	Octapharma USA, Inc. 117 West Century Road Paramus, NJ 07652
Study Number:	NGAM-10
IND Number / BLA Number:	IND 14121 / BLA 125587
Development Phase:	Phase 4
Planned Clinical Start:	Q1 2020
Planned Clinical End:	Q1 2022
Date of Protocol:	27 Apr 2020
Version:	04 (Incorporating Amendment 3)

STUDY OUTLINE

Name of Sponsor/Company: Octapharma USA	
Name of Investigational Product: PANZYGA	**Protocol Identification Code:** NGAM-10
Name of Active Ingredient: Immune globulin human-ifas	**Date of Final Protocol:** 27Apr2020

Title of Study:

Post-Marketing Study to Evaluate the Efficacy and Safety of PANZYGA in Pediatric Patients with Chronic Immune Thrombocytopenia (ITP)

Indication:

Chronic Immune Thrombocytopenia (ITP)

Number of Study Centre(s):

Up to 8 sites in the USA

Objectives:

Primary Objective:

The primary objective is to evaluate the efficacy of PANZYGA in increasing the platelet count in pediatric patients with chronic ITP.

Secondary Objectives:

The secondary objectives of this study are to:

- Assess safety of up to 2 g/kg PANZYGA (1 g/kg PANZYGA on Day 1 and an optional dose of 1 g/kg PANZYGA on Day 3) infused in the pediatric population within the scope of the clinical study
- Determine the time to reach a platelet count of $\geq 50 \times 10^9$/L
- Determine duration of time during which the platelet count is maintained at the level $\geq 50 \times 10^9$/L
- Determine the maximum platelet count during the study

Study Design:

This is a prospective, open-label, single-arm, multicenter, Phase 4 study evaluating the efficacy and safety of PANZYGA in pediatric patients with chronic ITP.

Name of Sponsor/Company: Octapharma USA	
Name of Investigational Product: PANZYGA	**Protocol Identification Code:** NGAM-10
Name of Active Ingredient: Immune globulin human-ifas	**Date of Final Protocol:** 27Apr2020

Number of Patients:

At least 20 patients

Patient Selection Criteria:

Inclusion Criteria:

1. Females and males aged from ≥1 year to <18 years old

   Note: Patients who turn 18 years old during study participation must be re-consented at their next study visit with an adult informed consent form.
2. Confirmed diagnosis of Chronic Immune Thrombocytopenia (ITP) according to American Society of Hematology (ASH) 2019 guidelines
3. Platelets count $<30x10^9$/L at the Baseline Visit
4. Voluntarily given written informed consent (provided by patient's parent or legal guardian) and assent (provided by patient [if age-appropriate per IRB requirements])
5. Sexually active females who have been using at least 1 acceptable form of birth control for a minimum of 30 days (or a minimum of 3 months for hormonal contraceptives) prior to the Screening visit, and must agree to use at least 1 acceptable method of contraception throughout the study and for 30 days after the last dose of PANZYGA. Acceptable methods of birth control for this study include: intrauterine device (IUD), hormonal contraception, male or female condom, spermicide gel, diaphragm, sponge, or cervical cap. For non-sexually active females who have begun menstruating, abstinence is considered an acceptable method of birth control.
6. Parent or legal guardian must agree and be willing to assist the participant attend study visits, and to follow all protocol requirements and instructions of the study doctor

Exclusion Criteria:

1. Thrombocytopenia secondary to other diseases (such as Acquired Immunodeficiency Syndrome [AIDS] or systemic lupus erythematosus [SLE]), drug-related thrombocytopenia, or congenital thrombocytopenia
2. Administration of intravenous immunoglobulin (IGIV) or anti-D immunoglobulin within 3 weeks (±3 days) before enrollment

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Name of Investigational Product: PANZYGA	**Protocol Identification Code:** NGAM-10
Name of Active Ingredient: Immune globulin human-ifas	**Date of Final Protocol:** 27Apr2020

3. Administration of thrombopoietin receptor agonists when the dose has NOT been stable within 3 weeks before enrollment and a dosage change is planned before Day 32
4. Administration of oral immunosuppressants when the dose has NOT been stable during the preceding 2 months (2 weeks for long-term corticosteroid therapy) and a dosage change is planned before Day 32 (Note: topical agents and inhaled corticosteroid therapy use is permitted)
5. Administration of long-term anti-prolific agents or attenuated androgen therapy when the dose has NOT been stable during the preceding 2 months and a dosage change is planned before Day 32
6. Consistently nonresponsive to previous treatment with IGIV or anti-D immunoglobulin
7. Evidence of an active major bleeding episode at Screening
8. Splenectomy in the previous 3 months or planned splenectomy throughout the study period
9. Evans syndrome (experiencing active disease with 2 out of 3 of the following: autoimmune thrombocytopenia, autoimmune hemolytic anemia, and/or autoimmune neutropenia)
10. Known or suspected human immunodeficiency virus (HIV), hepatitis B virus (HBV), and/or hepatitis C virus (HCV) infections
11. Emergency surgery in the previous 4 weeks
12. Severe liver and/or kidney disease (alanine aminotransferase [ALT] >3x upper limit of normal (ULN), aspartate aminotransferase [AST] >3x upper limit of normal (ULN), and/or creatinine >120 µmol/L)
13. History of severe hypersensitivity to blood or plasma derived products, or any component of the PANZYGA
14. Known immunoglobulin A (IgA) deficiency and antibodies against IgA
15. History of, or suspected alcohol or drug abuse in the previous year
16. Females who are pregnant or nursing
17. Unable or unwilling to comply with the study protocol
18. Receipt of any other investigational medicinal product within 3 months before study entry

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19. Risk factors* for thromboembolic events in whom the risks outweigh the potential benefit of PANZYGA treatment.
20. Any other condition(s), that in the Investigator's opinion, make it undesirable for the patient to participate in the study or may interfere with protocol compliance.

* Risk factors include, but are not limited to: obesity, advanced age, hypertension, diabetes, a history of atherosclerosis/vascular disease or thrombotic events, hyperlipidemia, multiple cardiovascular risk factors, acquired or inherited thrombophilic disorders, prolonged periods of immobilization, severe hypovolemia, central venous catheterization, active malignancy and/or known or suspected hyperviscosity.

Test Product, Dose, and Mode of Administration:

PANZYGA (Immune Globulin, intravenous, human-ifas). PANZYGA must be stored and transported light-protected at +2°C (36°F) to +8°C (46°F) and must be brought to room temperature before use.

Patients will receive a dose of 1 g/kg body weight PANZYGA given on Day 1 and optionally another dose of 1 g/kg PANZYGA given on Day 3; body-weight dependent doses will be based on each patient's weight collected at Baseline. Total PANZYGA doses will be 1 g/kg for patients receiving only 1 dose on Day 1 and 2 g/kg for those receiving the optional Day 3 dose. Prior to the Day 3 infusion, each patient's preinfusion platelet count will be reviewed by the Investigator. If the Day 3 platelet count is $>50x10^9$/L, the Day 3 infusion **will not be** administered. If the Baseline platelet count is still $\leq 50x10^9$/L, the Day 3 infusion **will be** administered.

PANZYGA will be delivered by intravenous infusion according to the recommended flow rates:

- Initial infusion rate of 0.01 mL/kg/min (60 mg/kg/hr) for the first 30 minutes (±5 minutes)
- If tolerated, increase to 0.02 mL/kg/min (120 mg/kg/hr) for the second 30 minutes (±5 minutes)
- If tolerated, increase to 0.04 mL/kg/min (240 mg/kg/hr) for the third 30 minutes (±5 minutes)
- If tolerated, increase to 0.08 mL/kg/min (480 mg/kg/hr) for the remainder of the infusion.

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Infusion rates should not exceed 0.08 mL/kg/min and should not exceed 8.0 mL/min. The infusion rate may be gradually increased as tolerated by the patient.

If a Grade 2 or higher (moderate) infusion-related adverse event (AE) occurs during infusion, the PANZYGA infusion will be stopped. After infusion-related symptoms subside, the infusion may be resumed at a lower rate. The infusion rate may be gradually increased as tolerated by the patient.

If a Grade 1 (mild) infusion-related AE occurs during infusion, the infusion rate should be reduced to half the rate at which the event occurred, or the infusion should be interrupted until symptoms subside. The infusion may then be resumed at a rate tolerated by the patient. The batch number(s) used will be recorded in the study documentation and electronic data capture (EDC) system.

Duration of Treatment:

Screening Period: 1 week

Treatment Period: up to 3 days

Follow-up Period: 29 days

Reference Therapy, Dose, and Mode of Administration:

Not Applicable

Study Outcome Parameters (Primary and Secondary Endpoints):

Primary Endpoint:

The primary efficacy parameter is defined as an increase in platelet count at least once to ≥$50x10^9$/L within 7 days after the first infusion, ie, by Day 8 (increase must occur at least once on any day up to and including Day 8). This definition of clinical response will serve as the basis for the primary endpoint, the response rate (ie, the proportion of patients with an elevation of platelet count at least once to ≥$50x10^9$/L within 7 days [ie, by Day 8] after the first infusion).

Secondary Endpoints:

- Time to reach a platelet count of ≥$50x10^9$/L
- Duration of platelet response defined as the number of days the platelet count remains above ≥$50x10^9$/L

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Name of Investigational Product: PANZYGA	**Protocol Identification Code:** NGAM-10
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- Maximum platelet count during the study

Safety Parameters:

- AEs
- Vital signs (blood pressure, heart rate, temperature, respiratory rate)
- Physical examination
- Laboratory parameters: hematology (including reticulocytes), hemolysis, platelet count, serum chemistry (including lactase dehydrogenase [LDH]).

Study Procedures:

The study will be conducted in accordance with ICH-GCP and US FDA regulations.

The Flow Chart of Assessments specifies the procedures that will be performed at each study visit.

Baseline Visit / Screening Period

After appropriate information about the study and PANZYGA has been provided and written informed consent/assent has been obtained, patients will be evaluated for study eligibility according to the inclusion/exclusion criteria. These evaluations will include demographics, medical/surgical history, current medications, physical examinations, blood and urine samples, along with other safety and baseline evaluations as specified in the Flow Chart of Assessments.

Infusion Visits (Day 1 and Day 3)

The first PANZYGA infusion must begin no more than 2 days after Baseline evaluations have been completed and eligibility criteria have been confirmed. If Baseline and Day 1 Visits occur on the same day, Day 1 investigations do not need to be repeated. If Baseline evaluations are completed more than 2 days before Day 1, then the platelet count must be repeated and evaluated by the Investigator prior to the first infusion.

Patients who have met all of the inclusion criteria and none of the exclusion criteria will return to the study site for their first PANZYGA infusion. Required assessments will be performed as specified in the Flow Chart of Assessments, including safety evaluations before and after each infusion. Patients will remain

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Name of Investigational Product: PANZYGA	**Protocol Identification Code:** NGAM-10
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at the study site during the infusion and for about 30 minutes after the end of each infusion to complete vital sign measurements.

Patients will receive a dose of 1 g/kg body weight PANZYGA on Day 1 and optionally another dose of 1 g/kg PANZYGA on Day 3; body-weight dependent doses will be based on each patient's weight collected at Baseline. Total PANZYGA doses will be 1 g/kg for patients receiving only 1 dose on Day 1 and 2 g/kg for those receiving the optional Day 3 dose.

Prior to the Day 3 infusion, the Investigator will assess each patient's preinfusion platelet count, hematocrit, and hemoglobin. If the Day 3 platelet count is $>50x10^9$/L, the Day 3 infusion will not be administered. If the Baseline platelet count is still $\leq 50x10^9$/L, the Day 3 infusion will be administered. If any of these parameters indicate a clinically relevant change such that, in the Investigator's opinion, it is not safe to administer the second infusion the patient should be withdrawn from study treatment but will be followed for safety through Day 32.

Assessment Day 5 though Day 22

Patients will return to the study site as indicated in the Flow Chart of Assessments for continued efficacy and safety evaluations.

Day 32 (End of Study/Early Termination Visit)

Patients will return to the study site on Day 32 for final safety assessments/End of Study (EOS) visit. Patients withdrawn early from the study will be encouraged to return to the study site and complete the EOS assessments.

Statistical Analysis:

All data collected will be presented descriptively. The time to reach the desired increase in platelet count as well as the duration of response will be presented in listings and summarized in statistical tables. Individual profiles of platelet count over time will be presented as Trellis plots. The primary endpoint for this study is the proportion of patients with an increase in platelet count to ≥50x10^9/L at least once within 7 days after the first infusion. This proportion will be assessed and presented together with its associated 95% confidence interval to facilitate comparison with results from other studies and published data. Because of the limited number of patients, no formal hypothesis test will be performed; any p-value or confidence interval presented is to be understood in the exploratory sense.

All safety data, including tolerability assessments, abnormal laboratory values, and AEs will also be listed and summarized statistically.

Statistical presentations will be fit to the nature of individual data items and include sample characteristics, frequency counts and rates. Product-limit survival function estimates (Kaplan-Meier Plots), confidence intervals and graphs will be included as appropriate.

The following populations will be considered for the statistical analysis:

- Safety Analysis Set (SAF): All patients who received at least part of one infusion of PANZYGA.
- Full Analysis Set (FAS): All patients in the SAF who satisfy all major eligibility criteria and for whom any post-baseline data is available. This is the set of eligible patients with treatment effects measured, according to the intention-to-treat (ITT) principle.
- Per-Protocol Set I (PP1): All patients in the FAS, excluding those with significant protocol deviations before the primary efficacy assessment on day 8 is completed, and which may have an impact on the evaluation of the primary endpoint.
- Per-Protocol Set II (PP2): All patients in the FAS, excluding those with significant protocol violations potentially affecting the (secondary) efficacy evaluations.

Only protocol deviations with the potential to significantly affect the study results or to invalidate the interpretation of the data obtained will lead to exclusion of patients from the PP sets. The inclusion of each patient in the respective analysis populations will be determined before database lock in a data review meeting by a panel consisting of a medical expert from the Sponsor, the clinical study manager, the data manager, and the study statistician.

A detailed Statistical Analysis Plan (SAP) will be compiled as a separate document.

FLOW CHART OF ASSESSMENTS

Table 1: Flow Chart of Assessments

ASSESSMENTS	Scr / BL[1]	Day 1	Day 3	Day 5[12]	Day 8[12]	Day 15[12]	Day 22[12]	Day 32[13]
Visit Window (Days)	**-7**	**0**	**0**	**±1**	**±1**	**±3**	**±3**	**±5**
Informed Consent	X							
Inclusion / Exclusion Criteria Review	X	X						
Demographics	X							
Medical and Surgical History[2]	X							
Body Weight and Height	X							
Physical Examination	X[3]	X[3]	X[3]	X[4]	X[4]	X[4]	X[4]	X[3]
Urine or Blood Pregnancy Test (females of child-bearing potential)	X							X
Hematology: CBC with white blood cell (WBC) differential, hematocrit, hemoglobin, platelet counts[1], reticulocytes	X[1]	X[5,6]	X[5,6,7]	X	X	X	X	X
Hemolysis: total, direct, and indirect bilirubin	X	X	X	X	X	X	X	X
Serum Chemistry: ALT, AST, creatinine, Na, Ca, K, BUN, LDH	X	X	X	X	X			X
Viral markers (HIV, HCV, HBV nucleic acid test [NAT])	X[7]							
Receive Sponsor written approval prior to enrollment		X						
PANZYGA INFUSIONS		**X**	**X**[8]					
Vital Signs: heart rate, blood pressure, temperature, respiratory rate	X	X[9]	X[9]					X
AE Monitoring[10]		X	X	X	X	X	X	X
Prior and Concomitant Therapy (drug and non-drug)[11]	X	X	X	X	X	X	X	X

Abbreviations: BL = Baseline, Scr = Screening

1) All Screening Period / Baseline evaluations must be completed within 7 days of Day 1 with the following exception: Baseline samples for platelet counts must be drawn and evaluated by the Investigator no more than 2 days before the Day 1 infusion. **Note:** If Screening/Baseline and Day 1 Visits occur on the same day, the Day 1 investigations need not be repeated.
2) Medical History will be collected for the previous year and will include the onset date of ITP. Surgical history will include the date of splenectomy (if applicable), and any other surgical procedures in the previous year.
3) Brief Physical Examination: general appearance, skin, heart, lungs, abdomen, extremities.
4) Targeted Physical Examination: limited to targeted body systems per Investigator discretion.
5) Pre-infusion
6) Platelet count, hematocrit, and hemoglobin results must be available and reviewed by the Investigator prior to start of the infusion.
7) HIV/HCV/HBV NAT Test: Infusions may begin before the results are back if the Investigator is not aware of, and the patient isn't exhibiting clinical signs of, any viral infection.
8) If the Day 3 preinfusion platelet count is >50x10^9/L, the Day 3 infusion **will not be** administered. If the Baseline platelet count is still ≤50x10^9/L, the Day 3 infusion **will be** administered.
9) Vital Signs: at the start of the infusion and every 60 minutes (±15 minutes) thereafter until the end of the infusion. In addition, vital sign measurements will be recorded just prior to every infusion rate change (-10 minutes), 15 minutes (+15 minutes) after each infusion rate change, and approximately 30 minutes (+15 minutes) after the end of the infusion.
10) The start date and start time will be collected for any adverse events starting at Day 1 through Day 32/EOS visit.
11) Prior medications will be collected for the 3 months. The start date and start time will be collected for any concomitant medications taken on Day 1 through Day 32/EOS visit.
12) Days 5, 8, 15, and 22 visits may be performed locally by patient's primary care physician or a local laboratory service upon agreement with the site Principal Investigator, the IRB, and the Sponsor.
13) Day 32 visit will correspond to the Early Termination visit for patients who are withdrawn early from the study.

PROTOCOL SIGNATURES

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and applicable regulatory requirements.

[redacted]

Octapharma Pharmazeutika Produktionsgesellschaft mbH
Oberlaaerstr. 235, A-1100 Vienna, Austria
Tel: [redacted]

[redacted]

Signature

Octapharma USA, Inc.
121 River Street, Suite 1201
Hoboken, NJ, USA
Tel: [redacted]

[redacted]

Signature Date

Octapharma Pharmazeutika Produktionsgesellschaft mbH
Oberlaaerstr. 235, A-1100 Vienna, Austria
Tel: [redacted]

[redacted]

07 MAY 2020

Signature Date

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Oberlaaerstr. 235, A-1100 Vienna, Austria
Tel: [redacted]

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LIST OF ABBREVIATIONS

Abbreviation	Description
ADR	Adverse Drug Reaction
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
ASH	American Society of Hematology
AST	Aspartate Aminotransferase
CIDP	Chronic Inflammatory Demyelinating Poly(radiculo)neuropathy
CRO	Contract Research Organisation
DEHP	Diethylhexylphthalate
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOS	End of Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
ifas	4-letter meaningless suffix assigned by FDA at the end of newly approved biologics
IgA	immunoglobulin A
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITP	Immune Thrombocytopenia
ITT	Intention-to-Treat
IUD	Intrauterine device
IGIV	Intravenous Immunoglobulin
LDH	lactase dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MMN	Multifocal Motor Neuropathy
NAT	Nucleic Acid Test
PMR	Post-Marketing Requirement
PREA	Pediatric Research Equity Act
PP	Per-Protocol
PP1	Per-Protocol Set 1

Abbreviation	Description
PP2	Per-Protocol Set II
PVC	Polyvinyl Chloride
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SLE	systemic lupus erythematosus
SOP	Standard Operating Procedure
TEAE	Treatment-emergent Adverse Event
TNBP	tri-n-butyl phosphate
TPO-RA	Thrombopoietin Receptor Agonists
ULN	Upper Limit of Normal
USC	United States Code

1 INTRODUCTION

Since more than five decades immunoglobulins have been used to provide antibodies for the prevention of viral and bacterial diseases (replacement therapy) in immunocompromised patients. Within the last 25 years intravenous immunoglobulin (IGIV) has been proven to be useful in a wide variety of clinical conditions other than replacement therapy of immunocompromised patients, in which IGIV exhibits an immunomodulatory effect. These include Idiopathic Thrombocytopenic (ITP) in children and adults at high risk of bleeding or prior to surgery to correct the platelet count, Kawasaki disease, and Guillain-Barré syndrome (GBS). More recently, single IGIV brands have also been licensed for Multifocal Motor Neuropathy (MMN) and Chronic Inflammatory Demyelinating Poly(radiculo)neuropathy (CIDP). Experimental off-label use of IGIV mostly in other neurological and dermatological indications is widespread.

ITP is an immune-mediated (disorder characterized by increased platelet destruction. The reason for platelet destruction is the development of autoantibodies to platelet-membrane antigens. These antibodies are particularly produced in the spleen which is also the major site of platelet destruction [1]. In patients suffering from ITP, several studies have shown IGIV effective in increasing platelet counts to prevent or control bleeding [2-4] The mechanism of action in ITP is not fully elucidated but includes immunomodulatory effects, particularly the modulation of cytokines, soluble cytokine receptors and cytokine receptor antagonists with anti-inflammatory effects as well as complement modulation.

Broadly, 2 categories of agents are available for the treatment of ITP: 1) those that rapidly and transiently interfere with the process of platelet destruction for management of acute bleeding or bleeding risk (front-line therapies), and 2) those with potential to provide a more durable improvement in the platelet count (second-line therapies). Corticosteroids, IGIV, and anti-D immune globulin remain the mainstay of front-line treatment of acute bleeding symptoms in both adults and children [5]. Although corticosteroids remain the most commonly used ITP therapy, controversy still exists surrounding selection of agent, dosing, and duration of therapy. For treatment with prednisone, it is generally accepted that shorter courses are preferable to chronic therapy. The 2010 International Consensus Report on the investigation and management of primary ITP developed by an international working group address three classes of second-line therapies: splenectomy, rituximab, and the thrombopoietin receptor agonists (TPO-RA). Due to a relative lack of data, their use was recommended only in patients who were refractory to splenectomy and other therapies. Further study results in 2016 demonstrated that TPO-RA agents are being used in children with ITP of varying duration and severity. The response was similar to clinical trials, but the sustainability of response varied. Future studies need to focus on the ideal timing and rationale for these medications in pediatric patients [6].

PANZYGA is a human immunoglobulin solution with 10% protein content for intravenous administration. PANZYGA is made from a pool of at least 1000 donations of human fresh-frozen plasma per batch.

PANZYGA was granted a US approval by the US Food and Drug Administration (FDA) in August 2018. The license in 2 indications (primary humoral

immunodeficiency diseases and chronic immune thrombocytopenia) was granted based on 2 completed studies. The first study in Primary Immune Deficiency included 51 children and adults from ages 2 years to 65 years who were dosed at 200 mg/kg to 800 mg/kg body weight every 3 to 4 weeks for 360 days. The second study in Immune Thrombocytopenia included 40 adults with chronic ITP receiving 2 gm/kg body weight over 2 consecutive days. Of the 36 subjects in the full analysis set, 29 patients (81%: 95% CI: 64% to 92%) responded to PANZYGA with a rise in platelet count to at least $50x10^9$/L within 7 days after the first infusion.

Further information can be found in the Investigator's Brochure (IB).

1.1 Rationale for Conducting the Study

Under the Pediatric Research Equity Act (PREA) (21 United States Code [USC] 355c) all applications for new active ingredients, new indications, new dosage forms, new dosing regimens or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this required is waived, deferred or inapplicable.

This post-marketing requirement (PMR) study was requested by the US FDA after PANZYGA received marketing approval in the United States. The rationale for conducting this PMR study is to investigate the efficacy and safety of PANZYGA in children suffering from primary ITP.

The study will be conducted in compliance with the protocol, International Conference on Harmonisation-Good Clinical Practice (ICH-GCP), US FDA Code of Federal Regulations, and other local regulatory requirements.

1.2 Dose Rationale

According to recent guidelines, IGIV is recommended for patients with platelet counts $<30x10^9$/L in case of severe bleeding and/or mucous membrane bleeding. Standard doses should be studied (0.8 g/kg to1 g/kg on Day 1, which may be repeated once within 3 days, or 0.4 g/kg/day for 2 to 5 days). If other dosage regimens are to be applied for, they should be supported by clinical data. [7,8]. The dose option for this study is within the recommended guidelines.

1.3 Benefit-Risk Statement

The safety profile of IGIV is well characterized and, in general, the same type of adverse reactions may be expected for PANZYGA. No new or unknown safety problems are expected to emerge which are not already described in the Investigator's Brochure.

Data obtained from the clinical trials conducted with PANZYGA in the adult ITP population clearly met the recommended clinical response criteria for efficacy as set out in the relevant FDA and EU guidelines. These data are comparable with available literature data on other commercial IVIGs and formed the basis for marketing authorization in Europe and the US. The safety profile of PANZYGA is satisfactory and the number of infusional AEs are below the levels as

recommended by the FDA for products of this class. Efficacy and safety data with PANZYGA in 3 clinical studies in 51 patients (also including pediatric patients) with primary immunodeficiency (PID) and in 40 patients with immune thrombocytopenia (ITP) are available. Available data are sufficient to expect favorable benefit-risk profile of PANZYGA in the pediatric ITP population. Expected clinical benefit of using PANZYGA in this study is an increase in platelets level to control or prevent bleeding. The main known risks are listed below:

- Thrombosis may occur with immune globulin intravenous (IGIV) products, including PANZYGA. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.
- Renal dysfunction, acute renal failure, osmotic nephropathy, and death may occur with the administration of IGIV products in predisposed patients. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. PANZYGA does not contain sucrose.
- For patients at risk of thrombosis, renal dysfunction, or renal failure, administer PANZYGA at the minimum infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.
- Standard measures are taken to prevent infections resulting from the use of medicinal products prepared from human blood or plasma. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. During the manufacturing process of PANZYGA, significant viral reduction is obtained.

Inclusion and exclusion criteria, recommendations on the rate of infusion, dosage, and monitoring procedures provided in this protocol sufficiently mitigate above mentioned risks and must be adhered to.

No new or unknown safety problems are expected to emerge in pediatric ITP population, which are not listed above or described in the Investigator's Brochure.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objective is to evaluate the efficacy of PANZYGA in increasing the platelet count in pediatric patients with chronic ITP.

2.2 Secondary Objectives

The secondary objectives of this study are to:

- Assess safety of up to 2 g/kg PANZYGA (1 g/kg PANZYGA on Day 1 and an optional dose of 1 g/kg PANZYGA on Day 3) infused in the pediatric population within the scope of the clinical study
- Determine the time to reach a platelet count of $\geq 50 \times 10^9$/L
- Determine duration of time during which the platelet count is maintained at the level $\geq 50 \times 10^9$/L
- Determine the maximum platelet count during the study

3 INVESTIGATIONAL PLAN

3.1 Primary and Secondary Endpoints

3.1.1 Primary Endpoint

The primary efficacy parameter is defined as an increase in platelet count at least once to ≥50x10^9/L within 7 days after the first infusion, ie, by Day 8 (increase must occur at least once on any day up to and including Day 8). This definition of clinical response will serve as the basis for the primary endpoint, the response rate (ie, the proportion of patients with an elevation of platelet count at least once to ≥50x10^9/L within 7 days [ie, Day 8] after the first infusion).

3.1.2 Secondary Endpoints

Secondary endpoints are defined to further evaluate the efficacy and safety of the PANZYGA infused in the pediatric population.

The following parameters will be used to for efficacy assessments:

- Time to reach a platelet count of ≥50x10^9/L
- Duration of platelet response defined as the number of days the platelet count remains above ≥50x10^9/L
- Maximum platelet count during the study

The following parameters will be used for safety assessments:

- AEs
- Vital signs (blood pressure, heart rate, temperature, respiratory rate)
- Physical examination
- Laboratory parameters: hematology (including reticulocytes), hemolysis, platelet count, serum chemistry (including lactase dehydrogenase [LDH])

3.2 Overall Study Design and Plan

This is a prospective, open-label, single-arm, multicenter, Phase 4 study evaluating the efficacy and safety of the investigational product, PANZYGA, in pediatric patients with chronic ITP.

The study will enroll at least 20 patients ≥1 year to <18 years old and will not be stratified by age group. A patient is considered enrolled into the study after successfully completing all baseline assessments and receiving at least a partial dose of PANZYGA.

Patients with a confirmed diagnosis of chronic ITP, without evidence of active major bleeding, may be enrolled in the study after written approval of the patient by the Sponsor has been obtained. Study procedures will only begin after written informed consent (from parent or guardian) and assent (from the patient, as age appropriate per Institutional Review Board [IRB] requirements) have been obtained. Patients who meet all of the inclusion and none of the exclusion criteria may receive the first infusion of PANZYGA within 2 days after Baseline investigations have been completed.

Each patient will be administered PANZYGA by intravenous infusion at a dose of 1 g/kg body weight PANZYGA on Day 1 and optionally another dose of 1 g/kg PANZYGA on Day 3; body-weight dependent doses will be based on each patient's weight collected at Baseline. Total PANZYGA doses will be 1 g/kg for patients receiving only 1 dose on Day 1 and 2g/kg for those receiving the optional Day 3 dose. Prior to the Day 3 infusion, Investigators will assess each patient's preinfusion platelet count, hematocrit, and hemoglobin. Patients whose platelet count is $>50x10^9$/L, the Day 3 infusion will not be administered. If the Baseline platelet count is still $\leq 50x10^9$/L, the Day 3 infusion will be administered. If any parameters indicate a clinically relevant change such that, in the Investigator's opinion, it is not safe to administer the second infusion, the patient should be withdrawn from study treatment; however, the patient will be followed for safety through Day 32.

Study interventions and procedures will be performed at predefined timepoints (see Section 6.1 and the Flow Chart of Assessments [Table 1]) including (but are not limited to): blood draws for safety evaluations, vital signs, body weight, physical examinations, AE monitoring, and changes in concomitant medication use. Patients will have clinic visits on Days 1, 3, 5, 8, 15, and 22. They will return to the clinic for a final safety follow-up evaluation at Day 32/End of Study (EOS) Visit.

PANZYGA infusions may be stopped or interrupted at any time if, in the Investigator's opinion, it is not safe to continue or is not in the patient's best interest. Patients who have received a partial dose of PANZYGA should be followed for safety evaluations through Day 32/EOS.

The study is planned to begin screening procedures Q1 2020 at up to 8 sites in the USA, with recruitment lasting approximately 24 months, and is anticipated to complete in Q1 2022. The study duration for a single patient will be approximately 39 days, including up to a 1-week Screening period.

3.3 Discussion of Study Design and Choice of Control Group(s)

3.3.1 Study Design

This study was designed to meet the US FDA's requirements under the PREA (21 USC 355c) for a post-approval study of PANZYGA in the pediatric population. US FDA is requiring a pediatric study for the treatment of ITP to evaluate PANZYGA for the treatment of ITP in patients ages ≥1 year to <18 years. All of the US FDA's recommendations have been incorporated into the protocol.

This study design is also in line with study protocols evaluating NGAM in adults, with the frequency of blood draws and number of visits reduced to accommodate a pediatric population. Because of the limited number of patients that will be enrolled in this study, along with the increased blood volume and additional site visits that would be required to meet the full recommendations in the European Medicines Agency (EMA) Guideline for confirmatory visits and blood draws, the secondary efficacy endpoints were selected to allow efficacy evaluations in this patient population.

3.3.2 Control Group(s)

A placebo control group will not be included in this post-approval study. An active control group is not considered relevant, as the objective of this study is to evaluate the efficacy and safety of PANZYGA in the pediatric population, not to compare the efficacy and safety of PANZYGA versus another IGIV treatment.

3.3.3 Study Parameters

The primary therapeutic target for ITP treatment is an increase in the platelet count. Therefore, the primary endpoint chosen for the study, namely the response rate (ie, the proportion of patients with an increase in platelets at least once to $\geq 50 \times 10^9$/L within 7 days after the first infusion), is appropriate to adequately describe the efficacy of treatment of PANZYGA in the pediatric population.

To assess the efficacy of PANZYGA in correcting the platelet count, this response rate has been chosen as the primary endpoint. There are several definitions of response published in guidelines and commonly used for the evaluation of ITP treatment; however, an increase in platelets to $\geq 50 \times 10^9$/L is the most established definition of response [7] and as such has been chosen for this post-marketing approval study.

The secondary efficacy endpoints chosen are in accordance with the primary endpoint, in order to further characterize the effect on the increase in platelet count.

The safety assessments, including AE, vital signs, laboratory results, and physical examination are appropriate and commonly used parameters to monitor the of IGIV treatment during a clinical study.

4 STUDY POPULATION

4.1 Population Base

At least 20 female or male patients ≥1 year to <18 years old with chronic ITP will be eligible for this study.

4.1.1 Inclusion Criteria

Patients who meet all of the following criteria are eligible for the study:

1. Females and males aged from ≥1 year to <18 years old

   Note: Patients who turn 18 years old during study participation must be re-consented at their next study visit with an adult informed consent form.
2. Confirmed diagnosis of Chronic Immune Thrombocytopenia (ITP) according to American Society of Hematology (ASH 2019) guidelines
3. Platelets count <30x10^9/L at the Baseline Visit
4. Voluntarily given written informed consent (provided by patient's parent or legal guardian) and assent (provided by patient)
5. Sexually active females who have been using at least 1 acceptable form of birth control for a minimum of 30 days (or a minimum of 3 months for hormonal contraceptives) prior to the Screening visit, and must agree to use at least 1 acceptable method of contraception throughout the study and for 30 days after the last dose of PANZYGA. Acceptable methods include: intrauterine device (IUD), hormonal contraception, male or female condom, spermicide gel, diaphragm, sponge, or cervical cap. For non-sexually active females who have begun menstruating, abstinence is considered an acceptable method of birth control.
6. Parent or legal guardian must agree and be willing to assist the participant attend study visits, and to follow all protocol requirements and instructions of the study doctor

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria are not eligible for the study:

1. Thrombocytopenia secondary to other diseases (such as Acquired Immunodeficiency Syndrome [AIDS] or systemic lupus erythematosus [SLE]), drug-related thrombocytopenia, or congenital thrombocytopenia
2. Administration of intravenous immunoglobulin (IGIV) or anti-D immunoglobulin within 3 weeks (±3 days) before enrollment
3. Administration of thrombopoietin receptor agonists when the dose has NOT been stable within 3 weeks before enrollment and a dosage change is planned before Day 32

4. Administration of oral immunosuppressants when the dose has NOT been stable during the preceding 2 months (2 weeks for long-term corticosteroid therapy) and a dosage change is planned before Day 32 (Note: topical agents and inhaled corticosteroid therapy use is permitted)
5. Administration of long-term anti-prolific agents or attenuated androgen therapy when the dose has NOT been stable during the preceding 2 months and a dosage change is planned before Day 32
6. Consistently nonresponsive to previous treatment with IGIV or anti-D immunoglobulin
7. Evidence of an active major bleeding episode at Screening
8. Splenectomy in the previous 3 months or planned splenectomy throughout the study period
9. Evans syndrome (experiencing active disease with 2 out of 3 of the following: autoimmune thrombocytopenia, autoimmune hemolytic anemia, and/or autoimmune neutropenia)
10. Known or suspected human immunodeficiency virus (HIV), hepatitis B virus (HBV), and/or hepatitis C virus (HCV) infections
11. Emergency surgery in the previous 4 weeks
12. Severe liver and/or kidney disease (alanine aminotransferase [ALT] >3x upper limit of normal (ULN), aspartate aminotransferase [AST] >3x upper limit of normal (ULN), and/or creatinine >120 µmol/L)
13. History of severe hypersensitivity to blood or plasma derived products, or any component of the PANZYGA
14. Known immunoglobulin A (IgA) deficiency and antibodies against IgA
15. History of, or suspected, alcohol or drug abuse in the previous year
16. Females who are pregnant or nursing
17. Unable or unwilling to comply with the study protocol
18. Receipt of any other investigational medicinal product within 3 months before study entry
19. Risk factors* for thromboembolic events in whom the risks outweigh the potential benefit of PANZYGA treatment.
20. Any other condition(s), that in the Investigator's opinion, make it undesirable for the patient to participate in the study or may interfere with protocol compliance.

* Risk factors include, but are not limited to: obesity, advanced age, hypertension, diabetes, a history of atherosclerosis/vascular disease or thrombotic events, hyperlipidemia, multiple cardiovascular risk factors, acquired or inherited thrombophilic disorders, prolonged periods of immobilization, severe hypovolemia, central venous catheterization, active malignancy and/or known or suspected hyperviscosity.

4.2 Prior and Concomitant Therapy

Details on medications taken within the previous 3 months prior to the Baseline Visit and any concomitant medications taken during the study must be recorded in the electronic case report form (eCRF).

4.2.1 Allowed Pre-medications

Use of H-1 blockers or antipyretics are allowed for patients who have history of hypersensitivity to IGIV treatment; this may minimize the severity of possible infusion-related reactions in patients already predisposed to hypersensitivity reactions. All pre-medications administered prior to PANZYGA administration must be recorded in the eCRF.

4.2.2 Prohibited Medications

Use of the following medications are forbidden during the study as specified below except if used on or after Day 8 for patient safety in the event of treatment failure (ie, platelet count has not reached >50x10^9/L) (Table 2):

Table 2: Prohibited Medications

Medication	Time Window
IGIV	prohibited for 3 weeks prior to Baseline Visit through Day 32
anti-D immunoglobulin	prohibited for 3 weeks prior to Baseline Visit through Day 32
oral immunosuppressants	prohibited during Screening Period through Day 32 **unless** patients have been receiving a stable dose for 2 months (2 weeks for long-term corticosteroid therapies) prior to Screening Visit
thrombopoietin receptor agonists	prohibited during Screening Period through Day 32 **unless** patients have been receiving stable dose for 3 weeks prior to Screening Visit
long-term anti-prolific agents or attenuated androgen therapy	prohibited during Screening Period through Day 32 **unless** patients have been on a stable dose for 2 months prior to Screening Visit
any other blood or plasma-derived product*	prohibited during Screening Period through Day 32
receipt of any other investigational product	prohibited within 3 months prior to Baseline Visit through Day 32

* Patients who are non-responders or requiring emergent ITP treatment (other than PANZYGA specified in this protocol) will be followed for safety and complete all assessments through Day 32.

Trade names of drugs corresponding to the categories provided in Table 2 will be provided in the Investigator Site Binder.

4.3 Withdrawal and Replacement of Patients

4.3.1 Premature Patient Withdrawal

Patients have the right to withdraw from the study at any time for any reason, without the need to justify their decision; parents or legal guardians also have the right to withdraw a patient on the patient's behalf. The Investigator also has the right to withdraw patients in case of AEs, poor compliance, or other reasons. Because an excessive rate of withdrawals can render the study noninterpretable, any unnecessary withdrawal of patients should be avoided.

For any withdrawals after study entry, the Investigator will obtain all the required details and document the reason(s) for discontinuation. If the reason for withdrawal of a patient is an AE, the main specific event or laboratory test will be recorded, and the Investigator will make thorough efforts to clearly document the outcome. Patients should return to the study site and have all safety evaluations, including safety laboratory tests, completed as specified at the Day 32 visit (See Section 6.1.6).

4.3.2 Patient Replacement Policy

Patients withdrawn from the study will not be replaced. Under no circumstances will patients who enroll in the study be permitted to re-enroll after study completion. Patients who fail during the Screening Period (also referred to as Screen Failures) may be re-screened upon written approval from the Sponsor.

4.4 Assignment of Patients to Treatment Groups

This is an open-label non-randomized study. All patients will receive PANZYGA.

4.5 Relevant Protocol Deviations

In case of any major protocol deviation, the Investigator and Octapharma will decide on the further participation of the patient in this study after having discussed all relevant aspects.

A list of all included patients with all deviations from the intended study procedures and other criteria that may affect the patient's data validity for statistical analysis will be prepared upon clinical completion of the study. This will also be discussed by a panel consisting of the clinical study manager, a medical expert of the Sponsor, the data manager and the study statistician. This panel will decide upon the membership of the patient in the Full Analysis Set (FAS), Per Protocol (PP) Set 1 (PP2), PP Set 2 (PP2), and Safety Analysis Set for statistical analysis.

4.6 Subsequent Therapy

If a patient withdraws from the study or is withdrawn by the Investigator by their parent/legal guardian, he/she will receive treatment by the Investigator or personal physician according to institutional standard of care.

5 INVESTIGATIONAL MEDICINAL PRODUCT

5.1 Characterization of Investigational Product

Name of Medicinal Product: PANZYGA

Active ingredient of PANZYGA: Immune globulin human-ifas

Table 3: Qualitative and Quantitative Composition of PANZYGA

Name of Ingredient	Amount
Total protein	9.0 – 11.0 g/100 mL
Protein composition	≥95% Ig (≥96% Ig)*
IgG content	86 – 110 mg/mL
Glycine	15.0 – 19.5 mg/mL (17.3 mg/mL)*
Water for Injection	*ad* 1mL

* Depending on regulatory requirements

PANZYGA is a solvent/detergent (S/D)-treated, sterile preparation of highly purified immunoglobulin G (IgG) derived from large pools of human plasma. PANZYGA is a solution for infusion to be administered intravenously.

This preparation contains approximately 100 mg of protein per mL (10%), of which not less than 96% is normal human immunoglobulin G. PANZYGA contains not more than 3% aggregates, not less than 90% monomers and dimers, and not more than 3% fragments. On average, the product contains 100 µg/mL of IgA, and lower amounts of IgM.

PANZYGA contains only trace amounts of sodium, and the pH is between 4.5 and 5.0. The osmolality is in the range of 240 to 310 mosmol/kg.

The manufacturing process for PANZYGA isolates IgG without additional chemical or enzymatic modification, and the Fc portion is maintained intact. PANZYGA contains the IgG antibody activities present in the donor population. IgG subclasses are fully represented with the following approximate percentages of total IgG: IgG1 is 65%, IgG2 is 28%, IgG3 is 3% and IgG4 is 4%.

PANZYGA contains a broad spectrum of IgG antibodies against bacterial and viral agents that are capable of opsonization and neutralization of microbes and toxins. PANZYGA contains glycine (15.0 to 19.5 mg/mL), but no preservatives or sucrose.

All units of human plasma used in the manufacture of PANZYGA are provided by FDA-approved blood and plasma establishments, and are tested by FDA-licensed serological tests for HBsAg, antibodies to HCV and HIV and Nucleic Acid Test (NAT) for HCV and HIV-1 and found to be non-reactive (negative).

5.2 Packaging and Labelling

PANZYGA for investigational use only will be labeled according to US FDA regulations. Details of the labeling will be included in the Pharmacy Manual.

The batch number(s) used will be recorded in the study documentation and EDC.

5.3 Conditions for Storage and Use

PANZYGA must be stored and transported light-protected at +2°C (36°F) to +8°C (46°F) and must be brought to room temperature before use.

Storage temperature must be maintained at +2°C (36°F) to +8°C (46°F) and will be monitored for the duration of the study by reviewing the temperature logs.

PANZYGA must not be frozen prior to use.

PANZYGA must not be used after its expiry date.

PANZYGA must not be mixed with other medicinal products.

Each PANZYGA bottle is for single use only.

Authorized personnel at the individual study sites will ensure that PANZYGA is stored in appropriate conditions in a secure refrigerator with restricted access and in compliance with national regulations.

5.4 Dose and Dosing Schedule

PANZYGA will be administered by intravenous infusion. Patients should be adequately hydrated prior to infusion.

Patients will receive a dose of 1 g/kg body weight PANZYGA given on Day 1 and optionally another dose of 1 g/kg PANZYGA given on Day 3; body-weight dependent doses will be based on each patient's weight collected at Baseline. Total PANZYGA doses will be 1 g/kg for patients receiving only 1 dose on Day 1 and 2 g/kg for those receiving the optional Day 3 dose. If the Day 3 platelet count is $>50x10^9$/L, the Day 3 infusion will not be administered. If the Baseline platelet count is $\leq 50x10^9$/L, the Day 3 infusion will be administered.

PANZYGA will be delivered by intravenous infusion according to the recommended flow rates:

- Initial infusion rate of 0.01 mL/kg/min (60 mg/kg/hr) for the first 30 minutes (±5 minutes)
- If tolerated, increase to 0.02 mL/kg/min (120 mg/kg/hr) for the second 30 minutes (±5 minutes)
- If tolerated, increase to 0.04 mL/kg/min (240 mg/kg/hr) for the third 30 minutes (±5 minutes)
- If tolerated, increase to 0.08 mL/kg/min (480 mg/kg/hr) for the remainder of the infusion

Infusion rates should not exceed 0.08 mL/kg/min and should not exceed 8.0 mL/min.

If a Grade 2 (moderate) or higher infusion-related adverse event (AE) occurs during infusion, the PANZYGA infusion will be stopped. After infusion-related symptoms subside, the infusion may be resumed at a lower rate. The infusion rate may be gradually increased as tolerated by the patient.

If a Grade 1 (mild) infusion-related AE occurs during infusion, the infusion rate should be reduced to half the rate at which the event occurred, or the infusion should be interrupted until symptoms subside. The infusion may then be resumed

at an infusion rate tolerated by the patient. The infusion rate may be gradually increased as tolerated by the patient.

5.5 Preparation and Method of Administration

All patients will be infused at the study site under the surveillance of authorized study site staff.

After calculating the volume required for the dose using the patient's Baseline body weight (see Section 5.4), the appropriate number of vials will be removed from the refrigerator. Vials of different sizes may be combined to reach the required amount of IgG. The dose will be administered, and the empty and partially used vials will be retained by the site for drug accountability and dose verification.

PANZYGA vials must be allowed to warm to room or body temperature before infusion. After PANZYGA vials have been brought to room or body temperature, they should be inspected visually for particulate matter and discoloration prior to administration. The solution should be clear or slightly opalescent. DO NOT USE IF TURBID, DISCOLORATION IS OBSERVED, AND/OR FLOATING PARTICLES ARE PRESENT. Solutions that are cloudy or vials that have a deposit must not be used and must be discarded according to local policy.

Aseptic technique must be used throughout the entire procedure.

The contents of bottles must be pooled under aseptic conditions into sterile infusion bags and administered immediately after pooling. Ideally polyvinyl chloride (PVC)-free, diethylhexylphthalate (DEHP)-free and latex–free, infusion bags can be used. Once pooled, a label will be applied on the infusion bag. Detailed instructions of this process and an example label will be included in the Pharmacy Manual.

PANZYGA will be infused into a vein using standard infusion supplies provided by the individual site. Standard procedures should be followed to prime the infusion line with a priming solution (eg, normal saline). At the end of each infusion, the infusion line will be flushed with normal saline solution or with the site's routine flushing solution.

Additional information regarding PANZYGA preparation and infusion procedures will be provided in a pharmacy manual.

Please refer to special warnings and precautions for use provided in the PANZYGA Investigator Brochure.

5.6 Blinding, Emergency Envelopes, and Breaking the Study Blind

Not applicable.

5.7 Treatment Compliance

5.7.1 Drug Dispensing and Accountability

The Sponsor or designee will provide and deliver all PANZYGA to participating Investigators. A Drug Inventory and Dispensing Log will be kept current by the

Investigator, detailing the dates and quantities of PANZYGA received, dispensed to each patient, and the quantity remaining at the study site.

The Drug Inventory and Dispensing Log will be available to the monitor to verify drug accountability during the study. The study monitor will inventory all empty and partially used vials of PANZYGA and will cross-check this inventory versus the patient source documentation (records), eCRF, and the Drug Inventory and Dispensing Log.

Unused and partially used vials may be destroyed at the study site or returned to the Sponsor for destruction according to institutional practice. Vials may be destroyed only after drug accountability has been verified and fully reconciled by the monitor and after the Sponsor has granted written approval of destruction.

Additional information regarding PANZYGA drug accountability procedures will be provided in a pharmacy manual.

If a study site pharmacy is required to follow their own drug dispensing and accountability procedures, adherence to these activities will take precedence over this protocol-specific guidance and will not be considered a protocol deviation.

5.7.2 Assessment of Treatment Compliance

All patients will be infused at the study site under the surveillance of authorized study personnel. Infusion details will be documented together with the batch number(s) in the source data and eCRF.

6 STUDY CONDUCT

Procedures performed at each study visit are presented in the Flow Chart of Assessments (see Table 1). Time windows and tolerances are provided in Table 4.

6.1 Observations by Visit

6.1.1 Baseline Visit/Screening Period (Day -7 to Day 1)

The following assessments will be performed during the Screening Period. The Screening Period can last up to 1 week (to accommodate patient schedules and the informed consent/assent process); however, all Baseline evaluations should be completed within 2 days before the first administration of PANZYGA.
Note: The Baseline/Screening and Day 1 Visits may occur on the same day (see Section 6.1.2).

- Obtaining voluntarily given, written (signed and dated) informed consent and assent (as age appropriate)
- Inclusion and exclusion criteria
- Demographic and baseline characteristics
- Medical and surgical history (previous 1 year)
- Splenectomy history
- Brief physical examination
- Vital signs
- Height
- Body weight
- Blood samples for serum chemistry, hematology, and hemolysis analytes

  Note: platelet evaluations must be completed within 2 days prior to Day 1 visit.
- Blood or urine pregnancy test (females of childbearing potential, only)
- Blood samples for viral markers
- Documentation of prior medications (previous 3 months), including administration of pre-medication(s) as appropriate (see Section 4.2.1)

6.1.2 Day 1

All Baseline/Screening evaluations must be completed no more than 7 days prior to the Day 1 Visit. Patients MAY NOT BE ENROLLED until after receiving written approval by the Sponsor. **Note:** If the Baseline/Screening and Day 1 Visits occur on the same day, the Baseline/Screening investigations do not need to be repeated. If the Baseline/Screening evaluations are completed more than 2 days before Day 1, **only** the platelet count must be repeated and evaluated by the Investigator prior to initiating the first infusion.

Before the administration/infusion of PANZYGA, patient eligibility will be re-evaluated. The following assessments/activities will be performed before PANZYGA infusion:

- Confirmation of inclusion and exclusion criteria
- Brief physical examination
- Vital signs
- Blood samples for serum chemistry, hematology, and hemolysis analytes
- Administration of pre-medication(s) as appropriate (see Section 4.2.1)

The following activities will be performed during or after PANZYGA infusion:

- PANZYGA infusion
- Vital signs (at the start of the infusion and every 60 minutes (±15 minutes) thereafter until the end of the infusion. In addition, vital sign measurements will be recorded just prior to every infusion rate change (-10 minutes), 15 minutes (+15 minutes) after each infusion rate change, and approximately 30 minutes (+15 minutes) after the end of the infusion
- Monitoring for AEs
- Documentation of concomitant medication use

6.1.3 Day 3

The following assessments/activities will be performed before PANZYGA infusion:

- Brief physical examination
- Vital signs
- Blood samples for serum chemistry, hematology, and hemolysis analytes
- **NOTE:** platelet, hemoglobin and hematocrit results must be available and reviewed by the Investigator prior to initiating the Day 3 infusion
- Administration of pre-medication(s) as appropriate (see Section 4.2.1)

The Investigator will assess each patient's Day 3 preinfusion platelet count, hematocrit, and hemoglobin. If the Day 3 platelet count shows evidence of clinical response, as indicated by the platelet count being $>50x10^9$/L, the Day 3 infusion will not be administered. If the Baseline platelet count is still $\leq 50x10^9$/L, the Day 3 infusion will be administered. In the event that the Day 3 infusion is not administered, all other Day 3 assessments will still be completed. If any of these hematology parameters indicate a clinically relevant change such that, in the Investigator's opinion, it is not safe to administer the second infusion the patient should be withdrawn from study treatment but will be followed for safety through Day 32.

The following activities will be performed during or after PANZYGA infusion:

- PANZYGA infusion
- Vital signs (at the start of the infusion and every 60 minutes (±15 minutes) thereafter until the end of the infusion. In addition, vital sign measurements will be recorded just prior to every infusion rate change (-10 minutes), 15 minutes (+15 minutes) after each infusion rate change, and approximately 30 minutes (+15 minutes) after the end of the infusion
- Monitoring for AEs
- Documentation of concomitant medication use

6.1.4 Day 5 and Day 8 (± 1 day)

Day 5 and Day 8 visits and assessments may be performed locally (by patient's primary care physician or local laboratory services) upon agreement with the site Principal Investigator, the IRB, and the Sponsor. Required interactions and communication channels between the primary care physician and the Principal Investigator (eg, telemedicine or other means of electronic communication) will be outlined in the Investigator Site Binder.

The following assessments will be performed at Day 5 and Day 8:

- Targeted physical examination
- Blood samples for serum chemistry, hematology, and hemolysis analytes
- Monitoring for AEs
- Documentation of concomitant medication use

6.1.5 Day 15 and Day 22 (± 3 days)

Day 15 and Day 22 visits and assessments may be performed locally (by patient's primary care physician or local laboratory services) upon agreement with the site Principal Investigator, the IRB, and the Sponsor. Required interactions and communication channels between the primary care physician and the Principal Investigator (eg, telemedicine or other means of electronic communication) will be outlined in the Investigator Site Binder.

The following assessments will be performed at Day 15 and Day 22:

- Targeted physical examination
- Blood samples for hematology and hemolysis analytes
- Monitoring for AEs
- Documentation of concomitant medication use

6.1.6 Day 32 (End of Study Visit) (± 5 days)

Patients will return to the study site on Day 32 for final safety assessments/EOS Visit. Patients who were withdrawn early from the study should return to the study site for a final safety assessment. The following assessments will be performed:

- Brief physical examination
- Vital signs
- Blood samples for serum chemistry, hematology, and hemolysis analytes
- Blood or urine pregnancy test (females of childbearing potential, only)
- Monitoring for AEs
- Documentation of concomitant medication use

After Day 32, the clinical study is considered completed for the patient. No further study-related assessments will be performed, unless safety concerns (eg, ongoing AEs) require follow-up.

6.1.7 Visit Windows Used in this Study, including Tolerances

In this study, the following time windows and tolerances apply (Table 4):

Table 4: Visit Windows Used in this Study

Time point	Tolerance
Screening/Baseline Evaluations	7 days prior to Day 1
Baseline Platelets[1]	2 days prior to Day 1
Day 1	none
Day 3	none
Day 5	±1 day
Day 8	±1 day
Day 15 and Day 22	±3 days
Day 32	± 5 days

1) Baseline platelet evaluations must be completed and evaluated by the Investigator no more than 2 days prior to the Day 1 visit.

6.2 Duration of Study

6.2.1 Planned Duration for an Individual Patient

The duration of the entire study for each patient will be approximately 39 days, including a 7-day Screening Period.

6.2.2 Planned Duration for the Study as a Whole

The study will be considered completed when all patients have completed the Day 32 EOS Visit.

The estimated start of the study (enrollment of first patient) is Q1 2020, and the estimated end of the study (last visit of last patient) is Q1 2022.

6.2.3 Premature Termination of the Study

Both the responsible Investigators and the Sponsor reserve the right to terminate the study at any time. Should this be necessary, study close-out procedures will be arranged on an individual site basis after review and consultation by both parties. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the patients' interests.

Furthermore, the Investigator should promptly inform the IRB and provide a detailed written explanation. Pertinent regulatory authorities and IRBs will be informed in accordance with applicable regulatory requirements.

6.2.3.1 Early Termination of the Entire Clinical Study

At any time, the study as a whole will be terminated prematurely if:

- New toxicological or pharmacological findings or safety reports invalidate the earlier positive benefit-risk-assessment for the pediatric population

- Any other reason rendering the continuation of the study impossible for the Sponsor

6.2.3.2 Early Termination at an Individual Study Site

At any time, the study can be terminated at an individual study site if:

- The site cannot comply with the requirements of the protocol
- The site cannot comply with GCP or other regulatory standards
- The site does not meet the required recruitment rate

Should the study be prematurely terminated, all study materials, including PANZYGA, must be returned to the Sponsor.

7 ASSESSMENTS AND METHODS

7.1 Demographic and Baseline Information

Demographic and baseline information will be recorded during the Screening Period:

7.1.1 Demographic and Baseline characteristics

The demographic and baseline characteristics are sex, age, race and ethnic origin, height, and weight.

7.1.2 Medical and Surgical history

The medical history will be collected for the previous year and will be obtained by interviewing the patient. Records of past diseases and treatments (eg, hospital discharge letters) will be obtained for the study files, if available. The onset date of ITP will be recorded.

Surgical history will include the date of splenectomy (if applicable) and any other surgical procedures in the previous year.

7.1.3 Viral Marker Tests

At the Screening Visit, blood samples for viral markers (HIV, HCV, HBV NAT) will be collected and tested at the local laboratory according to the site's standard procedures, to rule out secondary infections that may cause ITP. Infusions may begin before the results are back if the Investigator is not aware of, and the patient isn't exhibiting clinical signs of, any viral infection.

7.1.4 Prior and Concomitant Medication Use

Prior medication use will be obtained by interview and review of patient charts (if available). Patients will be queried specifically for use of H-1 blockers or antipyretics as pre-medications prior to previous IGIV treatments.

Concomitant medication use, defined as medications with a start date and time after the start of the Day 1 infusion, will be collected throughout the study. The start date and time of medication use will be collected on Day 1 and throughout the study.

7.2 Efficacy Assessments

All efficacy assessments will be based on platelet counts performed throughout the study.

Platelet counts will be performed at Baseline (within 2 days prior to the first PANZYGA infusion), at Day 1 and Day 3 prior to planned PANZYGA infusions, and then at all remaining study visits (Days 5, 8, 15, 22, and 32).

7.3 Safety Assessments

7.3.1 Assessments for Safety Evaluations

The following assessments will be performed to evaluate the safety of PANZYGA in the pediatric population:

- AEs and Serious Adverse Events (SAEs)
- Clinical laboratory tests
- Vital signs
- Physical examinations
- Pregnancies

7.3.2 Adverse Events

7.3.2.1 Definitions

- **Adverse event (AE):** An AE is any untoward medical occurrence in a study /patient receiving an investigational medicinal product (IMP) and which 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 an IMP, whether or not related to the IMP.
- **Adverse drug reaction (ADR):** An ADR is any noxious and unintended response to an IMP related to any dose. The phrase 'response to an IMP' means that a causal relationship between the IMP and an AE carries at least a reasonable possibility (ie, the relationship cannot be ruled out).
- **Other significant AEs:** Any marked laboratory abnormalities or any AEs that lead to an intervention, including withdrawal of drug treatment, dose reduction, or significant additional concomitant therapy.
- **Treatment-emergent AE (TEAE):** Any AE that newly appeared, increased in frequency, or worsened in severity following the time of the first IMP infusion until the end of the safety follow-up period.
- **Infusional AE:** Any AE that occurs from the time of infusion and within the 72 hour period after end of infusion.
- **Withdrawal due to AE/ADR:** AE/ADR leading to discontinuation of treatment with IMP. Any such events will be followed up by the Investigator until the event is resolved or until the medical condition of the patient is stable. All follow-up information collected will be made available to the Sponsor.

7.3.2.2 Collection of AEs

AEs will be collected from the start of the first infusion on Day 1. Any illnesses captured between signing the ICF and the first infusion will be captured under medical history. The condition of the patient will be monitored throughout the study. At each visit, whether scheduled or unscheduled, AEs will be elicited using a standard nonleading question such as "How have you been since the last

visit/during the previous study period?" In addition, the Investigator will check the patient diaries (if applicable) for any documented event.

Any AE or ADR which occurs during the study will be noted in detail on the appropriate pages of the eCRF. If the patient reports several signs or symptoms representing a single syndrome or diagnosis, the diagnosis should be recorded in the eCRF. The Investigator will grade the severity of all AEs or ADRs (mild, moderate, or severe), the seriousness (non-serious or serious), and the causality as defined in Section 7.3.2.3, Section 7.3.3, and Section 7.3.2.4, respectively. The Sponsor is responsible for assessing the expectedness of each ADR (expected or unexpected) as defined in Section 7.3.2.5.

In the event of clinically significant abnormal laboratory findings, the tests will be confirmed and the patient followed until the laboratory values have returned to normal and/or an adequate explanation for the abnormality has become available.

Diseases, signs and symptoms, and/or laboratory abnormalities already present before the first administration of IMP will not be considered AEs unless an exacerbation in intensity or frequency (worsening) occurs.

The Investigator will provide detailed information about any abnormalities and about the nature of and reasons for any action taken as well as any other observations or comments that may be useful for the interpretation and understanding of an AE or ADR.

7.3.2.3 Severity of AEs

The intensity/severity of AEs will be graded as follows:

- **Mild:** an AE, usually transient, which causes discomfort but does not interfere with the patient's routine activities
- **Moderate:** an AE which is sufficiently discomforting to interfere with the patient's routine activities
- **Severe:** an AE which is incapacitating and prevents the pursuit of the patient's routine activities

The grading of an AE is up to the medical judgement of the Investigator and will be decided on a case-by-case basis.

7.3.2.4 Causality of AEs

The relationship of AEs to the administered IMP will be assessed by the Investigator:

- **Probable:** reports including good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable. A reaction that follows a reasonable temporal sequence from administration of the IMP; or that follows a known or expected response pattern to the suspected medicine; or that is confirmed by stopping or reducing the dosage of the medicine and that could not reasonably be explained by known characteristics of the patient's clinical state.

- **Possible:** reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example because of missing data or insufficient evidence. A reaction that follows a reasonable temporal sequence from administration of the IMP; that follows a known or expected response pattern to the suspected medicine; but that could readily have been produced by a number of other factors.
- **Unlikely:** reports not following a reasonable temporal sequence from IMP administration. An event which may have been produced by the patient's clinical state or by environmental factors or other therapies administered.
- **Not related (unrelated):** events for which sufficient information exists to conclude that the etiology is unrelated to the IMP.
- **Unclassified:** reports which for one reason or another are not assessable.

7.3.2.5 Classification of ADRs by Expectedness

ADRs will be classified by the Sponsor as either expected or unexpected:

- **Expected:** an ADR that is listed in the current edition of the Investigator's Brochure or other reference safety information.
- **Unexpected:** an ADR that is not listed in the current edition of the Investigator's Brochure or other reference safety information, or that differs because of greater severity or greater specificity.

7.3.2.6 Outcome of AEs

The outcome of all reported AEs will be documented as follows:

1. Recovered, resolved
2. Recovering, resolving
3. Not recovered, not resolved
4. Recovered, resolved with sequelae
5. Fatal
6. Unknown

NOTE: A patient's **death** per se is not an event, but an outcome. The event which resulted in the patient's death must be fully documented and reported, even in case the death occurs within 4 weeks after IMP treatment end and regardless of whether or not it is considered treatment-related.

7.3.2.7 Action(s) taken

AEs requiring action or therapy must be treated with recognized standards of medical care to protect the health and well-being of the patient. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment in an emergency situation.

The action taken by the Investigator must be documented:

a) General actions taken in the event of an AE

- None
- Medication (other than IMP) or other (eg, physical) therapy started
- Test performed
- Other (to be specified)

b) IMP-related actions taken in the event of an AE

- None
- Product withdrawn
- Dose reduced
- Dose increased

The Investigator will follow up on each AE until it has resolved or until the medical condition of the patient has stabilized. Any relevant follow-up information will be reported to the Sponsor.

7.3.2.8 Managing Hypersensitivity Reactions

Severe hypersensitivity reactions may occur during PANZYGA infusions [9]. In the case of any subject exhibiting clinical signs of severe hypersensitivity reactions to PANZYGA, the PANZYGA infusion must be immediately stopped. Each site must have Epinephrine readily available and follow their institution's standard procedure for Epinephrine administration and monitoring. If a subject develops severe hypersensitivity or anaphylactoid reactions, any further PANZYGA administration should be discontinued and not resumed.

7.3.3 Serious Adverse Events

An **SAE** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (see below)
- requires hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is another important medical event

NOTE: The term 'life-threatening' refers to an event in which the patient was, in the view of the reporting Investigator, at immediate risk of death at the time of the event; it does not refer to an event which may hypothetically have caused death had it been more severe.

In deciding whether an AE/ADR is serious, medical judgment should be exercised. Thus, important AEs/ADRs that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definitions above should also be considered serious.

In addition, although not classified under the seriousness criteria, all suspected transmissions of an infectious agent should be reported as SAE. A suspected virus transmission means that virus antigen has been detected in the patient. A passive transmission of antibodies alone does not constitute a suspected virus transmission.

7.3.4 SAE Reporting Timelines

All SAEs, whether or not they are suspected to be related to study treatment, are to be reported immediately by telephone, fax, or email to the Clinical Project Manager or designee with the contact detailed provided to each site in the Investigator Site Binder. The contact details will also be communicated at the study initiation visit.

In addition, within 24 hours after recognition of the event, an Octapharma Serious Adverse Event Report must be completed and submitted to:

Octapharma's Corporate Drug Safety Unit
OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235, 1100 Vienna, Austria
Fax: [redacted]
E-mail: [redacted]

24 hours emergency telephone numbers:

[redacted] **or**
[redacted]

The Investigator must update the Octapharma Serious Adverse Event Report as soon as any additional information becomes available. The Investigator must also report SAEs to the IRB/IEC as required by local and national laws. The Investigator must maintain documentation of all communications to and from the IRB/IEC.

In accordance with 21 CFR 312.32 and local authorities, the Sponsor will submit to the FDA unexpected adverse reactions within 15 calendar days. Unexpected fatal or life-threatening adverse reactions will be submitted within 7 calendar days.

Waivers the from SAE Reporting Requirement

Waivers from the SAE reporting requirement include surgeries that are elective or were planned before study entry or prolongations of existing hospitalizations for economic or social, but not medical, reasons. Such surgeries or prolongations of hospitalizations should not be considered SAEs.

7.3.5 Laboratory Tests

Clinical laboratory parameters will be investigated during the study at the time points specified in the Flow Chart of Assessments (Table 1).

All of the study-specific laboratory tests will be performed at the local laboratories for each study site. The laboratory test and sample collection timing are specified below (Table 5).

Table 5: Laboratory Tests and Time Points

Test	Timing
Hematology (complete blood count, WBC differential, hematocrit, hemoglobin, platelet counts, reticulocytes)	During Screening (Baseline evaluation), at Days 1, 3, 5, 8, 15, 22, and at Day 32/EOS
Hemolysis (total, direct, and indirect bilirubin)	During Screening (Baseline evaluation), at Days 1, 3, 5, 8, 15, 22, and at Day 32/EOS
Serum chemistry (ALT, AST, creatinine, Na, Ca, K, BUN, LDH)	During Screening (Baseline evaluation), Days 1, 3, 5, 8, and at Day 32/EOS
Blood or Urine pregnancy test (females of childbearing potential)	During Screening (Baseline evaluation) and Day 32/EOS
Virology: HIV, HCV, HBV NAT	During Screening (Baseline evaluation, see Section 7.1.3)

Investigational sites will follow all site and local laboratory standard operating procedures for sample collection and handling and will provide the Sponsor with normal reference ranges and laboratory certification certificates. Upon agreement with site Principal Investigator, the IRB, and the Sponsor, Days 5, 8, 15, and 22 visits may be performed locally by the patient's primary care physician. Laboratory samples may be collected by a patient's primary care physician or by a local laboratory service (that draws, processes, and reports laboratory results) that is in the proximity of the patient's home; these samples must be analyzed according to the chosen laboratory's standard operating procedures. Normal reference ranges and laboratory certification certificates of any laboratories will also be provided to the Sponsor and the Form FDA 1572 must be updated to include the laboratory.

The methods of determination and normal ranges for each parameter from each local laboratory will be provided in the clinical study report.

7.3.6 Vital Signs

Vital signs will be collected at the time points specified in the Flow Chart of Assessments (Table 1) are blood pressure, body temperature, pulse rate, and respiratory rate.

On Day 1 and Day 3, vital sign measurements will be recorded before the start of the infusion and every 60 minutes (±15 minutes) thereafter until the end of the infusion. In addition, vital sign measurements will be recorded just prior to every infusion rate change (-10 minutes), 15 minutes (+15 minutes) after every infusion rate change, and approximately 30 minutes (+15 minutes) after the end of the infusion.

7.3.7 Physical Examination including Height and Body Weight.

Physical examinations will be performed at the visits specified in the Flow Chart of Assessments (Table 1). A "Brief Physical Examination" will include examinations of the patient's general appearance, skin, heart, lungs, abdomen, and extremities. A "Targeted Physical Examination" will be limited to targeted body systems per Investigator discretion.

Both height and weight will be measured at Baseline, only.

7.3.8 Other Relevant Safety Information

a) Post-study related safety reports

Any SAE which occurs during the study (ie, within 4 weeks after the last PANZYGA administration, which for most patients will be up to and including Day 32) will be reported by the Investigator to the Sponsor. Proactive monitoring for post-study SAEs is not required.

In case a post-study SAE is identified, the Investigator should complete an SAE form and also state the relation to the clinical study in the report.

Deaths occurring during the study (ie, within 4 weeks after the last PANZYGA administration, which for most patients will be up to and including Day 32) should also be reported, regardless of whether or not they are considered treatment-related.

b) Pregnancies

Every effort will be made to avoid a pregnancy during the use of an IMP. Pregnancies occurring during the study (fetal exposure to PANZYGA) need to be reported.

In case of pregnancy during the study, the Investigator should complete the Pregnancy Notification Form and send or fax it to the Clinical Project Manager or designee (Section 7.3.4).

Follow-up information on the outcome of both mother and fetus will be requested by a Sponsor representative.

c) Overdose, interaction, medication error and lack of efficacy

The following safety relevant information should be reported as an AE or, if the reaction fulfills one of the criteria for seriousness, as SAE.

d) Drug overdose

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol and higher than the known therapeutic dose that is of clinical relevance. The reaction must be clearly identified as an overdose.

e) Drug interaction

A drug interaction is a situation in which a substance or medicinal product affects the activity of an IMP, ie, increases or decreases its effects, or produces an effect that none of the products would exhibit on its own. The reaction must be clearly identified as a drug interaction.

f) Medication error

A medication error involves the inadvertent administration or unintended use of a medicinal product which may be caused by the naming, presentation of pharmaceutical form/packaging, or instructions for use/labelling. The reaction must be clearly identified as a medication error.

g) Lack of efficacy

Lack of efficacy is suspected when the therapeutic result is not as expected. One example of lack of efficacy could be platelets not increasing following the correct administration of IVIG.

7.4 Other Assessments

No additional assessments have been identified.

7.5 Appropriateness of Measurements

For efficacy evaluations, platelet counts provide a direct measure of the response to IGIV treatment in ITP patients and has been widely used for this purpose in many clinical trials of similar nature. The test is performed routinely at each hospital and is considered to be a reliable and robust parameter.

The definition of response used for the primary endpoint is the most established procedure to obtain a dichotomy of success/failure that can be used to calculate the response rate. It is also acceptable to US FDA and was used as the primary efficacy endpoint in their approval of PANZYGA in the treatment of chronic ITP in adults and is thus expected to best facilitate their review of the efficacy of PANZYGA in this pediatric population.

Monitoring AEs, vital signs, laboratory safety tests, and physical examinations are standard procedures used to evaluate the safety of investigational products in clinical studies.

8 DATA HANDLING AND RECORD KEEPING

8.1 Documentation of Data

8.1.1 Source Data and Records

Source data are defined as all information related to clinical findings, observations, or other activities in the study; written down in original records or certified copies of original records; or electronic medical records; allowing reconstruction and evaluation of the clinical study.

The Investigator will maintain adequate source records (eg, case histories or patient files for each patient enrolled). Source records should be preserved for the maximum period of time required by local regulations.

For each patient enrolled, the Investigator will indicate in the source record(s) that the patient is participating in this study.

All data entered in the eCRF must be supported by source data in the patient records.

The Investigator will permit study-related monitoring, audit(s), IEC/IRB review(s), and regulatory inspection(s), by providing direct access to the source data/records.

The Investigator may authorize site staff (eg, sub-Investigators, research nurses) to enter study data into the eCRF. This must be documented in the Delegation of Authority Log signed by the Investigator.

8.1.2 Electronic Case Report Forms

For each patient enrolled, an eCRF will be completed within the Electronic Data Capture (EDC) system and approved by the Investigator or an authorized sub-Investigator.

Study site staff (eg, research nurse, study coordinator, Investigator) will be responsible for entering patient data into the validated EDC system. All study site personnel will be trained on the EDC system and study-specific eCRFs prior to receiving access to the live database for data entry.

The study site will be provided with the approved eCRF Completion Guidelines to assist in data entry and data issues/questions. The study site will be notified once the eCRF is active to begin data entry. Additional site training may be provided as refreshers throughout the study, if needed. All persons allowed to enter or change eCRF data must be listed in the Delegation of Authority Log.

8.1.3 Changes to Electronic Case Report Form Data

Monitors will perform source data verification (SDV) as defined for the study.

If any errors or discrepancies in the eCRFs are found during data entry or review, discrepancies will be generated programmatically within the EDC system, and 'manual' queries will be generated by either a monitor or Data Management.

Discrepancies and queries can only be corrected by the Investigator(s) or other authorized site personnel. An audit trail documents all changes to the data over the entire study period. If the reason for a change is not obvious, a comment must be supplied in the query's response, stating the reason for the change, prior to closing. The study monitor should provide guidance to Investigator(s) and the Investigator(s)' designated representatives on making such corrections.

Once queries have been resolved by the site staff, the resolutions are assessed by Data Management. If the query response provided confirms the data as correct, the discrepancy will be closed. If the response does not adequately address the question raised, a new query will be issued for further clarification.

Manual checks will be performed, and electronic data check programs run, throughout the study until the data is clean and the database is ready for lock. All discrepancies will be resolved prior to database lock. There will be a final run of the programmed checks to ensure all discrepancies are closed out, SDV will be confirmed as complete by the monitor, and all eCRFs will be approved by the Investigator prior to database lock.

8.2 Information to Investigators

An IB will be handed out to the Investigator before the start of the study. The IB contains all information in the Sponsor's possession necessary for the Investigator to be fully and accurately informed about the safety of the IMP under evaluation and the respective benefit-risk ratio.

The IB will be updated by the Sponsor at regular intervals and whenever relevant new information concerning PANZYGA becomes available.

All participating investigators will be informed about relevant study procedures, about the methods for rating relevant study outcomes, and how to enter data into the eCRF in order to reduce discrepancies. At the study initiation visit, the eCRF will be explained to all study site staff entitled to document data in the eCRF.

The Investigator will be kept informed of important data that relate to the safe use of PANZYGA as the study proceeds.

8.3 Responsibilities

The Principal Investigator is accountable for the conduct of the clinical study. Responsibilities may be delegated to appropriately qualified persons.

A Delegation of Authority Log will be filled in and signed by the Principal Investigator. In accordance with this authority log, study site staff (eg, sub-Investigators, research nurses) are authorized to perform tasks relating to the study.

8.4 Investigator's Site File

At each study site, the Investigator is responsible for maintaining all records to enable the conduct of the study to be fully documented. Essential documents as required by GCP guidelines and regulations (eg, copies of the protocol, study approval letters, all original informed consent and assent forms, site electronic

versions of all eCRFs, drug dispensing and accountability logs, correspondence pertaining to the study) should be filed accurately and kept by the Investigator for the maximum period of time required by local regulations.

The Investigator is responsible for maintaining a confidential patient identification code list, which provides the unique link between named source records and eCRF data for the Sponsor. The Investigator must arrange for the retention of this confidential list for the maximum period of time required by local regulations.

No study document should be destroyed without prior written agreement between the Investigator and the Sponsor. Should the Investigator elect to assign the study documents to another party, or move them to another location, the Sponsor must be notified in writing.

8.5 Provision of Additional Information

On request, the Investigator will supply the Sponsor with additional data relating to the study, or copies of relevant source records, ensuring that the patient's confidentiality is maintained. This is particularly important when source documents are illegible or when errors in data transcription are encountered.

In the event of particular issues or governmental queries, it is also necessary to have access to the complete study records, provided that the patient's confidentiality is protected in accordance with applicable regulations.

8.6 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be established by the Sponsor. The IDMC will be composed of recognized experts in the fields of hematology and/or critical care who are not actively recruiting patients.

The IDMC will review relevant data periodically during the study and will give advice on the continuation, modification, or termination of the study. A written study-specific procedure will define in detail the composition, responsibilities, and procedures of the IDMC.

9 STATISTICAL METHODS AND SAMPLE SIZE

Statistical analysis will be delegated under an agreement of transfer of responsibilities to an external contract research organization (CRO). All Octapharma procedures and policies must be met by this CRO. Discrepancies or exceptions will be approved by the Sponsor's Manager of Biometrics.

9.1 Determination of Sample Size

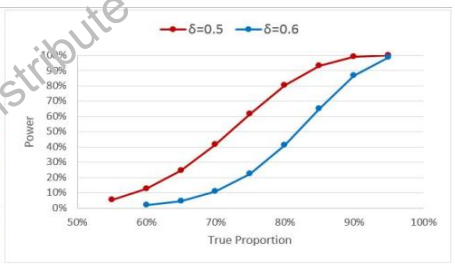
At least 20 patients who meet all eligibility criteria will be enrolled in the study.

The purpose of this study is to evaluate the efficacy and safety of PANZYGA in pediatric patients with chronic ITP; the chosen number of 20 patients to be enrolled is not derived from statistical considerations of power but driven by feasibility constraints with respect to finding pediatric ITP patient eligible and willing to participate in this study.

We expect the true proportion of responders to be comparable to results from similar studies in adult patients, as there is no published data or expert statement that would indicate otherwise. Looking at possible outcome scenarios, 20 evaluable patients give the following picture from a statistical point of view:

Power Considerations for 20 Evaluable Patients:

Responders		Exact 95% Confidence Limits		Hypothetical power to show that the true response rate is above δ (1-sided, α=0.025), given that it is in fact equal to the observed proportion	
Number	Proportion	Lower	Upper	δ=0.5	δ=0.6
11	55%	31,5%	76,9%	5,5%	
12	60%	36,1%	80,9%	12,6%	2,7%
13	65%	40,8%	84,6%	24,5%	4,4%
14	70%	45,7%	88,1%	41,6%	10,7%
15	75%	50,9%	91,3%	61,7%	22,5%
16	80%	56,3%	94,3%	80,4%	41,1%
17	85%	62,1%	96,8%	93,3%	64,8%
18	90%	68,3%	98,8%	98,9%	86,7%
19	95%	75,1%	99,9%	100,0%	98,4%
20	100%	83,2%	100,0%		



Even though the chosen number of 20 pediatric patients is thus not sufficient 'to power' the study, it will still allow the Sponsor to gather enough clinical evidence to obtain a sound and meaningful medical assessment of the efficacy and safety of PANZYGA in pediatric patients with chronic ITP.

9.2 Statistical Analysis

A formal statistical analysis plan describing all details of the analyses to be performed will be prepared by the study statistician and approved by the Sponsor prior to the start of the statistical analysis.

No confirmatory statistical analysis will be performed; the results of this study will be presented at the descriptive level only.

In general, and if not detailed otherwise in the Statistical Analysis Plan (SAP), all statistical presentations will be fit to the nature and type of the individual data items:

- Binary data (whether or not an event has occurred): counts and proportions
- Count data (the frequency of an event in a set time period): rate (count per unit time)

- Continuous data (measurements on a continuous scale, including quasi-continuous variables): arithmetic mean, standard deviation, median, lower and upper quartile, minimum, maximum
- Scales data (Ordinal and Non-ordinal): absolute and relative frequencies
- Time-to-event data (how long it takes to observe the outcome of interest, e.g. the initial treatment response): time to event or last evaluation (censored data in case subjects are lost to follow-up) and event rate. Such parameters may also be presented as Kaplan-Meier plots of the product-limit survival function estimates.

9.2.1 Populations for Analysis

The following populations will be considered for the statistical analysis:

- Safety Analysis Set (SAF): All patients who received at least part of 1 infusion of PANZYGA.
- Full Analysis Set (FAS): All patients in the SAF who satisfy all major eligibility criteria and for whom any post-baseline data is available. This is the set of eligible patients with treatment effects measured, according to the intention-to-treat (ITT) principle.
- Per-Protocol Set I (PP1): All patients in the FAS, excluding those with significant protocol deviations before the primary efficacy assessment on Day 8 is completed, and which may have an impact on the evaluation of the primary endpoint.
- Per-Protocol Set II (PP2): All patients in the FAS, excluding those with significant protocol violations potentially affecting the (secondary) efficacy evaluations.

Only protocol deviations with the potential to significantly affect the study results or to invalidate the interpretation of the data obtained will lead to exclusion of patients from the PP sets. The inclusion of each patient in the respective analysis populations will be determined before database lock in a data review meeting by a panel consisting of a medical expert from the Sponsor, the clinical study manager, the data manager, and the study statistician.

The analysis of safety will be based on the SAF.

The evaluation of the primary objective will be performed for the FAS (ITT analysis) and for the PP1 set (PP analysis) to assess the robustness of the results. The primary analysis will be the ITT analysis.

For secondary objectives ITT and PP2 analyses will be carried out; again the ITT analysis is considered the primary analysis and will be presented first in the report.

9.2.2 Efficacy Analysis Plan

The primary and secondary efficacy parameters will be determined on the basis of the patient's platelet concentration, listed individually, and presented descriptively.

Duration of platelet response is defined as the number of days the platelet count remains above ≥ $50x10^9$/L. Patients who do not drop below $50x10^9$/L after achieving ≥ $50x10^9$/L will be censored at the last evaluable assessment. Note that only patients who are responders will be included in this analysis. Though this should not occur, patients receiving emergent ITP treatment other than PANZYGA after achieving a platelet count ≥$50x10^9$/L will be censored at the time of emergent ITP treatment if the medication is administered while the patient's platelet count is ≥$50x10^9$/L. Patients receiving emergent ITP treatment other than PANZYGA prior to achieving a platelet count ≥$50x10^9$/L will not be included in this analysis.

The number and proportion of responders will be presented, together with the associated exact 95% confidence intervals.

The time to reach the desired increase in platelet count as well as the duration of response and the maximum platelet levels will be presented in listings and summarized in statistical tables.

Individual profiles of platelet count over time will be presented as Trellis plots.

9.2.3 Safety Analysis Plan

The safety analysis will comprise descriptive statistics, tabulations, and listings of all TEAEs, safety laboratory results, vital signs, and physical examination findings. All reported AEs will be coded according to the Medical Dictionary for Regulatory Activities) MedDRA.

An AE is defined as treatment-emergent if first onset or worsening is after start of the first infusion of PANZYGA. Only TEAEs are accounted for in the analysis.

AEs will be record at the start of the fist infusion of PANZYGA. AEs that occur between informed consent/assent and the start of the first PANZYGA infusion will be recorded under Medical History.

Incidences of treatment-emergent AEs will be given as the number and percentage of patients who experienced any or a particular AE, including serious and drug-related AEs.

The summary tables for AEs will be given by system organ class and preferred term. Additionally, AEs will be summarized by severity and relationship to study treatment. In addition to the tables presenting incidences including all AEs, incidences will be determined for the subset of SAEs and drug-related AEs.

Incidences of infusional AEs will be given as the number and percentage of patients who experienced any or a particular infusional AE, including serious and drug-related AEs.

The summary tables for infusional AEs will be given by system organ class and preferred term. Additionally, infusional AEs will be summarized by severity and relationship to study treatment. In addition to the tables presenting incidences including all infusional AEs, incidences will be determined for the subset of SAEs and drug-related AEs.

Narratives will be prepared describing each death, other SAEs, and other significant AEs that are judged to be of special interest because of clinical importance.

For each routine laboratory parameter at each visit the actual result, the change from baseline, the out-of-range flag and the assessment of clinical relevance will be summarized descriptively.

Vital signs include systolic and diastolic blood pressure, pulse rate, body temperature and the respiratory rate; descriptive tables on the sampling statistics of these parameters at each time point will be provided for the values as well as for their changes to baseline.

9.2.4 Handling of Missing Data

No replacement of missing data values is planned, but only observed results (and platelet counts) will be included in the analyses.

9.3 Randomization, Stratification, and Code Release

This is an open-label non-randomized study; therefore, no randomization code list or procedure for code release are required. Patients will not be stratified by age group.

9.4 Interim Analysis

No interim analysis is planned.

10 ETHICAL/REGULATORY, LEGAL AND ADMINISTRATIVE ASPECTS

10.1 Ethical/Regulatory Framework

This study will be conducted in accordance with the ethical principles laid down in the Declaration of Helsinki. The study protocol and any subsequent amendment(s) will be submitted to an IEC/ IRB and to the Regulatory Authority. The study will be conducted in compliance with the protocol, GCP guidelines, and applicable regulatory requirements.

The regulatory application or submission for regulatory approval will be made by the Sponsor or designated third party (eg, CRO) as required by national law.

10.2 Approval of Study Documents

The study protocol, a sample of the patient information and informed consent form, assent form, any other materials provided to the patient and their parent/legal guardian, and further requested information will be submitted by the Sponsor or the Investigator to the appropriate IEC/IRB and the Regulatory Authority. The study must be approved by the IEC/IRB and the Regulatory Authority before any IMP may be shipped to the study sites and any patient is exposed to a study-related procedure.

The Sponsor, the Investigator, and any third party (eg, CRO) involved in obtaining approval must inform each other in writing that all ethical and legal requirements have been met before the first patient is enrolled in the study.

10.3 Patient Information and Informed Consent

The Investigator will obtain freely given written consent from each the patient after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspect of the study which is relevant to the patient's decision to participate. The informed consent form must be signed, with name and date and time noted by the patient, before the patient is exposed to any study-related procedure, including screening tests for eligibility.

For patients not qualified to give legal consent, written consent must be obtained from the legal parent/guardian. If children are old enough to understand the risks and benefits of the study, they should also be informed and provide their written consent using an assent form.

The Investigator will explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, without any consequences for their further care and without the need to justify. The Investigator will complete the informed consent section of the CRF for each patient enrolled.

Each patient (and parent/legal guardian, as appropriate) will be informed that his/her medical (source) records may be reviewed by the study monitor, a quality assurance auditor, or a health authority inspector, in accordance with applicable regulations, and that these persons are bound by confidentiality obligations.

10.4 Protocol Amendments

Any prospective change to the protocol will be agreed between the Investigator (Co-ordinating Investigator in multi-center studies) and the Sponsor prior to its implementation. Any such amendments will be submitted to the any competent IEC/IRB and/or competent authority responsible as required by applicable regulations.

IEC/IRB approval will, at a minimum, be requested for any change to this protocol which could affect the safety of the patients, the objective/design of the study, any increase in dosage or duration of exposure to the IMP, an increase in the number of patients treated, the addition of a new test or procedure, or the dropping of a test intended to monitor safety.

10.5 Confidentiality of Patient Data

The Investigator will ensure that the patient's confidentiality is preserved. On eCRFs or any other documents submitted to the Sponsor, the patients will not be identified by their names, but by a unique patient identifier. Documents not intended for submission to the Sponsor, ie, the confidential patient identification code list, original consent and assent forms, and source records, will be maintained by the Investigator in strict confidence.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Periodic Monitoring

The monitor will contact and visit the Investigator periodically to review all study-related source data/records, verify the adherence to the protocol and the completeness, correctness and accuracy of all CRF entries compared to source data. The Investigator will cooperate with the monitor to ensure that any discrepancies identified are resolved.

For this study, the first monitoring visit shall take place shortly after the inclusion of the first patient. Thereafter, monitoring frequency will depend on study progress and in accordance with the study clinical monitoring plan.

The monitor must be given direct access to source documents (original documents, data, and records). Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the clinical study. Source data will be available for all data in the eCRFs, including all laboratory results.

In the event that federal, local, or institutional regulations or policies temporarily restrict monitors from conducting on site visits, the assigned Octapharma monitor may conduct remote monitoring visits. If this occurs, it will be documented in the monitoring reports. The Clinical Monitoring Plan will describe the requirements for remote monitoring procedures.

11.2 Audit and Inspection

The Investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the Sponsor, or to IEC/IRB/regulatory inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and welfare of the patients have been adequately protected, and that all data relevant for the assessment of safety and efficacy of PANZYGA have been reported to the Sponsor.

12 REPORTING AND PUBLICATION

12.1 Clinical Study Report

A clinical study report (in accordance with relevant guidelines and the Sponsor's Standard Operating Procedures [SOPs]) will be prepared by the Sponsor after completion of the study. The Co-ordinating Investigator will approve the final study report after review.

12.2 Publication Policy

The results of this study may be published or presented at scientific meetings.

If the Investigator wants to publish or present study results, the Investigator agrees to inform the Sponsor and to submit all manuscripts or abstracts to the Sponsor before submission to an editorial board or scientific review committee. This will allow the Sponsor to protect proprietary information and to provide comments based on information that may not yet be available to the Investigator.

In accordance with standard editorial and ethical practice, the Sponsor will support publication of multi-center studies only in their entirety and not as individual center data. Authorship will be determined by mutual agreement.

13 LIABILITIES AND INSURANCE

In order to cover any potential damage or injury occurring to a patient in association with PANZYGA or participation in the study, the Sponsor will contract insurance in accordance with local regulations.

The Investigator is responsible for dispensing PANZYGA according to this protocol and for its secure storage and safe handling throughout the study.

14 REFERENCES

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4. Newland AC, Burton I, Cavenagh JD, et al: Vigam-S, a solvent/detergent-treated intravenous immunoglobulin, in idiopathic thrombocytopenic purpura. Transfus.Med. 2001;11:37-44.
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15 APPENDICES

Not applicable.