Immunic THERAPEUTICS

CLINICAL TRIAL PROTOCOL

Randomized, double-blind, placebo-controlled, multicenter Phase 2 trial assessing the effect of IMU-838 on disease activity, as measured by magnetic resonance imaging (MRI), as well as safety and tolerability in patients with relapsing-remitting multiple sclerosis (RRMS)

(EMPhASIS)

EudraCT No:	2018-001896-19
Protocol no.:	P2-IMU-838-MS
Sponsor:	Immunic AG Lochhamer Schlag 21 82166 Graefelfing, Germany
Coordinating investigator:	Robert J. Fox, MD Staff Neurologist, Mellen Center for MS Vice-Chair for Research, Neurological Institute, Cleveland Clinic 9500 Euclid Ave, JJ-36 Cleveland, OH 44195 United States of America
Protocol version and date:	Final 3.0, 28-Aug-2020
Previous protocol versions and date:	Final 2.0, 15-Oct-2019 Final 1.0, 04-Sep-2018

REVISION CHRONOLOGY

- Original version: Version 1.0, dated 04-Sep-2018
- Version 2.0, dated 15-Oct-2019

  The following changes were included in Version 2.0 compared with Version 1.0:

  - Section 1 and Section 9.2 (Inclusion Criterion 5), and Section 11.3:

    Clarified that barrier methods of contraception include all kinds of condoms without any further specifications.
  - Section 1 and Section 9.2 (Inclusion Criterion 2 for optional extended treatment period):

    1. 24 weeks of main treatment
    2. ~~Valid~~ baseline MRI and Week 24 MRI, as well as 2 additional post-dose MRIs

    Replaced by

    1. **Completed** 24 weeks of main treatment
    2. Baseline MRI and Week 24 MRI, as well as 2 additional post-dose MRIs
  - Section 1 and Section 9.2:

    Continuation criteria for optional extended treatment period included as follows

    1. In case the initial Week 24 MRI was not evaluated at least partially assessable, availability of a repeated Week 24 MRI
    2. Week 24 MRI (initial or repeated one, if applicable) evaluated at least partially assessable
  - Section 1 and Section 9.3 (Exclusion Criterion 18), and Section 15.2.5:

    Clarified that a positive HIV-Ag/Ab test at Screening will be followed up by further HIV testing based on Nucleic Acid Amplification Technology (NAAT). A patient will only be considered HIV positive when both tests are positive.
  - Section 1 and Section 9.3 (Exclusion Criterion 18), Section 4, Section 15.2.5 and Section 15.2.6:

    – HCV replaced by HCV antibody or HCV-Ab, respectively.
  - Table 1:

    – To avoid redundancy, assessments of blood biochemistry, hematology, and urinalysis deleted for S1 as all 3 assessments are part of the screening labs, which will be done at S1.

    – Lab Kits for genotyping (G) and miR-122 (BM) assessment were listed separately.

- Under Lab Kits included that there will be **2** BM Kits at V0 because miR-122 will be assessed 2x at V0, at 0 and 4 hours after first IMP administration.
- Clarified that the extended treatment period can be blinded or unblinded (respective heading and footnote added).
- Included that the Week 24 MRI can be repeated if the initial MRI was not at least partially assessable.
- Time window for V2 (Week 6) changed from ±7 days to -7/+4 days, because the amount of IMP supplied at V1 lasts only for a maximum of 46 days.

o Section 1, Section 7.2:

- 'Time to relapse at time of final analysis of main part' added as secondary efficacy endpoint.
- Time periods for 'mean annualized relapse rate' specified i.e. 'during main and extended treatment period.'
- Timepoints to assess 'proportion of relapse-free patients' changed from '12-week intervals' to 'up to Week 24 and at extended periods thereafter.'
- All 3 endpoints above combined to 'relapse-related clinical endpoints, assessed for and compared between all individual treatments and between the pooled 30 mg/day and 45 mg/day groups and placebo.'
- 'Time to treatment discontinuation for any reason' and 'Rate of treatment discontinuations up to Week 24' added as secondary safety endpoints.

o Section 1 and Section 22:

Trial periods adjusted as recruitment was much faster than expected.

o Section 2 and Section 6:

- Outside vendors were added for HIV testing based on the NAAT and population PK modeling.
- Contact details were updated for IMGM Laboratories (only Section 2).

o Section 4 (definition of MS relapse) and Section 13.2:

- Bullet 1: 'Neurological abnormality…' replaced by 'Neurological deficit…'
- Paresthesia deleted in 'The occurrence of ~~paresthesia,~~ fatigue, mental symptoms, and/or vegetative symptoms without any additional symptom will not classify as a relapse,' because paresthesia is the most common manifestation of a relapse.

- Section 5.1.1 (3rd paragraph):

  'Genetic susceptibility plays a role in disease initiation [5,6] but currently unidentified environmental factors are also involved. [7]'

  Replaced by

  'A genetic basis plays a role in susceptibility to MS [5,6] and environmental factors such as hypovitaminosis D and Epstein-Bar virus infections have been identified. [7]'

- Section 5.1.2 and Section 9.3:

  For consistency reasons MOG-IgG-associated encephalomyelitis replaced by MOG-associated encephalomyelitis.

- Section 5.3 (2nd paragraph):

  'In a Phase 2 trial of teriflunomide on patients with relapsing forms of MS, a statistically significant decrease in combined unique active (CUA) lesions was observed with teriflunomide compared to placebo after ~~1~~ week of treatment.'

  Corrected to:

  'In a Phase 2 trial of teriflunomide on patients with relapsing forms of MS, a statistically significant decrease in combined unique active (CUA) lesions was observed with teriflunomide compared to placebo after **12** weeks of treatment.'

- Section 8.2 (6th paragraph):

  Brackets in 'The schedule of MRI testing selected is more frequent (every 6 weeks) than usually used in clinical routine, as Gd+ lesions offer the best evidence of recent inflammatory white matter lesions ~~(which cause clinical attacks)~~.' removed since not every white matter lesion causes a clinical attack.

- Section 10.5:

  Patient identifier changed from 'YY-XXZZ' to 'YYXX-ZZ.'

- Section 12.2:

  To avoid confusion 'evaluating physician' was replaced by 'independent MRI reader' in the following sentence under Screening Visit 2:

  'The quality of the baseline MRI will be assessed centrally and may be repeated as soon as possible, if considered necessary by the ~~evaluating physician~~ **independent MRI reader.**'

- Section 12.3 under Visit 5/EoMT (Week 24):

  Added that the Week 24 MRI can be repeated if it turns out to be not at least partially assessable and that patients without an at least assessable Week 24 MRI (initial or repeated one) must be withdrawn from the extended treatment period.

- Section 13.4:
  - Added that the treating physician will also be informed about the results of the central MRI assessment in case of any unexpected finding on the MRI likely not related to the underlying MS disease.
  - MRI restriction rules, Bullet 3a:To be consistent with Section 12.2 (Re-screening) the time window for re-screening changed from '…re-screened earliest 30 days after the end of the MS attack ' to '…re-screened earliest 30 days after the onset of the MS attack…'
- Section 14.2.1:

  'Neurofilaments ~~are indicative of neurodegenerative disease~~ and will be assessed as detailed in Table 1' replaced by 'Neurofilaments **light chain are an emerging serum biomarker for acute and chronic neuronal damage** and will be assessed as detailed in Table 1.'
- Section 14.2.3 and Section 15.2.4:

  Lab Kit G/BM replaced by either Lab Kit G (for genotyping) or Lab Kit BM (for miR-122).
- Section 15.1.1.3:

  Clarified that 'new malignancies that occur during the participation in the trial are defined as important medical events and must be reported as SAEs.'
- Section 15.2.6:

  Missing parameters (i.e. lymphocytes and eGFR [CKD-EPI]) in Lab Kit S included; in 2nd bullet 'hematology' added.
- Section 17, patient withdrawal:
  - To clarify that the listed reasons for withdrawal represent stopping rules for a patient, the following was added before the withdrawal reasons: 'Patients will be withdrawn from the study for any of the following reasons'.
- To increase consistency, 'steroid' and 'glucocorticosteroid' replaced by 'corticosteroid'.
- Editorial changes.

- Version 3.0, dated 28-Aug-2020

  The protocol was primarily amended to include a Cohort 2 sub-trial with the objective to obtain more data for pharmacodynamic modelling of IMU-838 by evaluating a lower IMU-838 dose in the presumed effective dose range, i.e. 10 mg/day IMU-838. The analysis of the main treatment period showed equal safety and efficacy between the 30 mg/day and 45 mg/day doses. The sub-trial will be randomized, double-blind and placebo-controlled

with patients being randomized 1:4 to placebo and 10 mg/day IMU-838 for 24 weeks. The total number of patients will be approximately 60. Based on the results from an interim analysis of the ongoing Trial P2-IMU-838-UC, the 10 mg dose is part of the possible effective dose range of IMU-838 in immunological diseases. Assessments and procedures will mostly follow those described for the main treatment period in the main trial. An unblinded interim analysis on main parameters is planned to be performed after 12 weeks of treatment. Details of this Cohort 2 sub-trial study are described in an Appendix (Appendix 3) and a summary is included in Section 1. *This Cohort 2 sub-trial will not be valid in Romania*.

Additional changes included in Version 3.0 compared with Version 2.0 were:

- Title page and Section 2:

  Sponsor address changed.
- Table 1:
  - Clarified that blood collection to determine IMU-838 trough levels at EoT will only be performed until the last patient in the Cohort 2 sub-trial has completed the last sub-trial visit.
  - Description of visits for patients continuing from Cohort 2 was added.
- Section 1 and Section 22:

  Trial duration adjusted.
- Section 4

  Updated
- Section 6

  Additional eCRF provider added
- Section 11.2.3:

  Added that special care must be taken if ibuprofen is used as concomitant medication and whenever possible therapeutic alternatives should be used.
- Section 15.2:

  Clarified that clinically significantly abnormal values must be reported as AE, unless there are known circumstances unrelated to a disease or the medication (such as patient activities or sample handling) that are a likely explanations for the abnormal value.
- Section 15.2.2.1

  Added that serum samples collected at Baseline, stored but not used for the primary analysis (“B-sample”), may be used in future research to evaluate other MS related serum markers (e.g. Epstein-Barr Virus) and address MS-related research questions that may arise after trial completion.

- Editorial changes

1 Summary and flow chart

Trial code
P2-IMU-838-MS

Title of the trial
Randomized, double-blind, placebo-controlled, multicenter Phase 2 trial assessing the effect of IMU-838 on disease activity, as measured by magnetic resonance imaging (MRI), as well as safety and tolerability in patients with relapsing-remitting multiple sclerosis (RRMS)

Short title
Phas**E** 2 **M**RI trial to ex**P**lore t**h**e effic**A**cy and **S**afety of **I**MU-838 in relapsing remitting multiple **S**clerosis (EMPhASIS)

Principal investigators and trial centers
Planned: about 40 centers in Romania, Bulgaria, Ukraine, and Poland; potential additional centers in Hungary and Croatia

Coordinating investigator: Robert J. Fox, MD, Cleveland Clinic, Cleveland, United States of America

Clinical phase: 2

Trial duration

Cohort 1:

Actual start:	February 2019 (first patient in)
Actual recruitment period:	8 months
Actual end main treatment period:	April 2020 (main part: last patient out)
Estimated end extended treatment period:	December 2029 (last patient end-of-study [EoS] visit)

Cohort 2 (Planned, *not valid in Romania***):**

Estimated start:	October 2020 (first patient in)
Estimated recruitment period:	3 months
Estimated interim analysis:	March 2021 (main part: last patient completing Week 12 assessments)
Estimated end main treatment period:	May 2021 (main part: last patient out)
Estimated end extended treatment period:	December 2029 (last patient EoS visit)

Trial periods
Screening, main treatment period, optional extended treatment period

Trial objectives

Primary

- To evaluate the efficacy of 45 mg/day IMU-838 in the treatment of RRMS based on MRI assessments

Secondary

- To evaluate the efficacy of 30 mg/day IMU-838 in the treatment of RRMS based on MRI assessments
- To evaluate the safety and tolerability of 30 mg/day and 45 mg/day IMU-838 in RRMS patients

Tertiary

- To evaluate pharmacodynamic (PD) effects of IMU-838 in RRMS patients
- To evaluate IMU-838 trough values and population pharmacokinetics (PK)
- To evaluate the effects of IMU-838 on treatment satisfaction in patients with RRMS

Methodology

This is a Phase 2 multicenter, double-blind, placebo-controlled, randomized, parallel-group trial to assess the efficacy and safety of 2 once-daily oral doses of IMU-838 (30 mg/day and 45 mg/day) in patients with RRMS and evidence of active disease.

The trial consists of a screening period, a blinded 24-week main treatment period, and an optional initially blinded, then open-label extended treatment period of up to 9.5 years.

The trial includes 2 patient cohorts:

- Cohort 1 main trial: main Phase 2 trial with assessment of primary and key secondary endpoints.
- Cohort 2 sub-trial: additional sub-trial with a small double-blind, placebo-controlled, randomized, parallel-group assessment of a low IMU-838 dose (i.e. 10 mg/day) to provide additional data for pharmacodynamic modelling. No formal statistical analysis will be performed, however in addition to analysis of Cohort 2 a pooled exploration of Cohorts 1 and 2 for pharmacodynamic modeling will be performed *(this Cohort 2 sub-trial will not be valid in Romania)*.

Screening period

After the patient provided written informed consent, eligibility criteria will be checked and screening laboratory tests as well as a physical examination (including vital signs and electrocardiogram [ECG]) will be performed (Screening Visit 1).

For eligible patients based on the assessments of Screening Visit 1, a baseline MRI (Screening Visit 2) will be performed which will serve as MRI reference for subsequent MRI assessments during the main treatment period. The quality of the baseline MRI will be evaluated by a central independent MRI reader; if the quality of the MRI is unacceptable, the baseline MRI may be repeated once per patient, and the repeated MRI will be used as baseline MRI. The central independent MRI reader will also assess the presence of Gadolinium-enhancing (Gd+) lesions as well as the number and volume of T2 lesions on the baseline MRI.

Main treatment period

On Day 0, eligible patients will be randomized in a 1:1:1 ratio to once-daily oral treatment with 30 mg IMU-838 or 45 mg IMU-838, or placebo for 24 weeks. All patients will receive half the assigned dose during the first 7 days of the main treatment period (1 tablet per day) and then start taking the full assigned dose from Day 7 onwards (2 tablets once daily). Clinic visits after Day 0 during the main treatment period will be scheduled at Day 7, and at Weeks 6, 12, 18, and 24, including trial MRI examinations at Weeks 6, 12, 18, and 24. At Week 24 (end-of-main treatment period, EoMT), patients will have the option to continue into the extended treatment period if they meet respective eligibility criteria including an MRI at Week 24 (*see Inclusion criteria for optional extended treatment period and Exclusion criteria for optional extended treatment period).*

Extended treatment period (optional)

During the extended treatment period, patients will receive 30 mg/day or 45 mg/day IMU-838 for up to 9.5 years. All patients will be randomized. Patients receiving placebo will be randomized to 30 or 45 mg/day IMU-838. Patients on active treatment during the main treatment period will be randomized to continue their previous treatment assignment. Identical to the start of the main treatment period, all patients will receive half the assigned dose during the first 7 days of the extended treatment period and will then continue with the full assigned dose.

Clinic visits during the extended treatment period will be scheduled every 12 weeks.

Once the results of the main treatment period are available, investigators and patients currently in the extended treatment period will be unblinded and investigators will receive a top-line summary of trial results of the main treatment period. Considering these results, investigators may then recommend switching the dose for those patients currently remaining in the extended treatment period after time of study unblinding or thereafter (after discussion and in consultation with the patient). A potential dose switch can occur several times and at any clinic visit. A dose switch may allow patients to switch to a more effective dose or to an equally effective dose but with a lower risk for adverse events (AEs).

If at any time during this trial (main and extended treatment periods) a patient experiences between scheduled clinic visits symptoms indicative for a multiple sclerosis (MS) relapse or a clinically

relevant AE, which in the investigator's opinion requires additional safety assessments, the patient will be appropriately assessed at an unscheduled clinic visit.

End-of-study visit

All patients discontinuing treatment, as scheduled or prematurely, will undergo an EoS visit 30 days (+14 days) after last investigational medicinal product (IMP) administration.

Cohort 2 sub-trial

The objective of the Cohort 2 sub-trial is to obtain exploratory data on the dose response of IMU-838 by evaluating a lower IMU-838 dose i.e. 10 mg/day to provide additional data for pharmacodynamic modelling. The sub-trial will be randomized, double-blind and placebo-controlled with patients being randomized 1:4 to placebo and 10 mg/day IMU-838 for 24 weeks. The total number of patients will be approximately 60. Assessments and procedures will mostly follow those described for the main treatment period in the main trial. Only MRI machines with a field strength of 1.5 Tesla will be allowed (the main trial allowed ≥1.5 Tesla). In addition, an unblinded interim analysis of selected MRI data is planned to be performed after 12 weeks of treatment. Details of this sub-trial are described in an appendix and will not be further referred to in this synopsis *(this Cohort 2 sub-trial will not be valid in Romania)*.

Treatments

Test product

IMU-838 (vidofludimus calcium), a small molecule inhibitor of dihydroorotate dehydrogenase (DHODH)

Formulation:	Tablets with 15 mg and 22.5 mg IMU-838
Administration:	Tablets will be taken once daily
Main treatment period:	
Days 0 to 6:	1 tablet once daily, i.e. 15 mg/day or 22.5 mg/day IMU-838
Day 7 to Week 24 (EoMT):	2 tablets once daily, i.e. 30 mg/day or 45 mg/day IMU-838
Extended treatment period:	
Days 0 to 6:	1 tablet once daily, i.e. 15 mg/day or 22.5 mg/day IMU-838
Day 7 to end-of-treatment:	2 tablets once daily, i.e. 30 mg/day or 45 mg/day IMU-838

Reference product (only applicable during main period)

Matching placebo, once-daily oral administration of 1 or 2 tablets, as described for the test product

Administration

Tablets will be taken once daily in the morning in fasted state (no food after midnight, unrestricted intake of water is always allowed) and taken with a glass of water approximately 15 minutes to 1 hour before breakfast.

Number of patients (total and for each treatment) planned

In total, 195 patients are planned to be randomized 1:1:1 to treatment with 30 mg/day or 45 mg/day IMU-838, or placebo (65 patients each) in the main treatment period. During the extended treatment period, patients will be re-randomized such that patients previously on placebo will be re-randomized 1:1 to treatment with 30 g/day or 45 mg/day IMU-838, all other patients will be re-randomized to the same treatment they previously received.

Inclusion criteria

Main treatment period

1. Male or female patient (age ≥18 to 55 years, inclusive)
2. Diagnosis of RRMS according to the revised McDonald criteria (2017)[1]

   Note: The diagnosis of MS (including "dissemination in time") must have been established before the patient is screened for the trial.
3. Disease activity evidenced
   - by either at least 2 relapses in the last 24 months, or at least 1 relapse in the last 12 months before randomization (relapses must have been assessed and documented by a physician in the patient files), **AND**
   - ≥1 documented Gd+ MS-related brain lesion, in the last 6 months before informed consent (date of MRI examination as well as copy of MRI report or representative image has to be available and accessible as patient source data at the study site)
4. Expanded Disability Status Scale (EDSS) score between 0 and 4.0 (inclusive) at Screening Visit 1
5. Female patients
   - must be of non-child-bearing potential i.e. surgically sterilized (hysterectomy, bilateral salpingectomy, bilateral oophorectomy at least 6 weeks before Screening Visit 1) or post-menopausal (where postmenopausal is defined as no menses for 12 months without an alternative medical cause), or
   - if of child-bearing potential, must have a negative pregnancy test at Screening Visit 1 (blood test) and before the first IMP intake (Day 0 urine test). They must agree not to attempt to become pregnant, must not donate ova, and must use a highly effective

[1] Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018;17(2):162-73.

contraceptive method (see below) together with a barrier method between trial consent and 30 days after the last intake of the of the IMP.

Highly effective forms of birth control are those with a failure rate less than 1% per year and include:

- oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraceptives associated with inhibition of ovulation
- oral, injectable, or implantable progestogen-only hormonal contraceptives associated with inhibition of ovulation
- intrauterine device or intrauterine hormone-releasing system
- bilateral tubal occlusion
- vasectomized partner (i.e. the patient's male partner underwent effective surgical sterilization before the female patient entered the clinical trial and is the sole sexual partner of the female patient during the clinical trial)
- sexual abstinence (acceptable only if it is the patient's usual form of birth control/lifestyle choice; periodic abstinence [e.g. calendar, ovulation, symptothermal, postovulation methods] and withdrawal are no acceptable methods of contraception)

Barrier methods of contraception include:

- Condom
- Occlusive cap (diaphragm or cervical/vault caps) with spermicidal gel/film/cream/suppository

6. Male patients must agree not to father a child or to donate sperm starting at Screening Visit 1, throughout the clinical trial and for 30 days after the last intake of the IMP. Male patients must also
   - abstain from sexual intercourse with a female partner (acceptable only if it is the patient's usual form of birth control/lifestyle choice), or
   - use adequate barrier contraception during treatment with the IMP and until at least 30 days after the last intake of the IMP, and
   - if they have a female partner of childbearing potential, the partner should use a highly effective contraceptive method as outlined in inclusion criterion 5
   - if they have a pregnant partner, they must use condoms while taking the IMP to avoid exposure of the fetus to the IMP
7. Willingness and ability to comply with the protocol
8. Written informed consent given prior to any trial-related procedure

Inclusion criteria for optional extended treatment period

1. Completed 24 weeks of main treatment
2. Baseline MRI, a Week 24 MRI as well as 2 additional post-dose MRIs

Continuation criteria for optional extended treatment period

1. In case the initial Week 24 MRI was not evaluated at least partially assessable, availability of a repeated Week 24 MRI
2. Week 24 MRI (initial or repeated one, if applicable) evaluated at least partially assessable

Exclusion criteria

MS-related exclusion criteria

1. Any disease other than MS that may better explain the signs and symptoms, including history of complete transverse myelitis
2. Signs and symptoms suggestive of transmissible spongiform encephalopathy, or family members who suffer(ed) from these
3. Clinical signs or presence of laboratory findings suggestive for neuromyelitis optica (NMO) spectrum disorders or myelin oligodendrocyte glycoprotein (MOG)-associated encephalomyelitis (i.e. presence of anti-NMO [aquaporin-4] antibodies or anti-MOG-antibodies)
4. MS types other than RRMS
5. Any MRI finding, atypical for MS, including but not limited to a longitudinally extensive spinal cord lesion
6. Any active and uncontrolled coexisting autoimmune disease, other than MS (except for type 1 diabetes mellitus and inflammatory bowel disease)
7. An MS relapse within 30 days before Screening Visit 1 and/or during the screening period (until Day 0)

Therapy exclusion criteria

8. **Any previous or current use of the following MS treatments:** monoclonal antibodies (natalizumab, alemtuzumab, daclizumab, ocrelizumab, anti-CD4, rituximab or belimumab, including their biosimilars), total lymphoid irradiation, bone marrow transplantation, stem cell transplantation, or any use of DHODH inhibitors, including teriflunomide (Aubagio™) or leflunomide (Arava™)
9. **Any use of the following MS treatments within 12 months before the date of informed consent:** any cytokine (other than interferon) or anti-cytokine therapy, intravenous immunoglobulin, mitoxantrone, cytotoxic or immunosuppressive therapy (including, but not limited to azathioprine and cyclophosphamide, excluding only systemic corticosteroids or adrenocorticotrophic hormone [ACTH]), tofacitinib, methotrexate, mycophenolate mofetil,

mycophenolate sodium, fingolimod, any calcineurin inhibitors (e.g. tacrolimus, cyclosporine, or pimecrolimus)

10. **Any use of the following MS treatments within 30 days before the date of informed consent**: interferon-β, glatiramer acetate, dimethyl fumarate and plasmapheresis
11. **Within 30 days before the baseline MRI:** Use of systemic corticosteroids (intravenous or oral) or ACTH.
12. Use of the following concomitant medications is prohibited **at Screening Visit 1 and throughout the duration of the trial**:
    - any medication known to significantly increase urinary elimination of uric acid, in particular lesinurad (Zurampic™) as well as uricosuric drugs such as probenecid
    - treatments for any malignancy, in particular irinotecan, paclitaxel, tretinoin, bosutinib, sorafinib, enasidenib, erlotinib, regorafenib, pazopanib and nilotinib
    - any drug significantly restricting water diuresis, in particular vasopressin and vasopressin analogs
    - use of rosuvastatin at daily doses higher than 10 mg
13. Use of any investigational product within **8 weeks or 5 x the respective half-life before the date of informed consent**, whichever is longer, and throughout the duration of the trial

Immune response exclusion criteria

14. Conditions negatively affecting the immune response such as previous organ transplant
15. Clinically significantly low lymphocyte and/or neutrophil count (Common Terminology Criteria for AEs Grade of 2 or higher), i.e.
    - lymphocyte count <800/mm³ (0.8 x 10^9/L), and/or
    - neutrophil count <1,500/mm³ (1.5 x 10^9/L)
16. History of chronic systemic infections within 6 months before the date of informed consent, including but not limited to tuberculosis, human immunodeficiency virus (HIV), hepatitis B or C
17. Positive interferon-gamma release assay for *Mycobacterium tuberculosis* at Screening Visit 1
18. Positive hepatitis B virus surface antigen, hepatitis B core antibody, positive hepatitis C virus antibody and/or HIV-antigen-antibody test[2] at Screening Visit 1
19. Any live vaccinations within 30 days before the date of informed consent except for the influenza vaccine

[2] A positive HIV-Ag/Ab test will be confirmed by further testing based on Nucleic Acid Amplification Technology (NAAT). If the NAAT test is negative, the patient will be considered HIV negative.

Other medical history and concomitant disease exclusion criteria

20. Presence of the following laboratory values at Screening Visit 1:
    - platelet count <100,000/mm³ (<100 10^9/L)
    - serum creatinine >1.5 x upper limit of normal (ULN)
    - total bilirubin, alanine aminotransferase, or gamma-glutamyl transferase >1.5 x ULN
    - Serum uric acid levels at Screening Visit 1 >1.2 x ULN (for women >6.8 mg/dL, for men >8.4 mg/dL)
    - indirect (unconjugated) bilirubin >1.2 x ULN (i.e. >1.1 mg/dL)
21. Known history of nephrolithiasis or underlying condition with a strong association of nephrolithiasis, including hereditary hyperoxaluria or hereditary hyperuricemia
22. History or clinical diagnosis of gout
23. Renal impairment defined as estimated glomerular filtration rate[3] ≤60 mL/min/1.73m²
24. Known or suspected Gilbert syndrome
25. Diagnosis or suspected liver function impairment which may cause fluctuating liver function tests during this trial, as assessed by the investigator
26. History or presence of serious or acute heart disease such as uncontrolled cardiac dysrhythmia or arrhythmia, uncontrolled angina pectoris, cardiomyopathy, or uncontrolled congestive heart failure (New York Heart Association [NYHA] class 3 or 4)

    Note: NYHA class 3: Cardiac disease resulting in marked limitation of physical activity. Patients are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain. NYHA class 4: Cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.
27. Clinically relevant, severe pulmonary diseases, uncontrolled hypertension, or poorly controlled diabetes
28. Concurrent malignancy or prior malignancy within the previous 10 years except for the following: adequately-treated non-melanoma skin cancer and adequately-treated cervical cancer
29. History or presence of any major medical or psychiatric illness (such as severe depression, psychosis, bipolar disorder), history of suicide attempt, or current suicidal ideation that in the opinion of the investigator could create undue risk to the patient or could affect adherence with the trial protocol
30. Epilepsy or seizures not adequately controlled by treatment

[3] Calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation.

31. Any other substantial medical condition that in the opinion of the investigator could create undue risk to the patient or could affect adherence with the trial protocol

General exclusion criteria

32. Current or past (within 12 months of Screening Visit 1) alcohol or drug abuse
33. Any condition that would prevent the patient from undergoing an MRI scan, including:
    - claustrophobic conditions
    - unable to receive Gd-based MRI-contrast agents due to history of hypersensitivity to Gd-based contrast agents, or severe renal insufficiency
    - presence of metallic implants incompatible with brain MRI
34. Legal incapacity, limited legal capacity, or any other condition that makes the patient unable to understand the patient information and informed consent form
35. Pregnant or breastfeeding
36. An employee of an investigator or sponsor or an immediate relative of an investigator
37. Patients institutionalized due to judicial or administrative order

Exclusion criteria for optional extended treatment period

1. Any ongoing, clinically significant (as assessed by the investigator) treatment-emergent (started after intake of IMP) AE or laboratory abnormality (including blood chemistry and urinalysis)[4]
2. Significant treatment or trial non-compliance during the main treatment period (as assessed by the investigator), and/or inability or unwillingness to follow instructions by trial personnel
3. Treatment compliance <70% during the main treatment period
4. Significant protocol deviations during the main treatment period that are assessed by the investigator to negatively affect further patient cooperation in this trial

Endpoints

Primary

Efficacy

Difference between 45 mg/day IMU-838 and placebo in the cumulative number of combined unique active (CUA)[5] MRI lesions up to Week 24

[4] If treatment-emergent AEs are the reason for exclusion from the extended treatment period, the eligibility can be re-assessed up to 30 days following the last treatment in the main treatment period.

[5] Sum of the number of all new Gd+ lesions on T1-weighted MRI and the number of all new or substantially enlarged lesions on T2-weighted MRI (non-enhancing on T1-weighted MRI), avoiding double counting.

Key secondary (hierarchical testing to primary efficacy)

Efficacy

Difference between 30 mg/day IMU-838 and placebo in the cumulative number of CUA MRI lesions up to Week 24

Secondary

Efficacy

- Difference between 45 mg/day IMU-838 and 30 mg/day IMU-838 in the cumulative number of CUA MRI lesions at Week 24
- Difference between 30 mg/day IMU-838 and placebo, 45 mg/day IMU-838 and placebo, and 30 mg/day and 45 mg/day IMU-838 for the following MRI parameters:
  - Mean number of CUA lesions per patient per scan at Weeks 6, 12, 18 and 24
  - Cumulative number of CUA MRI lesions up to Weeks 6, 12, and 18
  - Volume changes of T2 lesions at Weeks 6, 12, 18 and 24 compared to Baseline
  - T2-lesion load at Weeks 6, 12, 18 and 24 compared to Baseline
  - T1-lesion load at Weeks 6, 12, 18 and 24 compared to Baseline
  - Cumulative number of new Gd+ lesions up to Weeks 6, 12, 18 and 24
  - Cumulative number of new T2 lesions up to Weeks 6, 12, 18 and 24
  - Cumulative number of new T1 lesions up to Weeks 6, 12, 18 and 24
  - Proportion of patients without new Gd+ lesions over 24 weeks
  - Proportion of patients without new or enlarging T2-weighted lesions over 24 weeks
  - Proportion of patients with CUA lesions at Week 24
  - Proportion of patients with Gd+ lesions at Week 24
  - Proportion of patients with T2 lesions at Week 24
- Differences between individual treatments and between the pooled 30 mg/day and 45 mg/day groups and placebo in the following relapse-related clinical endpoints:
  - Mean annualized relapse rate (during main and extended treatment period)
  - Proportion of relapse-free patients up to Week 24 and at extended periods thereafter
  - Time to relapse at time of final analysis of main part
- Differences between treatments in changes of disease activity as measured by the following clinical parameters:
  - Mean change in the EDSS as compared to Baseline during the main and extended period (every 12 weeks starting at Week 12)
  - Proportion of patients with EDSS progression during the main and extended period (every 12 weeks starting at Week 12, and cumulatively)

- Correlation of MRI-based assessments with quartiles of IMU-838 trough levels at Week 6 and Week 24

Safety

- AEs, serious AEs and clinically significant laboratory abnormalities (as assessed by the investigator)
- AEs of special interest:
  - Red blood cell urine positive, at least of moderate intensity
  - Hematuria
  - Retroperitoneal colicky pain with suspected or confirmed nephrolithiasis
- Proportion of patients treated with 30 mg/day or 45 mg/day IMU-838 as compared to placebo who experienced at least one of the following AEs:
  - Neutropenia
  - Lymphopenia
  - Diarrhea
  - Alopecia
  - Hemorrhage
  - Abnormalities in alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, and total bilirubin with both elevations >1.5 x ULN and ≥35% elevated compared to Baseline
- ECG, physical examination, and vital signs
- Micro ribonucleic acid-122 expression (Change from Baseline to 4 hours after first dose)
- Presence of John Cunningham virus (JCV) deoxyribonucleic acid (DNA) in urine in patients with detectable JCV-DNA in urine at Screening Visit 1, at Week 24, and at EoS
- Time to treatment discontinuation for any reason
- Rate of treatment discontinuations up to W24

Pharmacokinetics

- Population PK at Week 6 (3-10 hours post-dose)
- Plasma trough levels of IMU-838 at Days 7 and Weeks 6, 12, 18, and 24

Pharmacodynamics

- Changes from Baseline in lymphocyte subset parameters as measured by flow cytometry at Weeks 6 and 24 (in selected Biomarker Centers only)
- Changes from Baseline in biased T-cell clonal repertoire based on T-cell receptor deep sequencing at Weeks 6 and 24 (in selected Biomarker Centers only)

- Changes from Baseline in serum neurofilament at Week 24

Health outcome

- Treatment Satisfaction Questionnaire for Medication at Week 6, Week 24 and EoS

Statistical methods

The primary analysis will be performed after the end of the main treatment period and will be based on the full analysis set. The primary and key secondary endpoints (cumulative number of CUA MRI lesions at Week 24) will be analyzed with a generalized linear model with a negative binomial distribution and a logarithmic link function. Treatment group, baseline volume of T2 lesions, field strength of the MRI machine (1.5 or 3.0 Tesla), and number of Gd+ lesions (the latter 2 are factor groups used for stratification) will be included as independent effects in the models. The primary and the key secondary efficacy endpoints will be analyzed with a hierarchical testing procedure. Both tests will be performed at a significance level of 0.1 (1-sided). In case of a non-significant result for the primary endpoint, the hierarchical testing procedure will be stopped, and the analysis of the key secondary endpoint will be exploratory.

The sample size calculation is based on the primary endpoint assessed at Week 24 after the main treatment period.

Assumptions:

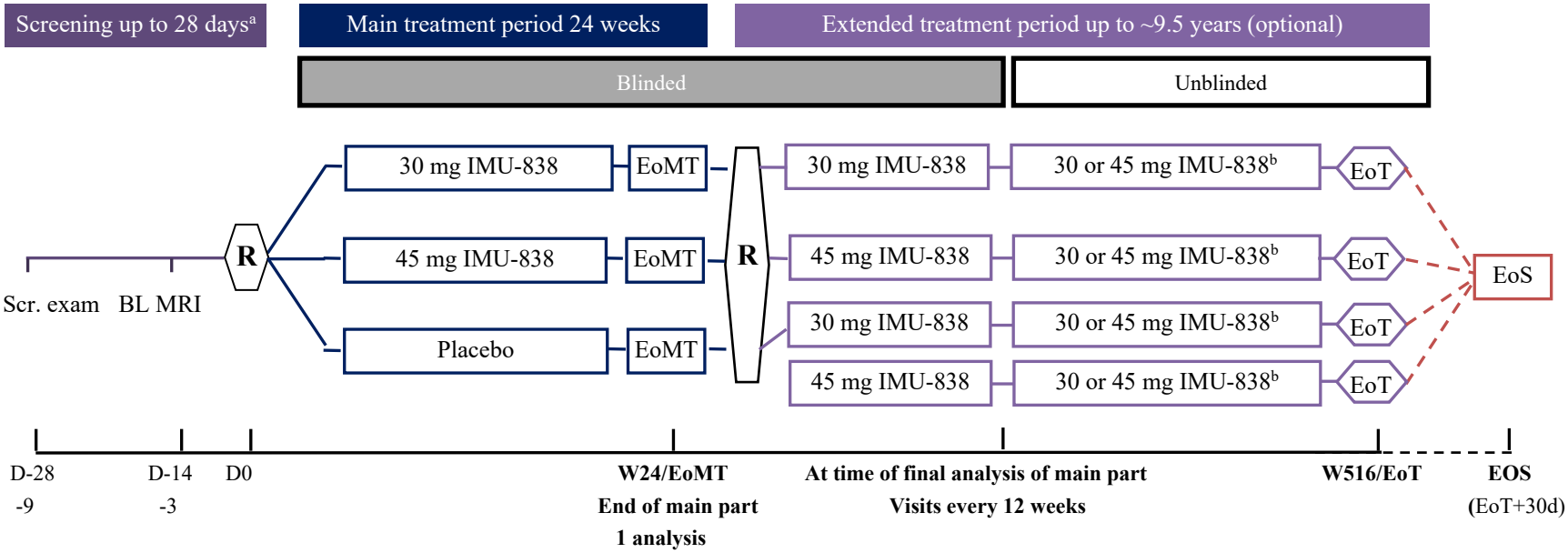
Primary endpoint: cumulative number of CUA MRI lesions up to Week 24

Randomization ratio:	1:1 (45 mg/day IMU-838:placebo)
Power:	80%
Significance level:	0.1, 1-sided
Average exposure time:	24 weeks
Mean event rate per 24 weeks for 45 mg/day IMU-838:	4.5
Mean event rate per 24 weeks for placebo:	8.0
Negative binomial dispersion parameter:	1.7

Based on these assumptions the necessary sample size per group is 51. Assuming a drop-out rate of 25%, about 65 patients will be randomized to each of the dose groups.

Schedules of assessments and flow chart

Figure 1: Trial flow chart



[a] Can be interrupted/extended, if the baseline MRI must be repeated due to poor quality (to be done as soon as possible). If results of the central MRI assessment are not available in time for randomization, the screening period can be extended by up to 7 days, if needed.

[b] After unblinding of the main treatment period, the investigator can decide with the patient if and at which dose the treatment will be continued.

BL = baseline, D = day, EoMT = end-of-main treatment, EoS = end-of-study, EoT = end-of-treatment, exam = examination, MRI = magnetic resonance imaging, R = randomization, Scr. = screening, W = Week.

Table 1: Schedule of assessments

	Screening		Blinded treatment						Blinded and unblinded[q]			Unscheduled visit		EoS
		BL MRI	Main treatment (MT) period						Extended treatment (ET) period (optional)			due to MS-related symptoms	due to safety	(end of study visit)
	S1[a]	S2[k]	V0	V1	V2	V3	V4	V5/ EoMT	V6[t]	V7 to V45[t]	V46/ EoT[t]			
	D-28 - D-9	D-14 - D-3	D0	D7	W6	W12	W18	W24	W36[t]	Every 12 weeks	W516[t]			30 d after last IMP
Assessments				±1 d	-7/+4 d	±7 d	±7 d	±7 d	±14 d	±14 d	±14 d			+14 d
Informed consent	•													
Demographics	•													
In-/exclusion criteria	•		•					(•)[p]						
Randomization			•					(•)[j,p]						
Medical history[b]	•													
Previous therapy	•													
Concomitant medications/procedures	•	•	•	•	•	•	•	•	•	•	•	•	•	•
MS disease history	•													
Physical examination	•		•					•			•	•	•	•
New MS related neurological symptoms (treating physician)	•		•	•	•	•	•	•	•	•	•	•		
EDSS (evaluating physician)	•		•	(•)[m]	(•)[m]	•	(•)[m]	•	•	•	•	(•)[m]		
MS relapse (treating physician)			•	(•)[m]	(•)[m]	•	(•)[m]	•	•	•	•	(•)[m]		
MRI scan		•			•	•	•	•[r]						

continued

Table 1: Schedule of assessments *(continued)*

	Screening		Blinded treatment						Blinded and unblinded[q]			Unscheduled visit		EoS
		BL MRI	Main treatment (MT) period						Extended treatment (ET) period (optional)			due to MS-related symptoms	due to safety	(end of study visit)
	S1[a]	S2[k]	V0	V1	V2	V3	V4	V5/ EoMT	V6[t]	V7 to V45[t]	V46/ EoT[t]			
	D-28 - D-9	D-14 - D-3	D0	D7 ±1 d	W6 -7/+4 d	W12 ±7 d	W18 ±7 d	W24 ±7 d	W36[t] ±14 d	Every 12 weeks ±14 d	W516[t] ±14 d			30 d after last IMP +14 d
Assessments														
Central MRI quality & eligibility assessment as well as BL stratification variables		•												
Central MRI assessment of efficacy variables					•	•	•	•						
PRO questionnaires (TSQM)					•			•						•
Laboratory assessments														
Central screening labs, incl. blood pregnancy test[f]	•													
Local screening lab (Tbc-IGRA)	•													
Blood biochemistry			•	•	•	•	•	•	•	•	•	•	•	•
Hematology			•	•	•	•	•	•	•	•	•	•	•	•
Coagulation[g]			•	•				•						
IMU-838 trough level[g]			•	•	•	•	•	•						•[s]

continued

Table 1: Schedule of assessments *(continued)*

	Screening		Blinded treatment						Blinded and unblinded[q]			Unscheduled visit		EoS
		BL MRI	Main treatment (MT) period						Extended treatment (ET) period (optional)			due to MS-related symptoms	due to safety	(end of study visit)
	S1[a]	S2[k]	V0	V1	V2	V3	V4	V5/ EoMT	V6[t]	V7 to V45[t]	V46/ EoT[t]			
	D-28 - D-9	D-14 - D-3	D0	D7 ±1 d	W6 -7/+4 d	W12 ±7 d	W18 ±7 d	W24 ±7 d	W36[t] ±14 d	Every 12 weeks ±14 d	W516[t] ±14 d			30 d after last IMP +14 d
Assessments														
Urinalysis			•	•	•	•	•	•	•	•	•	•	•	•
Population PK[g]					•[l]									
Local urine pregnancy test[d]			•[i]		•	•	•	•	•	•	•			•
Genotyping			•											
miR-122[g]			0+4h											
JCV-DNA in urine	•							•						•
PBMC-based PD parameters[e]			•		•			•						
Neurofilament[g]			•		•			•						
Lab kits used														
Screening lab kit	S													
Trial lab kit			A	A	B	B	B	A	C	C	C	C	C	C
JCV-DNA	JCV							JCV						JCV
miR-122			2xBM											
Genotyping			G											
Neurofilament			NFL		NFL			NFL						
PK kit			PK	PK	2xPK	PK	PK	PK						PK[s]
PD kit (PBMC)[e]			PD		PD			PD						

continued

Table 1: Schedule of assessments *(continued)*

	Screening		Blinded treatment						Blinded and unblinded[q]			Unscheduled visit		EoS
		BL MRI	Main treatment (MT) period						Extended treatment (ET) period (optional)			due to MS-related symptoms	due to safety	(end of study visit)
	S1[a]	S2[k]	V0	V1	V2	V3	V4	V5/ EoMT	V6[t]	V7 to V45[t]	V46/ EoT[t]			
	D-28 - D-9	D-14 - D-3	D0	D7 ±1 d	W6 -7/+4 d	W12 ±7 d	W18 ±7 d	W24 ±7 d	W36[t] ±14 d	Every 12 weeks ±14 d	W516[t] ±14 d			30 d after last IMP +14 d
Assessments														
Shipment to central lab														
Ambient temperature	•		•	•	•	•	•	•	•	•	•	•	•	•
Dry ice					•[o]			•[o]						•[n]
Safety														
AE assessment	•	•	•	•	•	•	•	•	•	•	•	•	•	•
12-lead ECG	•				•			•			•		•	
Vital signs	•[c]		•[c]	•[c]		•[c]		•[c]	•[c]	•[c]	•[c]			•[c]
IMP														
IMP administration[h]														
IMP dispensing			•		•	•	•	•	•	•				
No. of bottles disp.			1		2	2	2	3	3	3				
IMP accountability					•	•	•	•	•	•	•			

Assessments in brackets (•) indicate assessments which must not always be performed. Refer to the respective footnote.

[a] Within 28 days from Baseline (Day 0). If the baseline MRI is repeated, the screening period maybe extended. However, patients must be randomized within 14 days of the repeated baseline MRI. Screening Visit 1 assessments will be valid for up to 60 days until the day of randomization, but will have to be repeated if exceeding 60 days. If results of the baseline MRI assessments are not available within 14 days (either after the first or, if applicable, after the repeated MRI) randomization can be delayed by up to 7 days, which may also result in an extension of the screening period.

[b] Including the history of autoimmune diseases (other than MS).

[c] Including height (only at Screening), respiratory rate, weight, blood pressure, pulse rate, and body temperature.

[d] Any positive local urine pregnancy test has to be followed up with a confirmatory local blood pregnancy test.

[e] Includes PBMC-based lymphocyte subset analysis and T-cell clonal repertoire. To be performed in a subset of patients and at selected “Biomarker Centers” only.

[f] Serum pregnancy test at central laboratory.

[g] Samples to be stored at -20°C until next scheduled dry-ice shipment to central laboratory.

[h] During the first week of treatment in the main and extended treatment period: 1 tablet once daily; other weeks: 2 tablets once daily.
[i] The result of this local pregnancy test must be available and negative before the first IMP can be taken.
[j] Patients who received placebo during the main treatment period will be re-randomized to 30 mg or 45 mg IMU-838. Patients previously on IMU-838 will be re-randomized to the same treatment they received during the main treatment period.
[k] If the central reader evaluates the quality of the baseline MRI as not sufficient, the MRI must be repeated as soon as possible.
[l] Taken at 3 to 10 hours post-dose (in addition to the sample which is collected pre-dose at the same day for IMU-838 trough values).
[m] If, based on new neurological symptoms of the patient, the treating physician suspects that the patient may have an MS relapse (as defined in this protocol), an EDSS assessment by the evaluating physician and an assessment of MS relapse by the treating physician (based on the EDSS) must be performed at this visit.
[n] The sample can be stored at -20°C for up to 1 year and dry ice shipment can be combined with another dry ice shipment.
[o] The dry ice shipment should be generally done immediately after the Week 6, Week 24 or EoS visit. However, it may be delayed by up to 2 weeks if the dry ice shipment can be combined with the dry ice shipment for another patient at the same site.
[p] Only for patients who continue into the extended treatment phase.
[q] Blinded until the data base lock and final analysis of the main treatment part; thereafter unblinded.
[r] Can be repeated if initial MRI scan is not at least partially assessable.
[s] To be performed only up to the time of last patient last visit of the main treatment period in the Cohort 2 sub-trial (Week 24). Investigators will be notified immediately.
[t] The extended treatment period will be terminated for patients in the Cohort 2 sub-trial, at the day the last patient of the Cohort 1 main trial has completed or discontinued the extended treatment period (which allows up to 9.5 years of ET period). The ET period for these patients will thus be shorter (approximately up to 8.5 years).

AE = adverse event, BL = baseline, D = day, disp. = dispensed, DNA = deoxyribonucleic acid, ECG = electrocardiogram, EDSS = Expanded Disability Status Scale, EoMT = end-of-main treatment, EoS = end-of-study, EoT = end-of-treatment, ET = extended treatment, IMP = investigational medicinal product, incl. = including, JCV = John Cunningham virus, miR-122 = micro ribonucleic acid-122, MRI = magnetic resonance imaging, MS = multiple sclerosis, MT = main treatment, No = number, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamic, PK= pharmacokinetic, PRO = patient reported outcome, S = screening, Tbc-IGRA = Tuberculosis interferon gamma release assay, TCR =T-cell receptor, TSQM = Treatment Satisfaction Questionnaire for Medication, V = Visit; W = Week.

Study P2-IMU-838-MS

Reminder what should be considered for patient visits at the trial center

- Patients should be reminded throughout the trial to drink a generous amount of fluid per day (approximately 1.5 liters per day are recommended) to ensure adequate urine flow.
- At all visits throughout the trial:
  - Patients should arrive at the center in fasted condition (no food after midnight and in the morning before visit) but patients are allowed to drink water even during periods of fasting (from midnight to next day visit).
  - For an individual patient visits should be scheduled at the same time in the morning so that visits are all within ±2 hours of the Day 0 visit.
  - At each visit, patients need to bring the IMP container to the center.

- Applies only to main treatment period:
  - Patients should arrive at the center without having taken the IMP.
  - If patients have inadvertently taken the IMP within 1.5 hours of arriving at the trial center, blood samples for trough levels will still be drawn. If the IMP intake was longer than 1.5 hours before arriving at the trial center, trough levels will not be determined. Either case will be recorded as protocol deviation. Blood samples for biochemistry can be collected in any case and no additional visit to collect a blood sample for trough plasma levels needs to be scheduled.

2 Addresses and responsibilities

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Micro ribonucleic acid-122 (miR-122) assessment and genotyping	IMGM Laboratories GmbH Lochhamer Str. 29a 82152 Martinsried, Germany Phone: + 49 89 4524 667 0 Fax: + 49 89 4524 667 410

Local contract research organizations for local project management and monitoring

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A complete list of trial personnel will be available in the trial master file.

3 Table of contents

Page

Table of tables

Table of figures

4 Abbreviations and definition of terms

ACTH	Adrenocorticotrophic hormone
ADR	Adverse drug reaction
AE	Adverse event
AESI	AEs of special interest
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
ARR	Annual relapse rate
AST	Aspartate aminotransferase
BCRP	Breast cancer resistance protein
BUN	Blood urea nitrogen
C4	7α-hydroxy-4-cholesten-3-one
CA	Competent authority
Ca	Calcium
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cl	Chloride
CNS	Central nervous system
CRO	Contract research organization
CRP	C-reactive protein
CUA	Combined unique active
CYP	Cytochrome P450
DHODH	Dihydroorotate dehydrogenase
DMF	Dimethylfumarate
DMT	Disease modifying treatment
DNA	Deoxyribonucleic acid
EAE	Experimental autoimmune encephalomyelitis
ECG	Electrocardiogram
eCRF	Electronic case report form
EDSS	Expanded Disability Status Scale
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EoMT	End-of-main treatment
EoS	End-of-study
EoT	End-of-treatment
EU	European Union
FAS	Full analysis set
FGF-19	Fibroblast growth factor 19

GCP	Good Clinical Practice
Gd(+)	Gadolinium (enhancing)
GGT	Gamma glutamyl transferase
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HCV(-Ab)	Hepatitis C virus(-antibody)
HDL	High-density lipoprotein
HIV(-Ag/Ab)	Human immunodeficiency virus(-antigen/antibody)
HPF	High powered field
i.v.	Intravenous
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
IFNγ	Interferon gamma
IgG(M)	Immunoglobulin G(M)
IL	Interleukin
IMP	Investigational medicinal product
INR	International normalized ratio
IWRS	Interactive web-based response system
JCV	John Cunningham virus
K	Potassium
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
miR-122	Micro ribonucleic acid-122
MOG	Myelin oligodendrocyte glycoprotein
MR(I)	Magnetic resonance (imaging)
MS	Multiple sclerosis
Na	Sodium
NMO	Neuromyelitis optica
NYHA	New York Heart Association
OAT1(3)	Organic anion transporter 1(3)
OATP1B1(3)	Organic anion transporting polypeptide 1B1(3)
P	Inorganic phosphate
PBMC	Peripheral blood mononuclear cell
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PP	Per-protocol set

RA	Rheumatoid arthritis
RBC	Red blood cells
RRMS	Relapsing-remitting multiple sclerosis
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SUSAR	Suspected unexpected serious adverse reaction
Tbc-IGRA	*Mycobacterium tuberculosis* IFNγ-release assay
TEAE	Treatment-emergent adverse event
TSQM	Treatment Satisfaction Questionnaire for Medication
UGT1A1	UDP-glucuronosyltransferase 1A1
ULN	Upper limit of normal
URAT1	Urate anion transporter 1
USA	United States of America

Drugs

4SC-101	Tablet or capsule formulation containing vidofludimus free acid
IMU-838	Tablet formulation containing vidofludimus calcium

If not indicated otherwise 'investigator' as used throughout this protocol refers to the treating physician (or deputy) of this trial.

Definitions

RRMS	Relapsing-remitting multiple sclerosis, as defined by the revised 2017 McDonald criteria [1]
Gd-lesion	Acute multiple sclerosis (MS) lesion in the brain that disrupts the blood-brain barrier and is characterized by enhancement with Gadolinium (Gd)-containing contrast agents in post-contrast T1-weighted magnetic resonance (MR) images, at least 3 mm in size
T2-lesion	Focal supratentorial ovoid lesions observed as hyper- or hypointense area on T2-weighted MR images, at least 3 mm in size

CUA lesions (combined unique active) lesions	Sum of the number of all new Gd-enhanced (Gd+) lesions on T1-weighted magnetic resonance imaging (MRI) and the number of all new or substantially enlarged lesions on T2-weighted MRI (non-enhancing on T1-weighted MRI), avoiding double counting.
MS relapse:	All of the following criteria must be met for a clinical event to qualify as a relapse: 1. Neurological deficit, either newly appearing or re-appearing, with abnormality specified by both o Neurological abnormality separated by at least 30 days from onset of a preceding relapse, AND o Neurological abnormality lasting for at least 24 hours 2. Absence of fever or known infection (i.e. temperature [axillary, oral, or intra-auricular] ≤37.5ºC) 3. Neurological impairment, defined as either o Increase in at least one of the functional systems of the Expanded Disability Status Scale (EDSS), OR o Increase of the total EDSS score. In both cases, the increase in EDSS must correlate with the patient's reported symptoms The occurrence of fatigue, mental symptoms, and/or vegetative symptoms without any additional symptom will not classify as a relapse. The treating physician will decide if the observed signs and symptoms qualify as a relapse; the EDSS results will be provided by the blinded evaluating physician. Only relapses confirmed by the investigator and meeting the above criteria will be reported in the electronic case report form (eCRF). Relapses and their underlying neurological symptoms will not be reported as adverse events (AE), as they represent an important efficacy parameter.

EDSS progression: An increase of the EDSS score compared to Baseline:

- of at least 1.0 point for patients with a baseline EDSS score of 1 to 4.0,

OR

- of at least 1.5 points for patients with a baseline EDSS score of 0.

In case of inconsistencies between text in the protocol and the schedule of assessments (Table 1), the schedule will predominate.

5 Introduction

5.1 Multiple sclerosis

5.1.1 Background

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating disease of the central nervous system (CNS) and is one of the most common causes of neurological disability in young adults. It affects up to 2.5 million people worldwide. Its prevalence varies between races and geographical latitudes, ranging from more than 100 per 100,000 people in Northern and Central Europe to 50 per 100,000 people in Southern Europe.

It is characterized by multi-focal recurrent events of neurological symptoms and signs, with variable recovery. Most patients eventually develop a progressive clinical course. [2-4]

The exact cause of MS is unknown, although an autoimmune process is implicated. A genetic basis plays a role in susceptibility to MS [5,6] and environmental factors such as hypovitaminosis D and Epstein-Bar virus infections have been identified. [7] In one hypothesis, CNS auto-reactive lymphocytes are triggered outside the CNS, become active, and proliferate in the peripheral secondary lymphoid organs. Upon migration via the blood circulation, the expression of adhesion molecules on the surface of these encephalitogenic lymphocytes permits adhesion to activated brain or spinal cord endothelial cells, with subsequent migration into the CNS compartment. These cells again proliferate upon interacting with CNS myelin antigens and initiate a pro-inflammatory cascade within the brain that results in either target-directed immune damage or bystander damage. Important cellular and humoral elements are T-and B-lymphocytes, macrophages, microglial cells, and metalloproteinases, chemokines and cytokines, including interferon-gamma (IFNγ) and tumor necrosis factor-alpha. [8-11]

5.1.2 Clinical variants

Four clinical forms of MS are recognized: primary progressive, progressive-relapsing, secondary progressive, and relapsing-remitting. [12]

Patients with relapsing-remitting multiple sclerosis (RRMS) have acute exacerbations or MS attacks with subsequent variable recovery (remission). At the onset of MS, 80% to 85% of patients will have RRMS. In most cases of RRMS, Expanded Disability Status Scale (EDSS) scores are below 4.

Over the past few years myelin oligodendrocyte glycoprotein (MOG) was shown to be a disease entity distinct from classic MS and from Aquaporin 4-IgG-positive neuromyelitis optica spectrum disorders, and which is now often referred to as MOG-associated encephalomyelitis. MOG-associated encephalomyelitis is relevant not only for differences in clinical and

paraclinical presentation, but more importantly also for treatment response and prognosis. [11,13,14]

5.2 IMU-838

5.2.1 Background

Vidofludimus free acid (SC12267) was previously developed by 4SC AG using capsules or tablets containing amorphous vidofludimus (4SC-101). Immunic AG acquired all rights and data of SC12267 and has developed a new pharmaceutical form containing the calcium salt of vidofludimus (INNM: vidofludimus calcium) in a new pharmaceutical formulation (tablets containing a specific polymorph).

Both formulations depend on the same active moiety i.e. vidofludimus which is released from the tablets in the gut and enters the blood stream. Hence, the 2 formulations share the same mechanism of action, pharmacology, and toxicology. Vidofludimus calcium may exhibit, however, superior pharmaceutical properties compared with the former vidofludimus free acid film-coated tablet.

5.2.2 Mode of action

The investigational medicinal product (IMP) IMU-838 (vidofludimus calcium) is a new compound that selectively inhibits the human enzyme dihydroorotate dehydrogenase (DHODH). As it is chemically and structurally different from teriflunomide, a DHODH inhibitor approved in the United States of America (USA) and European Union (EU) for the treatment of RRMS, it also differs in the mode of DHODH inhibition.

The mechanism of action in all therapeutic indications proposed for IMU-838 is the targeting of lymphocytes, which are activated through the inflammatory process. Thus, IMU-838 selectively affects activated, rapidly proliferating lymphocytes through inhibition of DHODH, which plays a major role in the *de-novo* pyrimidine synthesis and is specifically expressed at high levels in proliferating or activated lymphocytes. Resting lymphocytes satisfy their pyrimidine requirements through a DHODH-independent salvage pathway. The metabolic stress secondary to DHODH inhibition leads to a reduction of pro-inflammatory cytokine release including interleukin (IL)-17 (IL-17A and IL-17F) and IFNγ, and to an increased apoptosis in activated lymphocytes. [15] IMU-838-mediated DHODH inhibition does not induce unselective immunosuppression and therefore offers to patients the selective targeting of disease-relevant effector cells.

IMU-838 is further characterized by a short blood half-life of 30-40 hours making it ideal for once-daily dosing and resulting in only little accumulation after daily dosing (steady state

concentrations are reached within 4-8 days with an accumulation factor of 2). Importantly due to the short blood half-life, the wash-out period for IMU-838 is considerably shorter than for teriflunomide.

5.2.3 Non-clinical studies

Pharmacodynamics

Vidofludimus strongly inhibits activated lymphocytes and reduces the release of pro-inflammatory cytokines and other physiologic effects of activated lymphocytes in *in-vivo* studies.

The metabolism of vidofludimus involves primarily cytochrome P450 (CYP)1A1 (about 60%), followed by CYP2C8 (about 20%) and CYP2E1 (about 10%). Vidofludimus is primarily eliminated via feces (about 70%).

Vidofludimus mildly to moderately inhibits several transport systems, including the urate anion transporter 1 (URAT1), the breast cancer resistance protein (BCRP), the organic anion transporters (OAT)1 and OAT3, the organic anion transporting polypeptides (OATP)1B1 and OATP1B3, and the bile salt export pump.

Consistent with the important role of DHODH for viral replication in human cells, vidofludimus inhibited viral replication of hepatitis C virus (HCV) in an *in-vitro* assay.

Inhibition of lymphocyte proliferation of vidofludimus was tested *in vitro* on lymphocytes from mouse, rat and human. Vidofludimus is about 200-fold less active on rat lymphocytes, but an about 10 times more potent inhibitor of activated human lymphocytes than teriflunomide, the active metabolite of leflunomide.

In a spinal cord extract-induced experimental autoimmune encephalomyelitis (EAE) model in rats, vidofludimus showed dose-dependent inhibition of EAE motor symptoms with a strong and comparable effect at the doses 20 and 60 mg/kg. In addition, even the lowest dose of 4 mg/kg reduced the weight loss caused by EAE.

5.2.4 Clinical trials

Except for two Phase 1 trials performed with IMU-838 and an ongoing Phase 2 trial in ulcerative colitis, all previous clinical trials were performed using vidofludimus free acid (4SC-101). So far, no clinical trials have been performed in MS. However, vidofludimus showed beneficial clinical effects in other autoimmune and chronic inflammatory diseases.

Two clinical trials investigated the beneficial effects of 4SC-101 in patients with rheumatoid arthritis (RA). 4SC-101 improved various clinical parameters versus placebo. A pronounced effect was observed for inflammatory parameters.

In a small Phase 2 trial in patients with corticosteroid-dependent inflammatory bowel disease (Crohn's disease and ulcerative colitis), 4SC-101 showed beneficial effects in the remission maintenance therapy. Compared with historical placebo data, 4SC-101 treatment showed a significantly higher response rate (88.5% total response) as well as a corticosteroid sparing effect.

No 4SC-101-associated clinically significant adverse reactions were observed at doses of <70 mg once daily including the potential target organs liver and kidney as identified in non-clinical or early clinical trials. At higher 4SC-101 doses (>70 mg/day or single doses of 210 mg) potential drug-related increases of red blood cells (RBC) in urine and hematurias were observed (see also Section 8.3).

Two Phase 1 clinical trials were performed for calcium vidofludimus (IMU-838). In Trial P1-IMU-838-SAD, doses from 10 to 40 mg IMU-838 resulted in dose-linear blood pharmacokinetics (PK) under fasted conditions. For the 30 mg dose (the dose expected to be closest to an effective dose), the terminal plasma half-life was approximately 40 hours and the median concentration peaked at 5 hours. Comparing single dosing of 10 mg under fasted and fed conditions, no detrimental effect of food intake was found. Single oral doses of 10 to 40 mg IMU-838 were well tolerated. No adverse events of special interest (AESI; including hematuria or clinically significant RBC in urine high) were observed in that clinical trial.

In Trial P1-IMU-838-MAD, repeated oral dosing of IMU-838 over 14 days in doses from 30 to 50 mg resulted in dose-proportional blood PK under fasted conditions. Geometric mean half-life at steady state ranged from 28.6 to 30.4 hours. Overall, median peak concentration following multiple oral doses of IMU-838 occurred between 2 to 3 hours after the first and after repeated dosing. Steady-state levels were reached within about 4 days for 25 mg IMU-838, within 6-8 days for 30 mg, within about 6 days with 40 mg, and within about 8 days with 50 mg IMU-838. Repeated once-daily oral doses of 30 to 50 mg IMU-838 over 14 consecutive days were well tolerated. Mild or moderate treatment-emergent AEs (TEAEs) were reported by 31 subjects (59.6%); overall 53 TEAEs, reported by 29 subjects (55.8%) were considered drug-related. The number of subjects with drug-related TEAEs or the number of drug-related TEAEs did not increase with increasing dose.

Most individual laboratory values were within the normal ranges. There were no clinically relevant differences between pre- and post-dose assessments and between the treatment groups for any parameter.

5.2.5 Safety of IMU-838

To date, 351 individuals have been exposed to vidofludimus. Of these 351 subjects, 299 were dosed with 4SC-101 and 52 with IMU-838.

The safety analysis of all exposed subjects provided the following findings:

- No deaths
- No serious adverse event (SAE) during Phase 1 with IMU-838
- The most frequent AEs for IMU-838 during Phase 1 were:
    - Headache
    - Flatulence
    - Common cold
    - Positive urine dipstick for hemoglobin

Importantly, vidofludimus (free acid) at a daily dose of 35 mg showed no increase of adverse reactions compared with placebo, and no increased infection rate.

IMU-838 is a selective DHODH inhibitor and did not inhibit any kinase (of a panel of over 100 tested protein kinases) at blood concentrations that are found at therapeutic dose levels. However, both teriflunomide and IMU-838 inhibit organic anion transporters such as URAT1, which potentially could affect renal uric acid elimination.

In conclusion, IMU-838 is expected to have a favorable safety profile, as in more than 350 patients (with rheumatoid arthritis or inflammatory bowel disease) or volunteers no increased events of diarrhea, nausea, alopecia or headache as well as no increases in abnormal liver function tests were observed.

5.3 Rationale for the trial

MS is a chronic disorder of the CNS, which affects up to 2.5 million people worldwide. Efficacy, safety and tolerability of the currently approved MS therapeutics are regarded to be substantially different among the available treatment options. As all these therapeutic agents have to be administered chronically, a high treatment adherence is required, and therefore the need to increase the tolerability of the drug.

Among the available disease modifying treatments (DMTs), oral administration is preferred by patients with MS. One of the available DMTs for MS with oral administration is the DHODH inhibitor teriflunomide. In a Phase 2 trial of teriflunomide on patients with relapsing forms of MS, a statistically significant decrease in combined unique active (CUA) lesions was observed with teriflunomide compared to placebo after 12 weeks of treatment.

As outlined above, IMU-838 selectively inhibits pyrimidine synthesis in activated cells via inhibition of DHODH, which seems to be a promising approach to treat MS. Teriflunomide, currently approved in the USA and EU to treat RRMS, showed consistent effects across multiple markers of MS burden and activity, including annual relapse rate (ARR) and risk of disability progression in several clinical trials. However, teriflunomide is associated with hepatotoxicity and clinically important AEs, such as diarrhea, alopecia and neutropenia which are thought to be off-target effects related to inhibition of certain kinases and which limit the use of teriflunomide in patients with RRMS. Current data suggest that IMU-838 may show an improved safety and tolerability profile compared with teriflunomide. In addition, because teriflunomide has a prolonged half-life of 19 days in patients with MS, accelerated elimination with cholestyramine or charcoal may be considered when a treatment with teriflunomide must be terminated. The blood half-life of IMU-838 is roughly 30-40 hours and therefore well suited for once daily oral administration and a quick wash-out after treatment discontinuation.

Based on these data and the pharmacodynamics (PD) of vidofludimus, IMU-838 may represent a novel and efficacious oral treatment option for RRMS patients. Thus, trial P2-IMU-838-MS will evaluate the efficacy and safety of 2 different doses of IMU-838 in patients with RRMS.

6 Investigators, trial administrative structure, and committees

The clinical trial is funded by Immunic AG and it is planned to include about 40 trial centers in a variety of countries including Romania, Bulgaria, Ukraine, and Poland and potential additional centers in Hungary and Croatia.

At each center, a 2-physician concept will be established with at least 2 treating physicians and at least 2 evaluating physicians for each patient (i.e. one main physician and one deputy each, for details refer to Section 10.2).

The sponsor, Immunic AG, will be responsible for the overall supervision and administration of the trial. Global project management, data management, statistical analysis and report writing will be done by FGK Clinical Research GmbH, München, Germany (a contract research organization [CRO] - in the following referred to as sponsor's designee). Monitoring will be done by the following CROs:

- Bulgaria and Croatia: Resbiomed Ltd, Sofia, Bulgaria
- Romania and Hungary: Clinical Trial Center SRL, Timisoara, Romania
- Ukraine and Poland: verum.de GmbH, Germering, Germany

Other vendors used in the trial:

- Nuvisan GmbH, Neu-Ulm, Germany: PK measurement of IMU-838, labeling, packaging, and distribution of the IMP
- PharmaLex, Mont-Saint-Guibert, Belgium: PK (population PK modeling)
- LKF - Laboratorium für Klinische Forschung GmbH, Schwentinental, Germany: central clinical safety laboratory
- Labor Lademannbogen, Hamburg, Germany: HIV testing based on Nucleic Acid Amplification Technology
- Institut für Translationale Neurologie, Universitätsklinikum Münster, Germany: central biomarker laboratory
- IMGM Laboratories GmbH, Martinsried, Germany: micro ribonucleic acid-122 (miR-122) assessment and genotyping
- Siena Imaging S.R.L. Siena, Italy: central MRI quality control and evaluation
- Keosys Medical Imaging, Saint-Herblain, France: qualification of MRI sites, upload and anonymization of MRI examinations, technical quality assessment of MRI image files, queries to MRI sites, access of central readers to MRI examinations
- Trium Analysis Online GmbH, München, Germany: electronic case report form (eCRF) and interactive web response system (IWRS)
- Anju Software Belgium Holdings, Antwerpen, Belgium: eCRF for extended treatment period
- SCRATCH Pharmacovigilance GmbH, Butzbach, Germany: pharmacovigilance services

A **steering committee** will be established and provide advice on the conduct of the trial, regular reviews of safety data, and publications (for more details refer to Section 15.4). All members of the steering committee will stay blinded throughout the trial until data base lock and unblinding and will only review blinded data until then.

Addresses and telephone numbers of main responsible parties involved in the conduct of the trial are provided in Section 2.

7 Trial objectives and endpoints

7.1 Trial objectives

Primary

- To evaluate the efficacy of 45 mg/day IMU-838 in the treatment of RRMS based on MRI assessments

Secondary

- To evaluate the efficacy of 30 mg/day IMU-838 in the treatment of RRMS based on MRI assessments
- To evaluate the safety and tolerability of 30 mg/day and 45 mg/day IMU-838 in RRMS patients

Tertiary

- To evaluate PD effects of IMU-838 in RRMS patients
- To evaluate IMU-838 trough values and population PK
- To evaluate the effects of IMU-838 on treatment satisfaction in patients with RRMS

7.2 Trial endpoints

Primary

Efficacy

Difference between 45 mg/day IMU-838 and placebo in the cumulative number of CUA[6] MRI lesions up to Week 24

Key secondary (hierarchical testing to primary efficacy)

Efficacy

Difference between 30 mg/day IMU-838 and placebo in the cumulative number of CUA MRI lesions up to Week 24

Secondary

Efficacy

- Difference between 45 mg/day IMU-838 and 30 mg/day IMU-838 in the cumulative number of CUA MRI lesions at Week 24
- Difference between 30 mg/day IMU-838 and placebo, 45 mg/day IMU-838 and placebo, and 30 mg/day and 45 mg/day IMU-838 for the following MRI parameters:

[6] Sum of the number of all new Gd+ lesions on T1-weighted MRI and the number of all new or substantially enlarged lesions on T2-weighted MRI (non-enhancing on T1-weighted MRI), avoiding double counting.

- Mean number of CUA lesions per patient per scan at Weeks 6, 12, 18 and 24
- Cumulative number of CUA MRI lesions up to Weeks 6, 12, and 18
- Volume changes of T2 lesions at Weeks 6, 12, 18 and 24 compared to Baseline
- T2-lesion load at Weeks 6, 12, 18 and 24 compared to Baseline
- T1-lesion load at Weeks 6, 12, 18 and 24 compared to Baseline
- Cumulative number of new gadolinium enhancing (Gd+) lesions up to Weeks 6, 12, 18 and 24
- Cumulative number of new T2 lesions up to Weeks 6, 12, 18 and 24
- Cumulative number of new T1 lesions up to Weeks 6, 12, 18 and 24
- Proportion of patients without new Gd+ lesions over 24 weeks
- Proportion of patients without new or enlarging T2-weighted lesions over 24 weeks
- Proportion of patients with CUA lesions at Week 24
- Proportion of patients with Gd+ lesions at Week 24
- Proportion of patients with T2 lesions at Week 24

- Differences between individual treatments and between the pooled 30 mg/day and 45 mg/day groups and placebo in the following relapse-related clinical endpoints:
  - Mean annualized relapse rate (during main and extended treatment period)
  - Proportion of relapse-free patients up to Week 24 and at extended periods thereafter
  - Time to relapse at time of final analysis of main part
- Differences between treatments in changes of disease activity as measured by the following clinical parameters:
  - Mean change in the EDSS as compared to Baseline during the main and extended period (every 12 weeks starting at Week 12)
  - Proportion of patients with EDSS progression during the main and extended period (every 12 weeks starting at Week 12, and cumulatively)
- Correlation of MRI-based assessments with quartiles of IMU-838 trough levels at Week 6 and Week 24

Safety

- AEs, serious AEs and clinically significant laboratory abnormalities (as assessed by the investigator)
- AESI:
  - RBC urine positive, at least of moderate intensity
  - Hematuria

  - Retroperitoneal colicky pain with suspected or confirmed nephrolithiasis
- Proportion of patients treated with 30 mg/day or 45 mg/day IMU-838 as compared to placebo who experienced at least one of the following AEs:
  - Neutropenia
  - Lymphopenia
  - Diarrhea
  - Alopecia
  - Hemorrhage
  - Abnormalities in alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), and total bilirubin with both elevations >1.5 x ULN and ≥35% elevated compared to Baseline
- Electrocardiogram (ECG), physical examination, and vital signs
- MiR-122 expression (Change from Baseline to 4 hours after first dose)
- Presence of John Cunningham virus (JCV) deoxyribonucleic acid (DNA) in urine in patients with detectable JCV-DNA in urine at Screening Visit 1, at Week 24, and at end-of-study (EoS)
- Time to treatment discontinuation for any reason
- Rate of treatment discontinuations up to Week 24

Pharmacokinetics

- Population PK at Week 6 (3-10 hours post-dose)
- Plasma trough levels of IMU-838 at Days 7 and Weeks 6, 12, 18, and 24

Pharmacodynamics

- Changes from Baseline in lymphocyte subset parameters as measured by flow cytometry at Weeks 6 and 24 (in selected Biomarker Centers only)
- Changes from Baseline in biased T-cell clonal repertoire based on T-cell receptor deep sequencing at Weeks 6 and 24 (in selected Biomarker Centers only)
- Changes from Baseline in serum neurofilament at Week 24

Health outcome

- Treatment Satisfaction Questionnaire for Medication at Week 6, Week 24 and EoS

8 Trial design and design rationale

8.1 Overall trial design

8.1.1 Design overview

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled trial in patients with RRMS and evidence of active disease. The trial comprises a screening period, a 24-week blinded **main treatment period** evaluating the efficacy of 2 different doses of IMU-838 compared with placebo, and an (initially blinded then open-label) optional **extended treatment period** for up to 9.5 years, during which patients receive 2 doses of IMU-838.

Blinding to individual treatment assignments during the main treatment period and during the beginning of the extended treatment period will be maintained for patients, investigators, and other personnel involved in the conduct of this trial, until results of the data analysis of the main treatment period will be available. Once the results are known, the sponsor will unblind all involved personnel, except for the evaluating physician (see below) by sending a summary report of the results. Depending on the results of the main treatment period, investigators may recommend switching to the other dose in agreement with the patient (also see Section 8.1.4). An overview of the design is shown in Figure 1.

At each center, a 2-physician concept will be established i.e. at least 1 treating physician and at least 1 evaluating physician (and at least a deputy for each of the 2 physicians). The **treating physician** will be responsible for all aspects of the trial with the exception of neurological examinations which will be done by the **evaluating physician**. This 2-physician concept ensures that the EDSS will be assessed blinded to other trial-related assessments (for details on the 2-physician concept refer to Section 10.2).

8.1.2 Screening period and baseline MRI

Patients with a confirmed diagnosis of RRMS and an MRI confirmation of at least one MS-related brain lesion in the last 6 months before informed consent will be included in the trial. Presence of active disease (through presence of MS relapses in the past years) and other eligibility criteria will be confirmed at Screening Visit 1. For patients eligible for the trial following Visit 1 and after review of laboratory results, a baseline MRI will be performed (Screening Visit 2) that will serve as reference for further MRI assessments. The quality of the baseline MRI, as well as the presence of Gd+ and T2 lesions will be evaluated centrally. The baseline MRI may be repeated once for each patient, in case of not acceptable imaging quality. Randomization must be performed within 14 days following the baseline MRI (if the MRI assessment from the central reader is not available within these 14 days, randomization may be postponed by up to 7 days), and within 28 days (up to 35 days due to delay of the centralized

assessment of baseline MRI; or up to 60 days if the baseline MRI needs to be repeated for quality reasons) from Screening Visit 1. Randomization at the beginning of the main treatment period will be stratified by the number of Gd+ lesions (either 0 or ≥1 Gd+ lesions) and by the field strength of the MRI scanner used for trial MRIs (1.5T or 3.0T).

If the baseline MRI will be repeated, patients must be randomized within 14 days of the repeated baseline MRI. In this case, the Screening Visit 1 assessments will be valid for up to 60 days until the day of randomization, but will have to be repeated if 60 days are exceeded.

8.1.3 Main treatment period

On Day 0 of the main treatment period, approximately 195 patients will be randomized 1:1:1 to once-daily oral treatment with 30 mg/day or 45 mg/day IMU-838, or placebo (about 65 patients each) for 24 weeks. For the first 7 days of the main treatment period, patients will only receive half the dose they were randomized to, i.e. 1 tablet of 15 mg/day or 22.5 mg/day IMU-838, or placebo. From Day 7 onwards, patients will receive the full dose, i.e. 2 tablets up until Week 24. Tablets (either 1 or 2) will always be taken at the same time in the morning 15 to 60 minutes before breakfast (please note that on visit days, the patients should take their doses only after trough level blood collection at the site). During the main treatment period, symptomatic assessments (EDSS, clinical neurological symptoms, MRI), safety, biomarkers, and IMU-838 plasma trough levels will be evaluated (see Table 1 for details). The analysis of the main treatment period will be done after all patients completed the end-of-main treatment (EoMT) visit at Week 24.

If the MR image of a patient shows ≥8 Gd+ per scan (investigator alert criterion) as assessed by the central MRI assessment the investigator will be informed. The requirement and the nature of measures to be taken are at the investigator's discretion.

Patients who completed 24 weeks of main treatment and fulfilling further eligibility criteria (see Sections 9.2 and 1), have the option to continue into the extended treatment period.

8.1.4 Optional extended treatment period

All patients who completed the main treatment period, who are eligible, and who chose the option to continue treatment will be re-randomized to the following treatment for the initial blinded weeks of the extended treatment period:

- Patients who received placebo during the main treatment period will be randomized 1:1 to once-daily oral treatment with 30 mg/day or 45 mg/day IMU-838.
- Patients who were treated with IMU-838 during the main treatment period will be re-randomized to the same dose they previously received. Patients, investigator and other trial personnel will remain blinded and unaware to this continued treatment as these

patients will undergo the same randomization procedures and IMP assignments as patients who previously received placebo.

For the first 7 days of the extended treatment period, patients will receive half the dose, i.e. 1 tablet of 15 mg/day or 22.5 mg/day IMU-838. Thereafter and throughout the extended treatment period, patients will take 2 tablets of 15 mg/day or 22.5 mg/day IMU-838. Tablets (either 1 or 2) will always be taken at once in the morning 15 to 60 minutes before breakfast.

For the initial weeks of the extended treatment period, trial participants, treating physicians, evaluating physicians, central MRI readers and all other personnel directly involved in the conduct of the trial will remain blinded to all treatment assignments, until the results of the main treatment period are available. Once the results of the data analysis are available, the sponsor will provide summary results for all treatments of the main treatment period to the investigators. Investigators and patients currently in the extended treatment period will be unblinded to the treatment assignments of the main and the past extended treatment period. From this moment forward, the treatment in the remaining extended treatment period will be open label.

Depending on the results of the main treatment period, investigators may discuss the option of a dose switch for the remaining extended treatment period with those patients still participating in the extended treatment period. Doses may be switched more than once during the extended treatment period but switching should always be done at a clinic visit.

The decision of a dose switch should be a personal decision based on patient-specific circumstances and treatment history with IMU-838. The investigator will discuss any potential risks of a dose switch (i.e. the disease management on the current dose and the potentially added risk of switching to a higher dose). Patients will not be obliged to switch to another dose, even if the higher dose showed beneficial effects during the main treatment period.

During the extended treatment period, the safety, clinical neurological symptoms, and EDSS will be regularly assessed at clinic visits scheduled every 12 weeks (see schedule of assessments in Table 1). The extended treatment period will end with the end-of-treatment (EoT) visit after 9.5 years, unless the patient prematurely terminates the trial participation (for possible reasons see Section 17) or the sponsor terminates the trial (for reasons see Section 19).

All patients discontinuing the trial as scheduled or prematurely will be encouraged to undergo an EoS visit 30 days (+14 days) after the last intake of IMP.

8.2 Trial design rationale

This is a placebo-controlled, double-blind, randomized trial. A placebo arm is included due to regulatory recommendations to evaluate efficacy and adverse effects in randomized, double-blind, placebo-controlled trials. [16]

The distribution of male and female patients will be according to the natural distribution within the trial population, expecting more female than male patients. No corrective measures will be taken.

The trial uses a 2-physician concept, i.e. a treating physician and an evaluating physician for the EDSS, which ensures that neurological examinations will be assessed blinded to other trial-related assessments (for details refer to Section 10.2).

As this is a Phase 2 trial, the MRI based cumulative number of CUA lesions is considered an acceptable primary endpoint in line with the European Medicines Agency (EMA) Guideline on clinical investigation of medicinal products for the treatment of MS. [16] As recommended, the quality of the baseline MRI images will be centrally assessed. The MRI evaluation will be done by a central reader blinded to all clinical information and to treatment assignments (besides trial center and patient number to ensure the correct comparison with previous MRI scans). Investigators will be provided with a detailed MRI Manual to ensure standardized MRI procedures.

To mitigate any ethical concerns that may arise with the use of placebo in RRMS patients, and in line with suggestions from the EMA guidelines, the period of treatment with placebo will be limited to 24 weeks. To reduce the number of patients randomized to the placebo arm and to test 2 doses of IMU-838, a 3-arm design was chosen with 1:1:1 randomization, which will allow the treatment of twice the number of patients with IMU-838 than with placebo. Additionally, an MRI investigator alert criterion has been defined in this protocol.

The primary objective of this trial will be to compare the efficacy of 45 mg/day IMU-838 to placebo after 24 weeks of treatment. The schedule of MRI testing selected is more frequent (every 6 weeks) than usually used in clinical routine, as Gd+ lesions offer the best evidence of recent inflammatory white matter lesions. Enhancement is consistently observed in those lesions in relapsing remitting disease and usually lasts 2 to 6 weeks. Therefore, the time period between MRI scans was chosen to be 6 weeks to have the highest chance of capturing most or all Gd+ lesions.

MRI testing is an accurate and reliable method. The choice of objective MRI-based endpoints will allow to reduce both sample size and trial duration, as opposed to a trial with clinical endpoints only, which usually require a longer trial duration. Typically, MRI trials have a duration of at least 6 months. In this trial, only one treatment arm will be treated for 24 weeks with placebo. At the end of this period, eligible patients will be allowed to participate in an optional extension period under active treatment, which will last up to an additional 9.5 years. Therefore, the overall maximum duration of this trial was chosen to be 516 weeks, to assess all patients completing the blinded treatment period and (after unblinding) the open-label extended treatment period for long-term safety, tolerability and efficacy.

8.3 Risk-benefit assessment

Risks

Based on pre-clinical and clinical studies with the precursor drug 4SC-101 and the single and multiple dose Phase 1 studies with IMU-838, no serious adverse reactions are expected with IMU-838 at doses of <70 mg once daily.

In clinical studies with 4SC-101, including 486 subjects of whom 299 received 4SC-101, no drug-associated clinically relevant adverse reactions were observed at doses of <70 mg once daily. This included the potential target organs liver and kidney identified in animals or during early clinical trials. In a large placebo-controlled, randomized clinical trial of 4SC-101 in patients with RA, the AE profile of 35 mg/day 4SC-101 was similar to the AE profile of placebo. No increased rate of infections and infestations were seen in the treatment arm as compared to placebo in the same trial.

At high 4SC-101 doses (≥70 mg/day or single doses of ≥210 mg) potential drug-related decreases in blood uric acid and increases in urine RBC were observed, in very rare cases presenting as symptomatic hematuria during the first days of treatment. Laboratory findings were consistent with post-renal events and *de novo* precipitates in the urinary tract. However, no cases of symptomatic hematuria were seen at daily doses of 35 mg 4SC-101, the highest therapeutic dose used in previous clinical trials.

Non-significant effects on serum uric acid effects following 50 mg IMU-838 could be further reduced in a Phase 1 trial when subjects received half the dose i.e. 25 mg, during the first week of treatment confirming that the effect on serum uric acid is a treatment initiation effect. Pre-dosing with low doses may therefore further limit the potential risk of AEs of the renal and urinary system, like elevated RBC levels in urine or hematuria.

Based on these results, the underlying mechanism leading to increased RBC in urine appears to be an increased uric acid elimination during the initial days after drug administration. By inhibition of the urate transport system URAT1, IMU-838 may decrease the tubular re-uptake of uric acid in kidneys, leading to an increase in the urinary excretion of uric acid. Increased urine uric acid may in turn result in microcrystallization of uric acid in acidic urine and may lead to the occurrence of RBC in urine. Although this may not regularly lead to clinically relevant AEs or laboratory abnormalities at therapeutic doses, it may be important for patients with risk factors (including increased serum uric acid or higher propensity for urinary concrements) or in patients with a history of gout.

Thus, several risk mitigation measures for urinary events were implemented in this trial:

- Patients will be advised to drink sufficient fluid per day to ensure adequate urine flow.

- Patients will receive only half of their assigned full dose during the first week of treatment as the main changes on uric acid urinary excretion are expected during the initial treatment days.
- Regular urine dipsticks and urine sediment analysis will be performed to monitor presence of RBC in urine.
- Patients with a history of renal diseases, especially those favoring or resulting in nephrolithiasis, with serum uric acid levels at Screening Visit 1 >1.2 x upper limit of normal (ULN), and/or history of gout or symptoms suggestive of gout will be excluded from the trial.

During clinical trials using the previous formulation 4SC-101, 1 SAE of hepatitis was reported in a patient with Gilbert syndrome receiving 35 mg 4SC-101. Gilbert syndrome is a genetic disease characterized by a 70–80% reduction in the glucoronidation activity of UDP-glucuronosyltransferase 1A1 (UGT1A1). IMU-838 is a moderate inhibitor of UGT1A1 which may have contributed to this AE. Patients with known or suspected Gilbert syndrome or with elevation of indirect (unconjugated) bilirubin above 1.2 x ULN will therefore be excluded from this clinical trial.

A thorough analysis of the clinical data did not confirm a potential adverse effect of vidofludimus on liver function tests in patients other than those with Gilbert syndrome. However, patients with liver impairment or elevated liver functions tests (>1.5 x ULN) will be excluded from trial participation and liver enzymes and bilirubin will be regularly monitored throughout the trial. For more information please refer to the investigator's brochure.

Benefits

Vidofludimus has so far been evaluated in about 230 patients with RA and inflammatory bowel disease. A Phase 2 trial for ulcerative colitis is currently ongoing, but results are not available yet.

IMU-838 has currently not been tested for the treatment of RRMS. However beneficial effects are expected based on pre-clinical findings. In the rat spinal cord extract-induced EAE model, treatment with IMU-838 inhibited motor symptoms and reduced EAE-associated weight loss. Further the DHODH inhibitor teriflunomide is already authorized for the treatment of RRMS and similar effects can be expected for IMU-838. However, IMU-838 appears to have several advantages compared to teriflunomide. IMU-838 is safe and can be easily managed by the treating physician for the following reasons:

- The low intra- and inter-patient variation in IMU-838 plasma trough levels reduce the risk of under- or over-dosing of patients compared with teriflunomide.

- IMU-838 has a low risk of major safety issues compared with frequent side-effects observed with teriflunomide.
- In case of treatment termination, IMU-838 will be cleared from the body within a few days, whereas teriflunomide remains in the body for up to 2 years.

Risk management

Risk minimization procedures are implemented for this trial to minimize and assess potential risks to participating patients. These include, but are not limited to:

- specific inclusion and exclusion criteria which ensure that patients who present with characteristics that may increase the risk for an adverse outcome are excluded,
- close monitoring for RBC in urine,
- regular monitoring of liver enzymes
- a 1-week initiation dose at half-dose level.

Risk-benefit assessment

Considering the safety data, the implemented risk minimization measures, the positive data in animal models of MS, the expected benefits in the target population, and the medical need for further treatment in MS, the benefit-risk evaluation is considered favorable.

9 Patient selection

9.1 Sample size

The planned sample size in this trial is approximately 195 patients, randomized 1:1:1 to once-daily oral 30 mg/day or 45 mg/day IMU-838, or placebo (about 65 patients each) for 24 weeks in the main treatment period. During the extended treatment period, patients previously on placebo treatment will be randomized 1:1 to treatment with 30 mg/day or 45 mg/day IMU-838, all other patients will continue their previous treatment. For the sample size calculation see Section 16.1.

The maximum numbers of patients enrolled will be 35 per center and 120 per country.

9.2 Inclusion criteria

Main treatment period

1. Male or female patient (age ≥18 to 55 years, inclusive)
2. Diagnosis of RRMS according to the revised McDonald criteria (2017) [1]

   Note: The diagnosis of MS (including "dissemination in time") must have been established before the patient is screened for the trial.

3. Disease activity evidenced
   - by either at least 2 relapses in the last 24 months, or at least 1 relapse in the last 12 months before randomization (relapses must have been assessed and documented by a physician in the patient files), **AND**
   - ≥1 documented Gd+ MS-related brain lesion, in the last 6 months before informed consent (date of MRI examination as well as copy of MRI report or representative image has to be available and accessible as patient source data at the study site)
4. Expanded Disability Status Scale (EDSS) score between 0 and 4.0 (inclusive) at Screening Visit 1
5. Female patients
   - must be of non-child-bearing potential i.e. surgically sterilized (hysterectomy, bilateral salpingectomy, bilateral oophorectomy at least 6 weeks before Screening Visit 1) or post-menopausal (where postmenopausal is defined as no menses for 12 months without an alternative medical cause), or
   - if of child-bearing potential, must have a negative pregnancy test at Screening Visit 1 (blood test) and before the first IMP intake (Day 0 urine test). They must agree not to attempt to become pregnant, must not donate ova, and must use a highly effective contraceptive method (see below) together with a barrier method between trial consent and 30 days after the last intake of the of the IMP.

     Highly effective forms of birth control are those with a failure rate less than 1% per year and include:

     – oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraceptives associated with inhibition of ovulation
     – oral, injectable, or implantable progestogen-only hormonal contraceptives associated with inhibition of ovulation
     – intrauterine device or intrauterine hormone-releasing system
     – bilateral tubal occlusion
     – vasectomized partner (i.e. the patient's male partner underwent effective surgical sterilization before the female patient entered the clinical trial and is the sole sexual partner of the female patient during the clinical trial)
     – sexual abstinence (acceptable only if it is the patient's usual form of birth control/lifestyle choice; periodic abstinence [e.g. calendar, ovulation, symptothermal, postovulation methods] and withdrawal are no acceptable methods of contraception)

     Barrier methods of contraception include:

- Condom
- Occlusive cap (diaphragm or cervical/vault caps) with spermicidal gel/film/cream/suppository

6. Male patients must agree not to father a child or to donate sperm starting at Screening Visit 1, throughout the clinical trial and for 30 days after the last intake of the IMP. Male patients must also
   - abstain from sexual intercourse with a female partner (acceptable only if it is the patient's usual form of birth control/lifestyle choice), or
   - use adequate barrier contraception during treatment with the IMP and until at least 30 days after the last intake of the IMP, and
   - if they have a female partner of childbearing potential, the partner should use a highly effective contraceptive method as outlined in inclusion criterion 5
   - if they have a pregnant partner, they must use condoms while taking the IMP to avoid exposure of the fetus to the IMP
7. Willingness and ability to comply with the protocol
8. Written informed consent given prior to any trial-related procedure

Inclusion criteria for optional extended treatment period

1. Completed 24 weeks of main treatment
2. Baseline MRI, a Week 24 MRI as well as 2 additional post-dose MRIs

Continuation criteria for optional extended treatment period

1. In case the initial Week 24 MRI was not evaluated at least partially assessable, availability of a repeated Week 24 MRI
2. Week 24 MRI (initial or repeated one, if applicable) evaluated at least partially assessable

9.3 Exclusion criteria

A patient will not be eligible for inclusion if any of the following criteria applies:

MS-related exclusion criteria

1. Any disease other than MS that may better explain the signs and symptoms, including history of complete transverse myelitis
2. Signs and symptoms suggestive of transmissible spongiform encephalopathy, or family members who suffer(ed) from these
3. Clinical signs or presence of laboratory findings suggestive for neuromyelitis optica (NMO) spectrum disorders or MOG-associated encephalomyelitis (i.e. presence of anti-NMO [aquaporin-4] antibodies or anti-MOG-antibodies)

4. MS types other than RRMS
5. Any MRI finding, atypical for MS, including but not limited to a longitudinally extensive spinal cord lesion
6. Any active and uncontrolled coexisting autoimmune disease, other than MS (except for type 1 diabetes mellitus and inflammatory bowel disease)
7. An MS relapse within 30 days before Screening Visit 1 and/or during the screening period (until Day 0)

Therapy exclusion criteria

8. **Any previous or current use of the following MS treatments:** monoclonal antibodies (natalizumab, alemtuzumab, daclizumab, ocrelizumab, anti-CD4, rituximab or belimumab, including their biosimilars), total lymphoid irradiation, bone marrow transplantation, stem cell transplantation, or any use of DHODH inhibitors, including teriflunomide (Aubagio™) or leflunomide (Arava™)
9. **Any use of the following MS treatments within 12 months before the date of informed consent:** any cytokine (other than interferon) or anti-cytokine therapy, intravenous immunoglobulin, mitoxantrone, cytotoxic or immunosuppressive therapy (including, but not limited to azathioprine and cyclophosphamide, excluding only systemic corticosteroids or adrenocorticotrophic hormone [ACTH]), tofacitinib, methotrexate, mycophenolate mofetil, mycophenolate sodium, fingolimod, any calcineurin inhibitors (e.g. tacrolimus, cyclosporine, or pimecrolimus)
10. **Any use of the following MS treatments within 30 days before the date of informed consent**: interferon-β, glatiramer acetate, dimethyl fumarate and plasmapheresis
11. **Within 30 days before the baseline MRI:** Use of systemic corticosteroids (intravenous or oral) or ACTH
12. Use of the following concomitant medications is prohibited **at Screening Visit 1 and throughout the duration of the trial**:
    - any medication known to significantly increase urinary elimination of uric acid, in particular lesinurad (Zurampic™) as well as uricosuric drugs such as probenecid
    - treatments for any malignancy, in particular irinotecan, paclitaxel, tretinoin, bosutinib, sorafinib, enasidenib, erlotinib, regorafenib, pazopanib and nilotinib
    - any drug significantly restricting water diuresis, in particular vasopressin and vasopressin analogs
    - use of rosuvastatin at daily doses higher than 10 mg

13. Use of any investigational product within **8 weeks or 5 x the respective half-life before the date of informed consent**, whichever is longer, and throughout the duration of the trial

Immune response exclusion criteria

14. Conditions negatively affecting the immune response such as previous organ transplant
15. Clinically significantly low lymphocyte and/or neutrophil count (Common Terminology Criteria for AEs Grade of 2 or higher), i.e.
    - lymphocyte count <800/mm³ (0.8 x 10^9/L), and/or
    - neutrophil count <1,500/mm³ (1.5 x 10^9/L)
16. History of chronic systemic infections within 6 months before the date of informed consent, including but not limited to tuberculosis, human immunodeficiency virus (HIV), hepatitis B or C
17. Positive IFNγ release assay for *Mycobacterium tuberculosis* at Screening Visit 1
18. Positive hepatitis B virus surface antigen (HBsAg), hepatitis B core antibody (HBcAb), positive HCV-antibody (HCV-Ab) and/or HIV-antigen-antibody test[7] at Screening Visit 1
19. Any live vaccinations within 30 days before the date of informed consent except for the influenza vaccine

Other medical history and concomitant disease exclusion criteria

20. Presence of the following laboratory values at Screening Visit 1:
    - platelet count <100,000/mm³ (<100 10^9/L)
    - serum creatinine >1.5 x ULN
    - total bilirubin, ALT, or GGT >1.5 x ULN
    - Serum uric acid levels at Screening Visit 1 >1.2 x ULN (for women >6.8 mg/dL, for men >8.4 mg/dL)
    - indirect (unconjugated) bilirubin >1.2 x ULN (i.e. >1.1 mg/dL)
21. Known history of nephrolithiasis or underlying condition with a strong association of nephrolithiasis, including hereditary hyperoxaluria or hereditary hyperuricemia
22. History or clinical diagnosis of gout
23. Renal impairment defined as estimated glomerular filtration rate[8] ≤60 mL/min/1.73m²

[7] A positive HIV-Ag/Ab test will be confirmed by further testing based on Nucleic Acid Amplification Technology (NAAT). If the NAAT test is negative, the patient will be considered HIV negative.

[8] Calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation.

24. Known or suspected Gilbert syndrome
25. Diagnosis or suspected liver function impairment which may cause fluctuating liver function tests during this trial, as assessed by the investigator
26. History or presence of serious or acute heart disease such as uncontrolled cardiac dysrhythmia or arrhythmia, uncontrolled angina pectoris, cardiomyopathy, or uncontrolled congestive heart failure (New York Heart Association [NYHA] class 3 or 4)

    Note: NYHA class 3: Cardiac disease resulting in marked limitation of physical activity. Patients are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain. NYHA class 4: Cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.
27. Clinically relevant, severe pulmonary diseases, uncontrolled hypertension, or poorly controlled diabetes
28. Concurrent malignancy or prior malignancy within the previous 10 years except for the following: adequately-treated non-melanoma skin cancer and adequately-treated cervical cancer
29. History or presence of any major medical or psychiatric illness (such as severe depression, psychosis, bipolar disorder), history of suicide attempt, or current suicidal ideation that in the opinion of the investigator could create undue risk to the patient or could affect adherence with the trial protocol
30. Epilepsy or seizures not adequately controlled by treatment
31. Any other substantial medical condition that in the opinion of the investigator could create undue risk to the patient or could affect adherence with the trial protocol

General exclusion criteria

32. Current or past (within 12 months of Screening Visit 1) alcohol or drug abuse
33. Any condition that would prevent the patient from undergoing an MRI scan, including:
    - claustrophobic conditions
    - unable to receive Gd-based MRI-contrast agents due to history of hypersensitivity to Gd-based contrast agents, or severe renal insufficiency
    - presence of metallic implants incompatible with brain MRI
34. Legal incapacity, limited legal capacity, or any other condition that makes the patient unable to understand the patient information and informed consent form
35. Pregnant or breastfeeding

36. An employee of an investigator or sponsor or an immediate relative of an investigator
37. Patients institutionalized due to judicial or administrative order

Exclusion criteria for optional extended treatment period

1. Any ongoing, clinically significant (as assessed by the investigator) treatment-emergent (started after intake of IMP) AE or laboratory abnormality (including blood chemistry and urinalysis)[9]
2. Significant treatment or trial non-compliance during the main treatment period (as assessed by the investigator), and/or inability or unwillingness to follow instructions by trial personnel
3. Treatment compliance <70% during the main treatment period
4. Significant protocol deviations during the main treatment period that are assessed by the investigator to negatively affect further patient cooperation in this trial

10 Randomization, blinding and unblinding procedures

10.1 Blinding

Trial participants, treating and evaluating physicians (see below for details), central MRI readers and all other personnel directly involved in the conduct of the trial will be blinded to treatment assignments during the main treatment period and for the initial time of the extended treatment period. The evaluating physician will also be blinded to any clinical outcome or treatment change.

To maintain the blind, IMU-838 and placebo tablets will have identical appearance, shape and color, and will have identical labeling and packaging. To minimize the potential for bias, treatment randomization information will be kept confidential by the responsible personnel and will not be released to investigators, other trial center personnel, or the sponsor's designee(s) during the main treatment period and the blinded phase of the extended treatment period.

To maintain the blind during re-randomization for the extended treatment period, all patients will be randomized after Week 24 (see Section 10.6), although patients already assigned to treatment with IMU-838 will be re-assigned to their previous treatment.

The MRI evaluation will be blinded by means of the central MRI assessment procedure.

Once the results of the main treatment period are available, treating physicians, participants, and other involved personnel, except for the evaluating physician, will be unblinded. The evaluating

[9] If treatment-emergent AEs are the reason for exclusion from the extended treatment period, the eligibility can be re-assessed up to 30 days following the last treatment in the main treatment period.

physician will remain blinded to patients' clinical characteristics and treatment assignment during the entire clinical trial.

10.2 Two-physician concept

To achieve blinding for the evaluation of clinical endpoints, a 2-physician concept will be applied, consisting of a 'treating physician' and an 'evaluating physician'. For each role, one deputy must be nominated. Therefore, in total at least 4 staff members have to be involved in the treatment and evaluation of patients at each center. Throughout this protocol, references to the treating physician and evaluating physician include their respective deputies.

The investigator responsible for the conduct of the trial and for supervision of the management of individual patients at the center should not take the role of evaluating physician.

10.2.1 Treating physician

The treating physician will be responsible for all aspects of treatment and clinical management of the patient, including the management of relapses, and will have the same level of blinding as the patient. The treating physician will perform the following activities:

- Physical examinations
- Evaluation of the patient's subjective findings
- Assigning (through IWRS randomization) the IMP and monitoring the trial medication
- Evaluating and managing (serious) AEs, concomitant medication, laboratory results, and relapses
- Relapse assessment of concurrent fever or infection, assessment of EDSS criteria for a relapse based on the current and the previous EDSS scores

The treating physician can never be involved in evaluating EDSS scores.

10.2.2 Evaluating physician

The evaluating physician will perform all standardized neurological examinations needed for the EDSS (see Section 13.3 and A-Table 1).

Throughout the trial, the evaluating physician will not exchange any treatment-related information with the patient or with the treating physician, will not have access to the eCRFs, or to any source documents, and will have no access to any MRI scans or laboratory reports. For all data recordings, the evaluating physician will use hardcopies of the Neurostatus tool forms (see Appendix 1), which will be forwarded to the treating physician after their completion for subsequent storage, both as hardcopies and through transcription of the data into the eCRF.

The interaction with the patient will be restricted to the neurological evaluation. The evaluating physician will not be allowed to talk with the patient about AEs, or any other issue that could potentially disclose the patient's treatment.

Thus, the evaluating physician will be completely blinded to all aspects related to the patient's treatment.

10.3 Patient's identification card

Patients will be provided with patient cards during their trial participation. The patient card allows the clinical trial patients to identify themselves as clinical trial participants, and thus ensures that health care providers (who are not part of this trial) have access to the information about this participation that may be needed to determine the course of the patient's medical treatment.

This may include the possibility of emergency unblinding if needed. In case of an emergency the health care provider should first contact the respective clinical trial investigator, whose name will be given on the patient card (investigator must agree to this). If the investigator is available, he/she will answer any questions. Any subsequent action (e.g. unblinding) will follow the standard processes established for the investigators.

10.4 Emergency unblinding

The premature breaking of the blind will be restricted to emergency cases in which knowledge of the administered drug is necessary for treatment of clinically significant AEs. Whenever possible, the investigator must contact the sponsor or the medical monitor before breaking the blind, and evaluate if the knowledge of the administered drug would have any impact on treatment decisions for the AE. If the blind is broken, the respective patient will be withdrawn from further treatment in this trial and a written explanation must be given by the investigator to the sponsor immediately. Emergency unblinding, if necessary, will be conducted via the IWRS of the eCRF.

10.5 Patient identification

A 6-digit patient identifier consisting of 2 digits each for country (YY), center (XX) and patient (ZZ) i.e. YYXX-ZZ will be assigned to each screened patient.

10.6 Randomization

The trial includes two randomizations, one randomization at the start of the main treatment period, and a second randomization at the start of the extended treatment period.

Eligible patients will be randomized by an IWRS within the eCRF. The IWRS will assign the IMP kits to each patient during the main treatment period and the blinded phase of the extended treatment period. The sites will be supplied with user guides for the IWRS in English or the national language.

Data on the presence or absence of Gd+ lesions needed to stratify the randomization in the main treatment period, will be forwarded by the central MRI reader. In case this information is not available within 14 days after the baseline MRI, the randomization may be delayed by up to an additional 7 days. The center will also use a dedicated single MRI machine for all trial-related MRI examinations, and the field strength of this MRI scanner (1.5 Tesla vs 3.0 Tesla) will also be used as stratification factor for randomization.

The investigators will be provided with technical options and password information to selectively break the code for an individual patient via the IWRS or (as backup) telephone. For further information see Section 10.4.

11 Treatments

11.1 Investigational medicinal product

All IMPs supplied by the sponsor will be manufactured, tested, and released according to current Good Manufacturing Practice guidelines and local requirements.

11.1.1 IMU-838

Name:	IMU-838
Manufacturer:	Immunic AG
Active ingredient:	Vidofludimus calcium (IM90838)
Inactive ingredients:	Microcrystalline cellulose EP, polyvidon K25, crospovidone EP type A, talc, and magnesium stearate
Formulation:	Tablets containing a specific polymorph of vidofludimus calcium
Matrix:	White uncoated tablets, biconvex shape, diameter of 8 mm
Dose strengths:	15 mg and 22.5 mg

11.1.2 Placebo

The placebo tablets will be identical to the IMU-838 tablets in terms of appearance, constitution of inactive ingredients, and packaging.

11.1.3 Packaging, labeling and dispensing

All IMP will be packed and labeled according to applicable regulatory requirements.

The labels will contain at least the following information: route of administration, trial code, randomization number, batch number, expiry date, and instructions for storage.

IMU-838 and placebo tablets will be packaged in 30 mL polyethylene bottles containing 85 tablets.

For the main treatment period, one bottle containing IMP will be dispensed at Day 0, then 2 bottles each at Weeks 6, 12 and 18 (Visits 2-4). For the extended treatment period, 3 bottles of IMP will be dispensed at Week 24/EoMT (Visit 5), and every 12 weeks (until EoT or until Week 504, whichever comes first).

11.1.4 Storage and stability

The investigator is responsible for the safe and proper handling and storage of the IMP at the investigational site. The IMP must be stored in a locked facility with access limited to the investigator and authorized personnel. The investigator must ensure that the IMP is administered only to patients enrolled in this trial.

In stability studies, IMP was stable at ambient (25°C/60% relative humidity) and at accelerated storage conditions (40°C/75% relative humidity), and does not require any special storage conditions. However, the tablets should be protected from direct sun light, moisture, freezing, and extended periods of excessive heat (defined as any temperature above 40°C [104 F]). It should also be advised to keep the bottle tightly closed to protect tablets from moisture.

11.1.5 Treatment dose, dose selection, and administration

The IMP will be administered once daily as oral tablets. Tablets (1 tablet per day for the initial week of treatment, 2 tablets per day thereafter) will be taken once daily in the morning in fasted state (no food after midnight, unrestricted intake of water is always allowed) and taken with one glass of water approximately 15 minutes to 1 hour before breakfast. If 2 tablets need to be taken, these will be taken at the same time.

The following must be considered for IMP intake:

- At all trial visit days in the main treatment period, tablets must be taken at the trial center to allow for pre-dose assessments (i.e. plasma IMU-838 trough levels).

- During the entire trial, patients will not be allowed to have breakfast before they arrive at the trial center (to allow for blood chemistry). Intake of water is always allowed and will not be restricted.
- The patient will be encouraged to drink sufficiently (approximately 1.5 liters per day throughout the trial).

Doses of 30 and 45 mg once daily were chosen based on 4SC-101 data where a daily dose around 35 mg/day was safe, and based on the results of the Phase 1 studies with IMU-838 showing comparable serum exposure of the free acid and calcium salt formulation of vidofludimus. Additionally, the Phase 1 trial of IMU-838 investigating multiple doses over a 14-day period found doses of 30 to 50 mg IMU-838 to be safe. The highest dose used in this trial will be 45 mg/day IMU-838. The area under the concentration time curve of this dose is expected to be far lower than that of 70 mg/day 4SC-101, which was associated with increased RBC in urine. To further reduce the risk of increased urine RBC, patients will receive only half the dose during the first week of treatment as the mechanism of increased uric acid excretion is thought to be more pronounced during treatment initiation.

An elimination half-life of 30-40 hours allows a once daily administration with minimal accumulation (accumulation factor of 2).

11.1.6 Drug accountability and patient compliance

The IMP must not be used outside the context of this trial protocol. The investigator must ask the patient to return excess IMP and all packaging materials (including empty containers) at all applicable visits (see Table 1) for drug accountability. Unused IMP cannot be used outside the context of this trial protocol. Dispensed and returned IMP cannot be re-used for any other patients.

The investigator or authorized staff must document the receipt, dispensing, and return of all IMP received during this trial. These records will include but are not limited to dates, quantities, batch numbers, patient identifiers, and unique interactive response technology codes, as applicable. The investigators must maintain records documenting that patients were provided with the IMP as outlined in the protocol. Furthermore, investigators will reconcile all IMP received from the sponsor and returned from the patient. It is the responsibility of the investigator to reason any discrepancies in IMP accountability. Forms will be provided to ease accountability.

At the end of the clinical trial, or as directed, all remaining and unused IMP must be accurately counted (final drug accountability) and destroyed according to the sponsor's instructions, i.e. to e.g. return all remaining and unused IMP to the sponsor or sponsor's designee.

11.2 Prior and concomitant medications

All medications administered within 1 month before the day of informed consent and until EoS must be documented in the corresponding section of the eCRF. In addition, all **MS-related** therapies since MS diagnosis will be documented in the eCRF.

All medications taken by the patients after giving informed consent and all treatments given in addition to the IMP during the trial are regarded as concomitant treatments and must be documented in the eCRF.

11.2.1 Permitted therapies

11.2.1.1 Corticosteroid treatment of MS relapses

In case of MS-related neurological events, whether or not they meet the protocol's clinical relapse criteria (Section 13.2), corticosteroid treatment will be provided at the discretion of the investigator.

It will be allowed to treat a clinical attack by a 3 to 5-day course of methylprednisolone 500 to 1000 mg/day intravenous (i.v.) without tapering-out.

Note: As corticosteroid treatment may affect the results of MRI scans, specific restrictions will be applied with respect to timing of corticosteroid treatment and planned MRI assessments (see Section 13.4).

11.2.1.2 Plasma exchange due to MS relapses

Only during the extended treatment period and only if with the corticosteroid treatment described above (Section 11.2.1.1) the patient remains non-responsive (and after assessing the risk-benefit ratio as well as treatment options outside of the trial), plasma exchange is allowed for a total of 5 sessions within 2 weeks.

If (in the assessment of the investigator) none of the above-mentioned rescue therapies (corticosteroid treatment and plasma exchange) are sufficiently able to treat the MS relapse, the patient must be discontinued from the trial immediately and other treatment options outside this trial should be considered (see Section 17).

11.2.1.3 Patient's self-medication

As this is an out-patient trial, special care will be taken in questioning the patients on any self-medication. All concomitant medications taken by the patient during the trial from the date of signature of informed consent must be reported in the appropriate section of the eCRF along with dosage information, dates of administration, and reasons for use. If the IMP is discontinued, all remaining medications taken must be recorded in the eCRF until the end of the trial. The

following conditions should be particularly addressed, documenting the reasons why the concomitant medication was administered:

- supportive therapy for MS-related conditions (e.g. pain, fatigue or weakness, incoordination, bladder dysfunction, spasticity etc.)
- medication and/or therapy for MS relapse (as allowed in this trial)
- for a medical condition already reported in the patient's medical history (e.g. any form of pain, especially lumbar pain and headache, depression, etc.)
- for prophylactic use
- as treatment of an AE

11.2.2 Prohibited medication

The use of the following medications and treatments will be prohibited during the trial:

- Monoclonal antibodies (including, but not limited to natalizumab, alemtuzumab, daclizumab, ocrelizumab, anti-CD4, rituximab or belimumab, including their biosimilars)
- Total lymphoid irradiation
- Bone marrow transplantation
- Stem cell transplantation
- Teriflunomide (Aubagio™)
- Leflunomide (Arava™)
- Any cytokine (other than interferon) or anti-cytokine therapy
- I.v. immunoglobulin
- Mitoxantrone
- Cytotoxic or immunosuppressive therapy, including, but not limited to azathioprine and cyclophosphamide
- Any chemotherapy treatment for malignancies, in particular irinotecan, paclitaxel, tretinoin, bosutinib, sorafinib, enasidenib, erlotinib, regorafenib, pazopanib, and nilotinib
- Tofacitinib
- Methotrexate
- Mycophenolate mofetil (CellCept™) or mycophenolate sodium (Myfortic™)
- Fingolimod

- Dimethyl fumarate (DMF, Tecfidera™)
- Any calcineurin inhibitors (e.g. tacrolimus, cyclosporine, or pimecrolimus)
- Interferon-β
- Glatiramer acetate
- ACTH
- Any uricosuric drugs, in particular lesinurad (Zurampic™) as well as probenecid
- Vasopressin of vasopressin analogues
- Rosuvastatin at daily doses higher than 10 mg
- Live vaccines
- Corticosteroid therapy other than for MS-relapses, as defined above (see Section 11.2.1.1) during the main treatment period; during the extended treatment corticosteroid therapy will be allowed also to treat conditions other than MS relapses
- Plasma exchange during the main treatment period; in the extended treatment period it is allowed as defined above (see Section 11.2.1.2)
- Any other IMP

Every treatment with oral or systemic corticosteroids must be reported. Furthermore, specific restrictions will be applied for the timing of MRI assessment relative to corticosteroid treatment (see Section 13.4).

11.2.3 Restricted medications

The concomitant administration of drugs metabolized for more than 70% by CYP2C8 (although not prohibited) should be carefully considered since it cannot be excluded that IMU-838 potentially increases their blood levels. Major substrates of CYP2C8 include

- amodiaquine (anti-malarial)
- dasabuvir (anti-viral), enzalutamide (anti-cancer)
- montelukast (anti-asthmatic), and
- pioglitazone and repaglinide (anti-diabetics)

In addition, concomitant administration of drugs being intermediate or minor CYP2C8 substrates (metabolized for 20-70% or <20% by CYP2C8, respectively) known to have a clinically relevant association with impaired CYP2C8 functionality such as paclitaxel, chloroquine, loperamide, ibuprofen and possibly diclofenac will also be considered with reasonable care. The use of these CYP2C8 substrates as concomitant medication is not prohibited during this trial. However, their use will be restricted in terms of dose and treatment

duration (if possible), alternatives to these drugs will be considered, and patients will be carefully monitored for any indication of toxicity. Given the narrow therapeutic window of ibuprofen, the use of ibuprofen should be carefully considered or, if possible, therapeutic alternatives should be used.

Care should be exercised when using medications that are substrates of the BCRP transport system, especially where the elimination of the medication depends on the BCRP transport system. Patients should be closely monitored for signs and symptoms of excessive exposure to the medicinal products and dosing of these medicinal products should be carefully considered. This is particularly true for statins, and their dose should be lowered to the lowest possible dose. Specifically, doses of rosuvastatin are not to exceed 10 mg daily.

11.3 Precautions and restrictions

Female patients:

- must be of non-child-bearing potential i.e. surgically sterilized (hysterectomy, bilateral salpingectomy, bilateral oophorectomy at least 6 weeks before Screening Visit 1) or post-menopausal (where postmenopausal is defined as no menses for 12 months without an alternative medical cause), or
- if of child-bearing potential, must have a negative pregnancy test at Screening Visit 1 (blood test) and before the first IMP intake (Day 0 urine test). They must agree not to attempt to become pregnant, must not donate ova, and must use a highly effective contraceptive method (see below) together with a barrier method between trial consent and 30 days after the last intake of the IMP.

  Highly effective forms of birth control are those with a failure rate less than 1% per year and include:

  - oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraceptives associated with inhibition of ovulation
  - oral, injectable, or implantable progestogen-only hormonal contraceptives associated with inhibition of ovulation
  - intrauterine device or intrauterine hormone-releasing system
  - bilateral tubal occlusion
  - vasectomized partner (i.e. the patient's male partner underwent effective surgical sterilization before the female patient entered the clinical trial and is the sole sexual partner of the female patient during the clinical trial)
  - sexual abstinence (acceptable only if it is the patient's usual form of birth control/lifestyle choice; periodic abstinence [e.g. calendar, ovulation,

symptothermal, postovulation methods] and withdrawal are no acceptable methods of contraception)

Barrier methods of contraception include:

- Condom
- Occlusive cap (diaphragm or cervical/vault caps) with spermicidal gel/film/cream/suppository

Male patients:

- must agree not to father a child or to donate sperm starting at Screening Visit 1 and throughout the clinical trial and for 3 months after the last intake of the IMP.
- must abstain from sexual intercourse with a female partner (acceptable only if it is the patient's usual form of birth control/lifestyle choice), **or**
- use adequate barrier contraception during treatment with the IMP and for at least 3 months after the last intake of the IMP, **and**
- if they have a pregnant partner, they must use condoms while taking the IMP to avoid exposure of the fetus to the IMP.

If male patients do have a female partner of childbearing potential, the female partner must use a highly effective contraceptive or other effective birth control method (see above) throughout the trial and for 30 days after the last intake of the IMP.

For restrictions concerning the administration of the IMP see Section 11.1.5.

12 Trial schedule

12.1 Trial conduct

An overview of the trial conduct is provided in Table 1. Patients will be given a patient's identification card at Screening Visit 1 stating the patient's name, that the patient is participating in a clinical trial, and the name, address and telephone number of the investigator. Patients must be advised to carry this identification card at all times during their participation in the trial (see also Section 10.3).

Patients will be advised to bring the IMP (including empty bottles) to specified visits. At each visit, patients will be advised to drink a generous amount of fluid per day (approximately 1.5 liters per day throughout the trial are recommended) to ensure adequate urine flow.

Patients will be asked to withhold IMP intake on days of clinic visits, because they will take the IMP at the clinic after all scheduled pre-dose assessments were completed. Patients will also be

asked to fast overnight before all clinic visits as specified in Section 11.1.5, but not to restrict their water intake.

Patients will rest for at least 5 min before any blood is drawn (if applicable) or vital signs are measured.

At all visits (except the EoS visit), patients will be reminded to return to the trial site for their next scheduled visit (see Table 1). However, patients will also be instructed to contact the trial site at any time if they experience a pronounced deterioration of their disease. Patients must be advised to inform the investigator in case of any emergency.

12.2 Screening

Screening Visit 1 (Day -28 to Day -9)

Patients for whom written informed consent (for consent procedures see Section 18.3) was obtained will undergo the assessments shown in Table 1. Patients will be screened for eligibility based on the trial's inclusion and exclusion criteria. The presence of active MS will be confirmed based on the review of previous MRI (performed locally no longer than 6 months before the Screening Visit 1).

Screening Visit 2 (Baseline MRI; Day -14 to Day -3)

A baseline MRI will be performed to serve as reference for all future MRI assessments during the trial. The quality of the baseline MRI will be assessed centrally and may be repeated as soon as possible, if considered necessary by the independent MRI reader. If then acceptable, the repeated MRI will serve as baseline MRI. The screening period may be extended by the time from initial MRI to repeat MRI. However, randomization must occur within 14 days of the repeated MRI. Assessments from Screening Visit 1 will be valid for up to 60 days between Screening Visit 1 and randomization. If 60 days are exceeded, Screening Visit 1-assessments must be repeated.

Re-screening

If the patient experiences a relapse during the screening period, the patient can be re-screened earliest 30 days after the onset of the MS attack.

12.3 Main treatment period

Randomization visit (Visit 0; Day 0)

Patients will undergo the assessments and procedures detailed in Table 1 and will be randomized to treatment with the IMP. Randomization must be performed within 14 days after the baseline MRI (if the baseline MRI was repeated, within 14 days of the repeated MRI) and within 28 days

from obtaining informed consent. Blood samples for assessing IMU-838 trough levels will be collected before IMP intake.

For female patients, the result of the local urine pregnancy test must be available and negative before the first IMP intake.

Visits 1 to 4 (Day 7, Weeks 6, 12 and 18)
Patients will undergo the assessments and procedures detailed in Table 1.

At each visit, blood samples will be taken pre-dose to assess IMU-838 trough levels. At Week 6, an additional plasma sample will be taken 3 to 10 hours post-dose for assessing IMU-838 population PK. Hence, the patient will be asked to remain at the trial site for at least 3 hours, or to return to the site 3 to 10 hours after IMP intake.

In case of premature discontinuation during the main treatment period, patients will undergo all assessments scheduled for the EoMT visit (Table 1).

Visit 5/EoMT (Week 24)
Patients will undergo the assessments and procedures detailed in Table 1 and, if they chose to continue into the optional extended treatment period, will be randomized for treatment in the extended treatment period. All patients who completed the assessments scheduled for this visit and fulfil the eligibility criteria for the extended treatment period have the option to continue into the extended treatment period.

If the Week 24 MRI turns out to be not at least partially assessable it can be repeated as soon as possible. If the repeated MRI is still not at least partially assessable, the patient must be withdrawn from the extended treatment period.

Patients prematurely discontinuing during the main treatment period will undergo the assessments scheduled for this visit (Table 1).

12.4 Extended treatment period

Visits 6 to 45 (Week 36 to Week 504; every 12 weeks)[10]

Patients will undergo the assessments and procedures shown in Table 1. Patients will be assessed every 12 weeks during the extended treatment period.

[10] For patients in the Cohort 2 sub-trial the extended treatment period will be terminated the day the last patient of the Cohort 1 main trial has completed or discontinued the extended treatment period. The extended treatment period for Cohort 2 patients may thus be shorter.

Visit 46/EoT (Week 516)[11]

Patients will undergo the assessments and procedures shown in Table 1 and will be asked to return all remaining IMP and its packaging (including empty bottles) to the trial center for IMP accountability checks.

Patients prematurely discontinuing during the extended treatment period will undergo the assessments scheduled for this visit (Table 1).

12.5 Unscheduled visit

A patient may return for an unscheduled visit at the discretion of investigator to undergo additional safety evaluations (i.e. laboratory re-testing, AE assessments), or for additional neurological evaluations, particularly in the case of neurological symptoms indicative of a potential MS relapse (see Section 13.2).

The data from unscheduled visits will be collected in the eCRF.

12.5.1 Unscheduled visit due to symptoms indicative for an MS relapse

Patients who experience symptoms indicating a potential MS relapse (in the absence of fever, as defined in Section 13.2) will undergo the assessments of an unscheduled visit as shown in Table 1. For allowed treatments of MS relapse, please refer to Section 11.2.1.

If the patient experiences fever, the unscheduled visit should be planned after fever has subsided and if neurological symptoms are still present.

12.5.2 Unscheduled visit due to safety

Patients who experience AEs of clinical relevance, i.e. AEs that in the investigator's opinion require additional safety assessments, or require laboratory re-testing will undergo the assessments of an unscheduled visit as shown in Table 1.

For follow-up of AEs including clinically relevant laboratory events please refer to Section 15.1.6.

12.6 Premature termination

If a patient prematurely discontinues the trial (for possible reasons, please see Section 17)

- during the main treatment period, i.e. before Week 24, all assessments scheduled for the EoMT visit should be performed;

[11] For patients in the Cohort 2 sub-trial the extended treatment period will be terminated the day the last patient of the Cohort 1 main trial has completed or discontinued the extended treatment period. The extended treatment period for Cohort 2 patients may thus be shorter.

- during the extended treatment period, i.e. before Week 516,[10] all assessments scheduled for the EoT visit should be performed.

All patients who prematurely discontinue the trial will be encouraged to complete the EoMT or EoT visit, as described above, as well as the EoS assessments at 30 days (+14 days) after the last IMP intake.

In case of premature withdrawal from the trial, reasons, circumstances and findings will be fully described on the corresponding page in the eCRF respecting the patient's rights.

12.7 End of study visit (EoS; 30 days +14 days after the EoT)

Patients who discontinue the treatment (at any time during the trial or as scheduled) will be asked to return for an EoS visit 30 days (+14 days) after their last IMP intake with assessments as shown in Table 1. For the follow-up of ongoing AEs at EoS, please refer to Section 15.1.6. For patients who have had the EoS visit but who have still ongoing AEs which need to be followed up (see Section 15.1.6) and thus require additional clinic visits, these visits should be documented as an unscheduled visit due to safety.

13 Efficacy assessments and procedures

13.1 Demographics and other baseline assessments

During Screening Visit 1, demographics (including sex, age, and race), a complete medical history including a detailed MS history and previous therapy will be collected. A previous MRI scan (not older than 6 months) will be used to assess the eligibility.

13.2 Neurological assessments and MS relapse

MS clinical events occurring during any of the trial periods must be evaluated to determine whether they qualify as "MS relapse" as defined in this protocol for efficacy assessment.

All of the following criteria must be met for a clinical event to qualify as a relapse:

1. Neurological deficit, either newly appearing or re-appearing, with abnormality specified by both
   - Neurological abnormality separated by at least 30 days from onset of a preceding relapse

   AND
   - Neurological abnormality lasting for at least 24 hours

2. Absence of fever or known infection (i.e. temperature [axillary, oral, or intra-auricular] ≤37.5ºC)
3. Neurological impairment, defined as either
   - Increase in at least one of the functional systems of the EDSS

   OR

   - Increase of the total EDSS score.

   In both cases, the increase in EDSS must correlate with the patient's reported symptoms.

The occurrence of fatigue, mental symptoms, and/or vegetative symptoms without any additional symptom will not classify as a relapse (please see Section 15.1.7 if and when such symptoms must be recorded as an AE).

To maintain blinding, the treating and evaluating physicians must fulfil different tasks in neurological and MS relapse assessments. Whereas the evaluating physician will perform the standardized EDSS assessment (as outlined in Section 13.3), the treating physician will assess neurological symptoms and confirm the presence of MS relapse based on all available data.

At each scheduled visit, the treating physician will ask the patient if any new MS-related neurological symptoms have occurred. If the treating physician expects that a protocol-defined MS relapse has occurred, the evaluating physician will be asked to do an EDSS assessment even if not planned according to the schedule of assessments. When the treating physician receives the EDSS score, he/she will also determine whether the EDSS criterion for an MS relapse is met.

In-between scheduled visits, the patient will be instructed to contact the treating physician immediately if he/she develops new, recurring, or worsening neurological (including visual) symptoms. If symptoms indicative of an MS relapse are reported by the patient, the treating physician will assess whether the symptoms occur in the presence of fever or infection (in case of an unscheduled phone contact, the treating physician may simply ask the patient).

If fever or infection is excluded, the evaluating physician must arrange for a neurological examination (assessment of EDSS) as soon as possible, at the latest within 7 days following the reporting of the event. If fever or infection cannot be excluded, the neurological examination by the evaluating physician will have to be postponed until the fever or the infection has ceased (provided that the symptoms indicative of an MS relapse are still present). Treatment of the MS event with corticosteroids should not begin prior to the assessment by the evaluating physician. For allowed MS relapse treatments in this trial, please refer to Section 11.2.1.

Based on the EDSS scores, in conjunction with the results from previous examinations, the treating physician will determine whether the EDSS criterion for an MS relapse is fulfilled.

Since corticosteroid treatment of MS relapses may affect the results of MRI scans, the occurrence of an MS relapse may result in the postponement of a scheduled MRI scan.

Neurological symptoms characteristic of MS that are captured as new MS related neurological symptoms in the EDSS and/or as MS relapse are efficacy measures and must generally not be documented as AEs. However neurological symptoms which are abnormally severe, not anticipated for the disease or are judged to be related to IMP treatment must be reported as AE (for more details please refer to Section 15.1.7).

13.3 Expanded Disability Status Scale

The EDSS [17] is a widely used and validated instrument evaluating the functional systems of the CNS to describe disease progression and the efficacy of MS therapy. The composite rating system ranges from 0 (normal neurological status) to 10 (death due to MS) in 0.5-unit increments.

The EDSS measures the impairment in 8 functional systems:

- pyramidal - weakness or difficulty moving limbs
- cerebellar - ataxia, loss of coordination or tremor
- brainstem - problems with speech, swallowing and nystagmus
- sensory - numbness or loss of sensations
- bowel and bladder function
- visual function
- cerebral (or mental) functions
- other

Each functional system is scored independently. The combination of findings from the functional system scores allows to establish the final EDSS score.

EDSS steps 1.0 to 4.5 refer to a functional status of patients with MS with some limitations within at least one functional system, but still able to walk without any aid. EDSS steps 5.0 to 9.5 are defined by the impairment to walk. Refer to A-Table 1 (Appendix 1) for details on the EDSS scores.

The EDSS will be assessed by the evaluating physician as scheduled in Table 1, and if possible, before any other assessments scheduled for that visit will be performed. To standardize the EDSS assessment, a paper-based Neurostatus tool set (provided by Neurostatus Systems AG, University Hospital Basel, Neurology, Switzerland) will be used (see Appendix 1) for the

scoring of the impairment within each functional system based on which the EDSS scores will be automatically calculated upon data entry into the eCRF.

To maximize data consistency, the same physician should perform the same assessments for a given patient at approximately the same time of day, whenever possible. The assessments must be performed without consulting the results from previous visits.

The Neurostatus tool should always be retained as a source document and the resulting scores (7 functional systems and 1 ambulatory) and final EDSS score be entered into the eCRF.

To ensure consistency of EDSS scoring across all sites, investigators will receive a standardized manual on scoring EDSS using the Neurostatus tool, which will be supplied to sites by the sponsor.

All evaluating physicians should be familiar with the Neurostatus tool, however no specific qualification level will be required. The qualification level previously obtained by the evaluating physicians participating in this trial will be collected and documented.

13.4 Magnetic resonance imaging

MRI assessments will be performed before the treatment with the IMP (baseline MRI, Section 12.2) and regularly during the main treatment period as scheduled in Table 1.

For central assessment, it is of vital importance that all scans adhere to the standardized MRI protocol (complying with the MRI manual) which will be provided separately. The same dedicated MRI machine (field strength of ≥1.5 Tesla) will be used for all patients at each trial site. The only contrast agents allowed in this trial are macrocyclic gadolinium-containing agents. Details on MRI protocol are described in the MRI Manual.

The baseline MRI and all following scans during the main treatment period will be assessed centrally and no local assessments will be done for trial endpoints. No MRI finding will be communicated to the treating and evaluating investigators involved in this trial as they need to remain blinded to MRI scans results of this trial (except for the investigator alert criteria as defined below). However, the local site needs to assure that every MRI scan is reviewed for any unexpected non-MS findings that would be important for the patient's health. Such important non-MS findings need to be communicated to the treating physician.

A local previously taken MRI scan will only be used to confirm presence of MS-related brain MRI lesions, which is an inclusion criterion (see Section 12.2).

The treating physician at the site will only be informed about the results of the central MRI assessment if the investigator alert criterion was met (i.e. ≥8 Gd+ lesions, observed at a single

post-treatment MRI scan performed at Weeks 6, 12, or 18) or in case of any unexpected finding on the MRI likely not related to the underlying MS disease.

MRI restriction rules

To reduce the impact of corticosteroid treatment on the MRI read-out, the following restrictions for the timing of MRI scans will be applied:

1. No MRI scan is to be performed while a patient is receiving i.v. corticosteroid therapy or for 30 days thereafter (counting from the date of treatment end).
2. Whenever possible, any planned MRI scan should be performed before corticosteroid treatment is initiated. Any post-randomization MRI scan may be prematurely performed for up to 2 weeks if a corticosteroid treatment needs to be initiated.
3. No further MRI scans will be performed until the following criteria has been met:
   a. If the baseline MRI scan at Screening Visit 2 (S2) cannot be performed due to corticosteroid treatment of a relapse, the patient may be fully re-screened earliest 30 days after the onset of the MS attack (including all local and central laboratory assessment, and baseline MRI).
   b. If any post-dose MRI scan after Day 0 cannot be performed due to corticosteroid treatment, the MRI scan for this timepoint will be postponed to fulfill the above mentioned criteria of 30 days following end of corticosteroid therapy.

14 Pharmacokinetics, pharmacodynamics, and health outcome assessments

14.1 Pharmacokinetics

IMU-838 plasma trough level concentrations will be determined by validated direct liquid chromatography tandem-mass spectrometry. This method determines the concentration of the active moiety vidofludimus contained in IMU-838. Details of the assay will be described in a separate bioanalytical report.

Plasma samples for IMU-838 trough levels will be assessed centrally at Nuvisan. Samples will be collected and subsequently stored at -20°C at the site, and shipped to the central laboratory as frozen samples, as appropriate. Investigators will be provided with detailed written instructions how to collect, handle, store, and ship the samples.

Plasma trough levels of IMU-838

Blood samples to assess IMU-838 serum trough values will be collected in all patients as specified in the schedule of assessments during the main treatment period (Table 1).

Patients are required to withhold intake of the IMP at each visit until after the blood sample collection. If the patient inadvertently took the IMP on those days, blood samples for trough levels will only be taken within 1.5 hours of IMP intake. If 1.5 hours are exceeded, no blood sample for trough levels will be collected. Both cases will be recorded as protocol deviations.

Trough levels of IMU-838 (trough level quartiles) will be correlated with selected safety and efficacy variables.

Population PK

Blood samples for population PK will only be collected at Week 6 (Visit 2) pre-dose, and a second sample at 3 to 10 hours post dose.

The first blood draw will be a trough level draw as on other study visits during the main treatment period. 15 minutes after patients have taken IMP, they are allowed to eat and drink. For the second post-dose blood sample on the same day, the patient may remain at the trial center for at least 3 hours or leave the center and return to the trial center any time between 3 and 10 hours of the morning blood draw. If feasible, these PK data will be evaluated (in combination with PK data from other trials) using a non-linear mixed effects modeling. A correlation with safety and efficacy may be evaluated if warranted by the data.

Plasma PK samples will be stored at -20°C at the site until the next scheduled dry ice shipment to the central laboratory (see Table 1).

14.2 Pharmacodynamics

14.2.1 Neurofilament

Neurofilaments light chain are an emerging serum biomarker for acute and chronic neuronal damage and will be assessed as detailed in Table 1. Samples will be centrally analyzed using Lab Kit NFL.

14.2.2 Peripheral blood mononuclear cell-based biomarkers

Peripheral blood mononuclear cell (PBMC)-based biomarkers will be assessed in a subset of patients only at selected Biomarker centers and will include lymphocyte subset analysis and T-cell clonal repertoire assessment (see Table 1). The lymphocyte subset will be analyzed by immunophenotyping and flow cytometry. The T-cell clonal repertoire will be analyzed by deep sequencing of T-cell receptors.

PBMC-based biomarkers will be assessed centrally using Lab Kit PD.

14.2.3 Blood genotyping

At Day 0 before dosing, a single blood sample per patient will be collected for genotyping. This includes assessment of gene and single nucleotide mutations for genes coding for metabolizing enzymes, transporter proteins, and for the target protein DHODH.

Samples for genotyping (Lab Kit G) will be collected and stored at -20°C at the center until the next scheduled dry ice shipment to the central laboratory for analysis. Investigators will be provided with detailed written instructions how to collect, handle, store, and ship the respective samples. Samples will be evaluated centrally.

14.3 Health outcome assessment

The patient rated outcome will be assessed based on answering questions of the Treatment Satisfaction Questionnaire for Medication (TSQM).

The TSQM is a reliable and valid instrument to assess patients' satisfaction with medication, providing scores on 4 scales: side effects, performance, convenience and global satisfaction. [18] Patients will be asked to indicate their level of satisfaction with the treatment by answering the 14 questions of the TSQM (refer to Appendix 2) as scheduled in Table 1. Patients will complete the TSQM during respective clinic visits and results will then be transferred to the eCRF.

15 Safety assessments

15.1 Adverse events documentation and reporting

15.1.1 Definitions

15.1.1.1 Adverse events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, 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 the IMP, whether or not related to the IMP.

Overdosing, defined as intake of more than twice the intended dose, will not be considered an AE but must be documented as protocol deviation. However, symptoms associated with overdose are considered adverse drug reactions (ADR, for definition see below).

Untoward medical experiences occurring during pre-treatment periods do not meet the above-mentioned definition of AE. Nevertheless, they have to be documented in the same way as AEs, if they occur in the safety monitoring period, i.e. between signing the informed consent form and completion of the EoS visit. Should they already be present at the Screening Visit 1 and don't worsen later on, they will only be documented as medical history.

A surgery or procedure scheduled to occur during the trial will not be considered an AE if the surgery or procedure will be performed for a pre-existing condition and the surgery or procedure was planned prior to trial entry. However, if the pre-existing condition deteriorates unexpectedly during the trial (e.g. surgery performed earlier than planned), then the deterioration of the condition for which the surgery or procedure is being done will be considered an AE.

Diagnostic medical or non-surgical procedures, including MRI will not be considered as AEs. Hospital admission for social or convenience reasons will also not be recorded as AE.

AEs that occur between signing the informed consent form and the time when the patient first administers the IMP (Day 0) are defined as pre-treatment AEs.

Treatment-emergent adverse events are defined as any event not present prior to the first intake of IMP or any event already present that worsens in either intensity or frequency following exposure to the IMP.

A continuous event with changing intensities will be considered as one event of the most severe intensity documented. A continuous event with a changing seriousness will also be considered as one event, but the start and stop date of the time the event is serious must be separately documented. Clearly separated episodes of an event will be considered as separate events.

For AESIs see Section 15.1.3.

15.1.1.2 Adverse drug reactions and unexpected adverse drug reactions

All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to the IMP qualify as ADR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

An unexpected ADR is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unapproved investigational product or package insert or summary of product characteristics for an approved product). Reports that add significant information on specificity or severity of a known, already documented AE constitute unexpected AEs, too. For example, an event more specific or more severe than described in the reference document would be considered 'unexpected'. Specific

examples would be: acute renal failure as a labeled AE with a subsequent new report of interstitial nephritis or hepatitis with a subsequent report of autoimmune hepatitis.

15.1.1.3 Serious adverse events

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

- results in death
- is life-threatening
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- results in a congenital abnormality or birth defect

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death, if it were more severe.

Medical and scientific judgment will be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These will usually also be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. In addition, new malignancies that occur during the participation in the trial are defined as important medical events and must be reported as SAEs.

An SAE requires that the underlying event is considered an AE as defined in Section 15.1.1.1.

Hospitalizations due to a surgery or procedure during the trial will not be considered an SAE if the surgery or procedure will be performed for a pre-existing condition and the surgery or procedure was planned prior to trial entry. However, if the pre-existing condition deteriorates unexpectedly during the trial (e.g. surgery performed earlier than planned), then the deterioration of the condition leading to hospitalization will be considered an SAE. Hospital admission for social or convenience reasons will not be recorded as SAE.

15.1.1.4 Suspected unexpected serious adverse reaction

A **suspected unexpected serious adverse reaction (SUSAR)** is a serious adverse reaction (SAR) that is unexpected or for which the development is uncommonly (unexpected issue)

observed during a clinical trial and for which there is at least a reasonable possibility of a causal relationship with the IMP.

15.1.2 Classification of adverse events

Classification of AEs will be performed by the investigator.

Causality

The causal relationship between the AE and the administration of the IMP or trial procedure will be assessed as follows:

- Related: Implies a reasonable possibility of a causal relationship between the event and the IMP or procedure. This means that there are facts (evidence) or arguments to suggest a causal relationship.
- Not related: Implies no reasonable possibility of a causal relationship between the event and the IMP or procedure. This means that there are neither facts (evidence) nor arguments to suggest a causal relationship.

Severity

Severity is a clinical observation and describes the intensity of the event.

- Mild: Any symptom, of which the patient is aware, but which is easily tolerated
- Moderate: Any symptom, which is discomforting enough to cause interference with a patient's usual activity
- Severe: Any symptom, which causes a patient's inability to perform usual activity

For the severity classification of hematuria see Section 15.1.3.

Outcome categories

Recovered:	The patient has fully recovered from the event or the condition has returned to the level observed at Baseline
Recovering:	The patient has recovered from the event, but the condition has not returned to the level observed at Baseline;
Not recovered:	The event is ongoing at the time of reporting and the patient has still not recovered
Recovered with sequelae:	As a result of the AE, the patient suffered persistent and significant disability/incapacity (e.g. became blind, deaf or paralyzed)

Fatal:	The patient died due to the event. If the patient died due to other circumstances than the event, the outcome should be stated otherwise (e.g. not recovered or recovering)
Unknown:	If the outcome is not known or not reported

15.1.3 Adverse events of special interest

The following AEs are defined as AESIs, if these events are different from any pre-existing conditions or a result from known conditions:

- RBC urine positive (as defined below), at least of moderate intensity
- Hematuria (as defined below)
- Retroperitoneal colicky pain with suspected or confirmed nephrolithiasis

Evaluation and assessments of RBC in urine

The evaluation of RBC in urine will be solely based on findings from microscopic examinations of urinary sediment and not from dipstick reading only. [19] Therefore all conspicuous dipstick readings will be followed up by a microscopic examination of urinary sediment. All findings of RBC in urine per high-powered field (HPF) will be listed as urinalysis abnormalities but not as an AE, if assessed by the investigator as not clinically significant. The investigator will also assess any increased RBC in urine as not clinically significant, if there are more likely alternatives to explain this finding. The following alternative explanations of RBC in urine high will be considered:

- The urine sample was not properly collected (random midstream clean-catch collection) or evidence of contamination (e.g. presence of bacteria or an unusual number of epithelial cells in urine sediment not explained by other conditions).
- Evidence of infection not considered secondary to a drug-induced damage.
- Likely benign causes, such as menstruation, vigorous exercise, viral illness, trauma, and infection.

If any finding of “RBC in urine high” is assessed by the investigator as clinically significant, this finding will be reported as the AE “RBC urine positive”.

Evaluation and assessment of hematuria

Any occurrence of RBC urine positive will only be defined as the AE “hematuria” if at least one of the following 2 conditions are met:

- ≥5 RBCs per HPF were found in at least 2 consecutive, properly collected urinalysis specimens, [20] **and/or**

- the finding of RBC urine positive had diagnostic or therapeutic consequences.

Severity assessment of hematuria

Severity is a clinical observation and describes the intensity of the event. The severity of hematuria is classified as follows:

- Mild: Asymptomatic hematuria; clinical or diagnostic observations only
- Moderate: Symptomatic hematuria; e.g. with moderate flank pain (and including short-term*, standard-dose therapy with oral nonsteroidal anti-inflammatory drugs, oral acetaminophen or oral aspirin), interfering with but not limiting activities of daily living
- Severe: Gross or macrohematuria

  Any hematuria with severe flank pain limiting activities of daily living.

  Any hematuria requiring additional treatment (e.g. oral anti-emetics or muscle relaxants, around the clock narcotic analgesics, use of narcotics or any intravenous treatment) or procedures for maintaining adequate urinary flow (e.g. urinary catheter or bladder irrigation).

* For less than 24 hours.

15.1.4 Documentation of adverse events

All AEs occurring between the date written informed consent was obtained and 30 days after the patient's last IMP intake (observation period) must be recorded. Information on AEs will be derived by non-directive questioning of the patients in general terms at each visit (e.g. "How do you feel?" or "How have you been since the last questioning?"), by patients' spontaneous reports, or by observation. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

All AEs that occur during the observation period of the trial as described above will be recorded in the patient's AE section of the eCRF and will include the following information: a description of the AE, date of onset and resolution, severity, relationship to the IMP, relationship to trial procedure, action taken, and outcome. For SAEs, the SAE form must be completed (see Section 15.1.5).

15.1.5 Documentation and reporting of immediately reportable adverse events

Any AESI (see Section 15.1.3), any unexpected AE that could adversely affect the safety of the patient or the conduct of the trial, and any SAE that occurs during this trial will be reported (via the "Adverse Event of Special Interest Form" or the "Serious Adverse Event Form") to the

sponsor immediately (i.e. within 24 hours). The information will include at least the following data:

- Name, address, and telephone number of the reporting investigator
- Investigational product(s)
- Trial code
- Patient identification number, sex, and date of birth
- Description of the AE, measures taken and outcome (at the time of reporting)
- Assessment of causality to the IMP by the investigator

Reports will be addressed to:

SCRATCH Pharmacovigilance GmbH	
Schlossstrasse 25, 35510 Butzbach, Germany	
E-mail:	safety-immunic@scratch-pv.com
Telephone:	+49 6033 74535 50
Fax:	+49 6033 74535 59

The sponsor ensures that all relevant information about SUSARs that are fatal or life threatening is recorded. Reporting of SUSARs to the independent ethics committee (IEC) and regulatory authorities will follow pertinent national legislation.

The sponsor will inform as soon as possible and following national pertinent national legislation the regulatory authorities and the IECs about any event that necessitates reconsideration of the benefit-risk-ratio of the IMP. These events are in particular:

- single cases of expected SARs with an unexpected outcome,
- an increased incidence of expected SARs considered clinically significant,
- SUSARs occurring after a concerned person has completed the trial,
- events related to the conduct of the trial or the development of the tested IMP possibly affecting the safety of the concerned persons.

All additional measures deemed necessary through new findings and taken by the sponsor or the investigator to protect the safety of the persons concerned and their triggering circumstances will be reported as soon as possible to the concerned regulatory authorities and the IECs, if applicable.

Periodic safety reporting to regulatory authorities and the IECs will follow pertinent national legislation.

In the event of a fatality, the "Trial participant's insurer" will be informed by the sponsor's designee within 24 hours of gaining knowledge of the event. In case of other SAEs, the "Trial participant's insurer" will be informed promptly.

15.1.6 Follow-up of adverse events

All SAEs judged to be related to the IMP must be followed by the investigator until the patient has recovered, recovered with sequelae, died, or until the investigator determines that the patient's condition is stable, whichever occurs first. All other AEs must be followed by the investigator until the conditions mentioned above are met or until the EoS visit (30 days after the last IMP intake), whichever comes first, and until all AE-related queries for the patient have been resolved. The investigator will take all appropriate and necessary therapeutic measures required for resolution of the AE, if applicable. All efforts to collect follow-up information must be documented in the source data.

Follow-up information should be supplied on the respective forms of the eCRF.

During and following a patient's participation in this trial, the investigator must ensure that adequate medical care is provided to a patient for any AEs related to the trial, including clinically significant laboratory values.

15.1.7 Handling of events typical for MS

The disease characteristics, in particular those neurological symptoms that are characteristic for MS and neurological functional systems scores during the EDSS assessment, will be regularly captured throughout the trial and are classified as efficacy assessments. For this reason, any MS-related symptoms should not be collected as AE, if any one of the following criteria applies:

- These MS-related symptoms were already present at Screening (and their fluctuations in pattern and intensity throughout the trial are considered anticipated based on the individual patient's disease history), or
- These MS-related symptoms had already occurred during the disease history of the patient prior to the trial and their pattern and intensity during the course of the clinical trial is consistent with the individual course of the disease, or
- These MS-symptoms are in close temporal correlation to an acute exacerbation of MS in this patient and (in the assessment of the investigator) have a clear relationship to this exacerbation event and have an anticipated intensity for such exacerbation event.

The terms "MS relapse", "MS attack", "MS exacerbation" or "worsening of MS" will not be considered as AEs, since MS relapse or worsening of EDSS score will be collected as efficacy parameters in this trial.

However, neurological symptoms should be collected as an AE (even if those symptoms are characteristic for patients with MS), if any of the following conditions applies:

- Any new or worsened neurological symptom if its course is abnormally severe or abnormal in its temporal pattern (even if any of the above-mentioned criteria for an exclusion from AE collection applies), or
- Any new neurological symptom that does not have a close temporal relationship to an exacerbation event and (in the assessment of the investigator) is not anticipated for the course of the disease, or
- Any new neurological symptoms that (in the assessment of the investigator) is correlated to start or change of IMP in this trial.

Only those neurological symptoms which qualify as AEs according to the definition above may potentially be reportable as SAEs. In these cases, the seriousness criterion (e.g. hospitalization) must be assessed and an SAE report completed and sent to the sponsor.

The terms “MS relapse”, “MS attack”, “MS exacerbation”, “worsening of MS” or other MS-related symptoms which should not be collected as AEs according to the description above, can per definition not qualify as SAE, even if they fulfill a seriousness criterion such as hospitalization.

15.1.8 Pregnancies

Should a pregnancy occur in a female patient, or in a female partner of a male patient, it must be reported to the sponsor within 24 hours of the first awareness of the event and be recorded on the appropriate pregnancy form. The trial participation of patients who become pregnant during the trial after signing the informed consent will be discontinued immediately.

A pregnancy is not regarded an AE unless there is a suspicion that the IMP may have interfered with the effectiveness of a contraceptive method. Whenever possible, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality, maternal and/or new-born complications) must be followed up and documented even if the patient was discontinued from the trial. All reports of congenital abnormalities or birth defects are SAEs. Spontaneous miscarriages will also be reported and handled as SAEs. Elective abortions without complications will not be handled as AEs.

Pregnancy follow-up will be recorded on the pregnancy form and will include an assessment of the possible relationship of the IMP to any pregnancy outcome.

15.2 Laboratory investigations

Clinical laboratory tests will be performed at the times indicated in the schedule of assessments (Table 1).

All laboratory samples must be clearly and fully labeled according to the central laboratory manual. The laboratory reports received from the central laboratory via email or fax will be printed, reviewed, signed, and dated by the investigator, and filed at the center. The laboratory results will be additionally imported into the eCRF.

Abnormal results will be assessed by the investigator and classified as clinically significant (yes/no). Clinically significantly abnormal values must be reported as AE, if not already clinically significantly abnormal at Baseline (i.e. pre-dose on Day 0) or Screening Visit 1 or if there are known circumstances unrelated to a disease or the medication (such as patient activities or sample handling) that are a likely explanations for the abnormal value.

Persistent clinically significant abnormal values must be followed up using local laboratory values until the cause is determined or until they returned to normal or to the level observed at Baseline (for follow-up of clinically significant laboratory values reported as AEs, see Section 15.1.6).

15.2.1 Pregnancy tests

Female patients of childbearing potential, i.e. not postmenopausal (where postmenopausal state is defined as no menses for 12 months without an alternative medical cause) or not surgically sterile, must have a negative pregnancy test before the first intake of the IMP. A blood pregnancy test is required at Screening Visit 1. Any local urine pregnancy test that shows a positive result must be followed up with a confirmatory local blood pregnancy test.

Additional urine pregnancy testing will be performed locally as scheduled in Table 1 for all female patients of childbearing potential. For follow-up procedures in case of pregnancy see Section 15.1.8.

15.2.2 Blood chemistry, hematology, and coagulation

15.2.2.1 Assessments

Blood chemistry, hematology and coagulation assessments will be performed using Lab Kits A, B and C as scheduled in Table 1. The following parameters will be tested:

Lab Kits A and B

- Hematology: Erythrocytes, leucocytes, differential leucocyte count (neutrophils, eosinophils, basophils, lymphocytes, monocytes),

hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), platelets.

- Biochemistry: ***Liver function monitoring:*** AST, ALT, alkaline phosphatase, GGT, total bilirubin, unconjugated (indirect) and conjugated (direct) bilirubin.
  Renal function monitoring: creatinine, uric acid, blood urea nitrogen (BUN). eGFR will be calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.
  Other parameters*:* Sodium (Na), potassium (K), magnesium, chloride (Cl), inorganic phosphate (P), calcium (Ca), creatine phosphokinase, lactate dehydrogenase, amylase, lipase, C-reactive protein (CRP), total protein, albumin, glucose, hemoglobin A1c, triglycerides, cholesterol
- Coagulation (only in Lab Kit A):
  Prothrombin time, activated partial thromboplastin time, and international normalized ratio (INR)

Lab Kit C

- Hematology: Erythrocytes, leucocytes, hemoglobin, hematocrit, MCV, MCH, platelets
- Biochemistry: ***Liver function monitoring:*** AST, ALT, AP, GGT, total bilirubin, unconjugated (indirect) and conjugated (direct) bilirubin.
  Renal function monitoring: creatinine, uric acid, BUN. eGFR clearance will be calculated according to the CKD-EPI equation.
  Other parameters*:* Na, K, Cl, P, Ca, CRP, total protein, amylase, lipase, albumin, glucose, triglycerides, cholesterol

Blood chemistry, hematology, and coagulation analyses will be done centrally (see Section 6). Abnormal results will be classified as clinically significant (yes/no). Clinically significantly abnormal values, which were not clinically significantly abnormal at Baseline, must be reported as AE.

Blood samples will be collected, handled and stored according to the instructions provided by the central laboratory. Coagulation samples will be collected and stored at -20°C at the site until the next scheduled shipment to the central laboratory for analysis. Dry ice shipments may be delayed for up to 2 weeks if another patient is expected to finish the respective visit.

Samples collected at Baseline, stored but not used for the primary analysis ("B-sample"), may be used in future research to evaluate other serum markers (e.g. Epstein-Barr Virus) and address research questions that may arise after trial completion.

15.2.2.2 Monitoring of hepatotoxicity

Patients will be monitored throughout the trial for evidence of hepatotoxicity with regular assessments (every 6 weeks during the main treatment period and every 12 weeks during the extended treatment period) of liver enzymes e.g. AST, ALT, AP, GGT and total and indirect bilirubin. In addition, the exploratory biomarker Micro ribonucleic acid-122 (miR-122) of drug-induced liver injury will be assessed pre-dose and at 4 hours after the first dose of the IMP in the main treatment period.

In case of an increase in ALT, GGT or AST to >3 x ULN, or indirect or total bilirubin >2 x ULN during dosing with the IMP, testing of all liver parameters (ALT, AST, GGT, total and indirect bilirubin) will be repeated as soon as possible (to be documented as unscheduled visit due to safety). Patients will also be asked about symptoms. Concomitant medication will be checked for hepatotoxic medications and possible drug-drug interactions.

If repeat testing still shows ALT or AST to be >3 x ULN, or bilirubin >2 x ULN close monitoring of the respective patient will be initiated (including but not limited to repeating liver enzymes and serum bilirubin tests 2 or 3 times weekly, detailed evaluation of medical history and concomitant drug use, ruling out any other cause of liver enzyme increases, and further liver function tests as considered appropriate by the investigator).

Treatment with the IMP will be discontinued if at least one of the following applies (hepatoxicity-related stopping rules):

- ALT or AST >8 x ULN
- ALT or AST >5 x ULN for more than 2 weeks
- ALT or AST >3 x ULN, and total bilirubin >2 x ULN or INR >1.5 x ULN
- ALT or AST >3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia
- Indirect bilirubin >3 x ULN

15.2.3 Urinalysis

15.2.3.1 Assessments

Urine assessments will be performed using Lab Kits A, B, and C as scheduled in Table 1, including the following parameters:

Lab Kits A and B

- pH, nitrites, hemoglobin, protein, albumin, glucose, ketones, uric acid, creatinine
- microscopic examination of the urine sediment: RBC, white blood cells, epithelial cells, bacteria, casts, crystals (including identification of crystals, if possible)

Lab Kit C

- pH, nitrites, hemoglobin, protein, albumin, glucose, ketones, uric acid, creatinine
- a dipstick analysis, including the assessment of RBC in urine, performed and read centrally[12]
- if the dipstick is positive for RBC in urine, a urine sediment analysis will be performed: RBC, white blood cells, epithelial cells, bacteria, casts, crystals (including identification of crystals, if possible)

Urinalysis will be done centrally (see Section 6). Abnormal results will be classified as clinically significant (yes/no). Clinically significantly abnormal values must be reported as AE, if not already clinically significantly abnormal at Baseline.

The handling and collection of urine samples will be detailed in the Laboratory Manual.

15.2.3.2 Monitoring of red blood cells in urine

Urinalysis for presence of RBC in urine (microscopic examination of urinary sediment) will be regularly assessed throughout the main treatment period. Urinary screening during the extended treatment period will be performed with urine dipstick assessments for RBC in urine. A positive dipstick assessment will trigger a full urine sediment analysis. In addition, plasma uric acid will be regularly monitored throughout the entire trial. Assessment of RBC in urine and hematuria as laboratory abnormality and/or AE should be based solely on findings from the microscopic examination of urinary sediment and not on dipstick readings only. [19] For further information see Section 15.1.3.

15.2.4 miR-122 expression and John Cunningham virus DNA

The biomarker **miR-122** is an early indicator of drug-induced liver injury. At Day 0, before dosing and 4 hours after dosing, a blood sample per patient will be collected for miR-122 expression. Samples will be centrally analyzed using Lab Kit BM. Samples for miR-122 quantification will be collected and stored at -20°C at the site until the next scheduled dry ice shipment to the central laboratory for analysis. Dry ice shipments may be delayed for up to 2 weeks if another patient is expected to finish the respective visit.

[12] The dipstick as well as the urine sample (to be included for potential urine sediment analysis) will be shipped to the central laboratory.

Detection of urinary **JCV-DNA**: at time points given in Table 1, urine samples will be used to determine whether the patient is an active secretor of the JCV-DNA in urine, and if this secretion is influenced by administration of IMU-838. Samples will be centrally analyzed using Lab Kit JCV.

Investigators will be provided with detailed written instructions how to collect, handle, store, and ship the respective samples.

15.2.5 Serology

Tests for HBsAg, HBcAb, HCV-Ab, and HIV-Ag/Ab combined test, and a *Mycobacterium tuberculosis* IFNγ-release assay (Tbc-IGRA) will be performed during Screening Visit 1. The HBcAb assay will be a combined IgG and IgM test. In case of a positive result, IgM will be evaluated separately.

A positive HIV-Ag/Ab test will be followed up by further HIV testing based on Nucleic Acid Amplification Technology. A patient will only be considered HIV positive, and must be excluded from the trial, when both tests are positive.

The Tbc-IGRA will be done locally, all other Screening Visit 1 tests will be done centrally using Lab Kit S.

15.2.6 Screening laboratory

The screening laboratory tests include:

- Blood pregnancy test
- Hematology and blood biochemistry: Neutrophils, lymphocytes, platelets, serum creatinine, ALT, AST, and GGT, total, direct and indirect bilirubin, uric acid, eGFR (CKD-EPI)
- Serology: Tbc-IGRA, HCV-Ab, HIV-Ag/Ab, HBsAg, HBcAb (IgG/IgM)

The screening tests for Tbc-IGRA will be done locally at the trial site. All other tests will be done centrally using Lab Kit S.

15.3 Vital signs, physical examination, and ECG

Vital signs, routine physical examinations, and ECG will be performed as scheduled in Table 1.

Vital signs

Vital signs will include: height (only at Screening), weight, body temperature (ºC), respiratory rate, pulse rates, systolic and diastolic blood pressures. Height in centimeters and weight in kilograms will be recorded without shoes.

Blood pressure (systolic and diastolic), and pulse must be measured with the patient in a seated position, after at least 5 minutes at rest.

Changes in vital signs judged by the investigator as clinically significant will be reported as an AE.

Physical examination

Physical examinations will cover the following body systems: general appearance, skin, neck (including thyroid), throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, neurological systems, and, if applicable, others.

Any new clinically significant finding compared to Screening Visit 1 must be documented as AE.

Any clinically significant finding at Screening Visit 1 must be documented in the medical history section of the eCRF.

12-lead electrocardiogram

The 12-lead ECG (I, II, III, aVR, aVL, aVF, V_1-V_6) will be recorded in supine position after at least 5 minutes at rest using the local standard ECG machine. The ECG will be analyzed qualitatively (normal or abnormal, if abnormal clinically significant [yes/no]). The heart rate, PQ-, QRS-, and QT-intervals, as well as the heart rate-corrected QT_c interval (according to Bazett's formula) will be determined. All procedures will be done according to local practice. Any findings from ECGs collected after the IMP administration will be captured as AEs if, in the opinion of the investigator, there was a clinically significant change from Screening Visit 1.

15.4 Steering committee

A steering committee will provide advice on the conduct of the trial, the review of safety data and for publications of trial results. The steering committee will include at least 5 members: the coordinating investigator, an independent clinical neurologist (with experience in MS clinical trials), an independent pharmacovigilance and safety expert, an MRI expert and at least one representative of the sponsor. All members of the steering committee will stay blinded throughout the trial until data base lock and unblinding, and will only review blinded data until then.

The first formal safety review will occur after about 60 patients have received the IMP for at least 3 months. Subsequently, periodic safety reviews will occur on regular intervals, at least once per year.

Recruitment will not be interrupted due to the scheduled safety reviews by the steering committee. The sponsor or any member of the steering committee may request an ad-hoc meeting for any reason, including a significant unexpected safety event, unplanned unblinding

of trial results, or a report external to the trial, such as results from a different trial. At each review, patient incidence rates of AEs (including all SAEs, serious treatment-related events, AESIs, and events leading the discontinuation of the IMP) will be tabulated by system organ class, preferred term, and severity grade. Listings and/or narratives of deaths and other serious AEs as well as reasons for discontinuations, stopping criteria regarding liver enzymes, and clinically significant laboratory abnormalities occurring during the trial will be provided.

Records of all meetings will be archived. The steering committee will recommend modification or termination of the trial to the sponsor, if considered necessary. Further details will be provided in a separate steering committee charter.

16 Biostatistical methods

16.1 Sample size calculation

The sample size calculation is based on the primary endpoint assessed at Week 24 after the main treatment period: the difference between 45 mg/day IMU-838 and placebo in the cumulative number of CUA MRI lesions at Week 24. In this early stage development trial, a higher α, i.e. 0.1, than the standard 0.025 level is considered appropriate. The assumptions for the effect size for this trial using IMU-838 are derived from a Phase 2 trial of teriflunomide, a drug that shares the mechanism of action with IMU-838. [21] For a sample size calculation based on a test for the ratio of two negative binomial rates, the negative binomial dispersion parameter has to be assumed, which is difficult without data of previous similar studies being available for analysis. Publications containing results of modeling the number of new enhancing lesions in MS using a negative binomial model were used to get an impression of the magnitude of the negative binomial dispersion parameter. [22,23] The values for the parameter ϑ reported in these two publications ranged from 0.6 to 0.75. Since the binomial dispersion parameter used in PASS 15.0.4 equals $1/\vartheta$, dispersion parameter values of 1.3 and 1.7 correspond to the published modeling results. To be conservative, the higher value of 1.7 was used for the sample size calculation. Additionally, medical experts generally agree that the overall activity status of patients suffering from MS declines secondary to improved diagnostic criteria, which allows early imaging-based diagnosis and early treatment start with broadly available effective treatment options in the countries selected for this trial. We believe that for these reasons the mean event rate for the placebo arm is likely lower than that observed in the historical Phase 2 trial of teriflunomide, and therefore slightly more conservative assumptions were made for the placebo event rate.

Underlying assumptions:

Primary endpoint: cumulative number of CUA MRI lesions up to Week 24

Randomization ratio:	1:1 (45 mg/day IMU-838:placebo)
Power:	80%
Significance level:	0.1, 1-sided
Average exposure time:	24 weeks
Mean event rate per 24 weeks for 45 mg/day IMU-838:	4.5
Mean event rate per 24 weeks for placebo:	8.0
Negative binomial dispersion parameter:	1.7

Based on these assumptions the necessary sample size per group is 51. Assuming a drop-out rate of 25%, about 65 patients will be randomized to each of the dose groups.

16.2 Analysis sets and types of analyses

Safety analysis set

The safety analysis set (SAF) will consist of all randomized patients who received at least one dose of IMP, i.e. any dose of IMU-838 or placebo. If it is uncertain if the patient has received any IMP, the patient will be included in the SAF. The analyses based on the SAF will be conducted on an "as treated" basis, i.e. all patients will be analyzed by the treatment they received.

Full analysis set

The full analysis set (FAS) will consist of all randomized patients who received at least one dose of IMP, i.e. any dose of IMU-838 or placebo. The analyses based on the FAS will be conducted on an intention-to-treat procedure, i.e. all patients will be analyzed by the groups to which they were randomized to.

Per-protocol set

All patients of the FAS will also be included in a per-protocol (PP) set if they did not violate any major protocol criteria. Protocol deviations will be identified and classified for each patient during a blind data review.

Assignment of analysis sets to analyses and allocation of patients

All efficacy analyses will be based on the FAS. The primary and the key secondary efficacy endpoint only will be additionally analyzed for the PP set. The analysis of the primary and the key secondary efficacy endpoint using the FAS will be considered confirmatory according to

the rules of the hierarchical testing procedure. All other analyses will be exploratory. Safety analyses will be based on the SAF.

The allocation of patients to the analysis sets for the final analysis of the main treatment period will be done during a blind data review meeting. The analysis sets to be used for the analysis of the extended treatment period will be defined in the corresponding statistical analysis plan (SAP).

16.3 Statistical analyses

For qualitative variables, the frequencies (absolute and relative) will be calculated. Quantitative parameters will be described by declaring the mean value, standard deviation, minimum, first quartile, median, third quartile, and maximum. The different treatment groups will be separately tabulated. A detailed description of the statistical analyses for all scheduled analyses (i.e. final analysis of the main treatment period and analyses for the extended treatment period) will be provided in an SAP and will be finalized before any data will be analyzed, i.e. before the final analysis of the main treatment period.

16.4 Primary and key secondary efficacy analyses

Since the primary and key secondary endpoint data (cumulative number of CUA MRI lesions at Week 24) represent count data, it is planned to analyze the primary and key secondary endpoint using a generalized linear model with a negative binomial distribution and a logarithmic link function. The following independent effects will be included in the models

- Treatment group
- Baseline volume of T2 lesions
- MRI field strength of 1.5 or 3.0 Tesla (factor groups used for stratification)
- Number of Gd+ lesions (factor groups used for stratification)

A hierarchical testing procedure will be applied for the primary and the key secondary efficacy endpoint. Both tests will be performed at a significance level of 0.1 (1-sided). In case of a non-significant result for the primary endpoint, the hierarchical testing procedure will be stopped and the analysis of the key secondary endpoint will be considered exploratory.

17 Patient withdrawal from trial participation

Participation in the trial is voluntary and patients may withdraw from the trial at any time and for any reason. However, all patients will be encouraged to complete the trial. All patients withdrawing from the trial will be encouraged to complete the EoS assessment 30 days (+14 days) after the last intake of the IMP (also refer to Section 12.7).

Patients will be withdrawn from the study for any of the following reasons (the primary reason leading to patient withdrawal will be documented):

- Patient withdraws consent due to
  - AE(s)
  - MS related clinical events
  - other reason (to be specified)
- Investigator decision due to
  - AE(s), which in the opinion of the investigator may jeopardize the patient's health or may compromise the trial objectives
  - relevant non-compliance with the protocol, which in the opinion of the investigator may jeopardize the trial integrity or scientific goals of the trial
  - reasons other than AE or non-compliance (to be specified)
- Pregnancy
- Fulfilling hepatoxicity-related stopping rules (see Section 15.2.2.2)
- Treatment with prohibited concomitant medication (see Section 11.2.2)
- Violation of inclusion or exclusion criteria noted only after randomization
- The trial is terminated by the sponsor

The primary reason for discontinuation from the trial is to be recorded in the source documents and on the early termination page of the eCRF.

If the patient withdraws consent, no further evaluations should be performed and no attempts should be made to collect additional data.

Patients who prematurely discontinue the trial will be treated according to the investigator's discretion and standard treatment guidelines, irrespective of the reason for withdrawal, and will not be replaced.

Reasonable efforts will be made to contact any patient lost to follow up, to complete assessments (including an EoS assessment) and to retrieve any outstanding data and IMP and supplies.

If the IMP will be prematurely discontinued, the primary reason for discontinuation is to be recorded in the appropriate section of the eCRF. Patients who discontinue therapy with study drug will be encouraged to continue with study-related assessments (including EoS visit) until their trial completion.

18 Ethical and legal requirements

18.1 Ethical conduct of the trial

The trial will be conducted in a manner consistent with all applicable regulatory authority and IEC regulations (e.g. International Council for Harmonisation [ICH] Guideline for Good Clinical Practice [GCP, CPMP/ICH/135/95] and the Declaration of Helsinki [version of 1996]) as well as in keeping with applicable local law(s) and regulation(s). The investigator must also comply with all applicable privacy regulations (for EU: General Data Protection Regulation [24]).

18.2 Independent ethics committee

Before the initiation of the clinical trial, the final protocol, any amendments if applicable, the patient information sheet and consent form, as well as any additional documents which are required by national regulations and the IEC will be submitted to the competent IEC for review. A favorable opinion for the clinical trial must be obtained from the IEC before any patient is enrolled at a center.

If appropriate, any additional requirements imposed by the IEC will be followed. Amendments to the trial documents will be notified to, or approved by, the IEC before implementation, if applicable.

18.3 Patient information and consent procedure

Before any clinical trial-related activities are performed, the investigator (or authorized designee) must review the informed consent form and explain the trial to potential trial participants. The investigator must ensure that the patient is fully informed about the aims, procedures, potential risks, any discomforts, and expected benefits of the clinical trial. Before consenting, the patient must be left with ample time to consider and ask questions. It must be emphasized that participation is voluntary and that the patient has the right to withdraw from the clinical trial at any time without prejudice. The patient and the investigator must then sign and date the consent form before the conduct of any trial procedures.

A copy of the patient information and informed consent form will be given to the patients for their records. The rights and welfare of the patients will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this clinical trial.

If amendments to the final trial protocol affect the patient’s participation in the clinical trial (e.g. a change in any procedure), the patient information and informed consent form must be updated

to incorporate this modification, and patients must agree to sign the amended form indicating that they re-consent to participate in the clinical trial.

18.4 Insurance coverage

Insurance coverage for damages emerging from the clinical trial will be provided according to applicable legal requirements. During the informed consent procedure, the investigator must inform the patient accordingly. Insurance details will be provided to the patient within the patient information sheet.

18.5 Submission to authorities

Documents required for the trial application will be submitted to the responsible competent authority (CA). The trial will not start until this authority has authorized the trial. Amendments to the trial protocol or to any other documents that must be reviewed by the CA will also be submitted to the CA in accordance with the regulatory requirements. If applicable, approval of the amendment must be awaited before implementing any changes.

18.6 Patient confidentiality

The trial protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the clinical trial or the data will be released to any unauthorized third party without prior written approval of the sponsor.

Personal patient data will be kept confidential in compliance with the General Data Protection Regulation [24], and other applicable international and national requirements.

The investigator must ensure that the confidentiality and anonymity of trial participants will be maintained and that their identities are protected from unauthorized parties. In eCRFs, compensation documentation, or any other documents submitted to the sponsor or sponsor's designee, patients must be identified only by their identification codes; it is not allowed to use their names, addresses, telephone numbers, or similar information. The investigator will keep the original of the Patient Identification Log (including complete name and date of birth of each patient) in his/her file. The investigator must maintain these documents in strict confidence.

To allow compliance with GCP, all patients will be asked for consent regarding the access to their personal clinical trial-related data for monitoring, audits, and inspections as well as regarding transmission and storage of their pseudonymous data; a respective statement will be part of the informed consent form. Professionals getting access to source data for monitoring, audits and inspections are bound to preserve strict confidentiality.

19 Criteria for premature termination of the trial and criteria for initializing and closing a trial center

19.1 Criteria for halting or terminating the trial

The sponsor reserves the right to halt or terminate the trial at any time. Reasons for termination include but are not limited to:

- Potential health risk for the patients
- High withdrawal rate
- New scientific knowledge becomes available that makes the objectives of the trial no longer feasible or valid
- Insufficient enrollment of patients

19.2 Criteria for closing a trial center

A trial center may be closed for the following reasons:

- The center is unable to recruit sufficient patients within the agreed time frame
- The center does not respond to trial management requests
- Multiple significant protocol deviations or substantial non-compliance
- The approval of the IEC in charge of the clinical trial is permanently revoked
- Additional local criteria might be established by written agreements between the sponsor and the trial center

The sponsor will notify the relevant CA, IEC(s), and investigator(s) in writing about the termination of individual centers or the whole trial.

The investigator may terminate his/her participation prematurely. If the investigator decides to terminate his/her participation before the trial is completed, he/she will notify the sponsor in writing stating the reasons for the early termination. In terminating the trial, the sponsor and the investigator will ensure that adequate consideration is given to the protection of the patients' interests.

The investigator will notify the relevant CAs and IEC(s) in writing, if required, submit a copy of that notification to the sponsor and return all IMPs and all related trial material, as applicable, to the sponsor. Concerned eCRFs will be archived at the site. Authorization to access and edit the eCRF will be removed from the investigator and all authorized delegates.

20 Trial protocol, documentation and archiving of data

20.1 Amendments to the protocol

Any change to the protocol concerning the purpose of the trial, the trial design, or the patient's eligibility can only be made in the form of a written amendment to the trial protocol. Such amendments must be discussed and signed by the sponsor and the investigator before implementation.

Substantial amendments, i.e. amendments likely affecting to a significant degree

- the safety or physical or mental integrity of the patients of the trial
- the scientific value of the trial
- the conduct or management of the trial, or
- the quality or safety of any IMP used in the trial

will be submitted to the CA and IEC for approval and favorable opinion as required by applicable regulations. If such amendments affect the patient's participation in the clinical trial (e.g. a change in any procedure), the patient information and informed consent form must be updated to incorporate this modification, and patients enrolled at the time of implementation of the amendment must re-consent to their participation in the clinical trial.

Non-substantial changes, e.g. minor corrections of administrative nature and/or rephrasing, which do not meet the above criteria for being substantial, are considered editorial changes. The IEC and CA do not need to be notified of such minor corrections. Non-substantial amendments will be signed by the sponsor only.

If new events occur related to the conduct of the trial or the development of the tested IMP that may affect the safety of the patients, the sponsor and the investigator will take appropriate safety measures to protect the patients against any immediate hazard. The sponsor will immediately inform the CA and IEC of the new events and the measures taken.

20.2 Protocol deviations

A protocol deviation is a failure to follow, intentionally or unintentionally, the requirements of the protocol. As required by national regulation or guidelines, reports of deviations will be provided to the IEC.

In emergency circumstances, deviations from the protocol may proceed without prior consultation with the sponsor and favorable opinion of the IEC, if the rights, safety and well-being of the patients need to be protected. Such deviations will be documented and reported to the sponsor and the IEC as soon as possible in accordance with national regulations.

All protocol deviations will be listed. If concerned patients are evaluable for data analysis will be discussed in a data review meeting prior to statistical analyses.

20.3 Data retention

The trial center and the sponsor or sponsor's designee(s) will maintain all trial records according to ICH GCP and applicable regulatory requirement(s). Records will be retained until at least 2 years after the last approval of a marketing application in an ICH region, until there are no pending or contemplated marketing applications in an ICH region, until at least 2 years have elapsed since the formal discontinuation of clinical development of the tested IMP, and at least 15 years after the end of the trial, whichever period is longer. The final report will be kept for another 5 years after the tested IMP was taken off the market according to legal stipulations. The documents will be archived for a longer period, if required by the applicable regulatory authorities or if agreed with the sponsor. It is the responsibility of the sponsor to inform the investigators when these documents need not to be retained any longer.

The medical files of trial patients must be retained in accordance with local legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

21 Data collection, monitoring and quality assurance

21.1 Data collection

All data will be collected on an eCRF separately for each patient. eCRFs will be provided as a regulatory compliant, electronically secure and protected web-based database, and will be handled in accordance with the instructions provided. An audit trail will record all entries and corresponding changes.

The trial sites will be provided with secure access to and training on the eCRF.

All data generated after the patient provided informed consent must be recorded in the eCRF. The treating investigator is responsible for ensuring accurate and proper completion of the eCRF.

Only treating physician and authorized designees will enter and edit data via a secure network and a secure access system. Completed data for each visit will be approved by the investigator or authorized designee using an electronic signature to confirm the accuracy of the data. Any change or addition will be recorded by an electronic audit trail system.

The investigator or designee has to carefully answer queries issued by data management.

21.2 Source data

Source data are defined as all data in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial (see ICH E3 GCP, 1.51). Source records should be stored for a time period as defined by local regulations.

The investigator must keep a patient file (medical file, original medical records) on paper or electronically for every patient included in the trial.

It must be possible to identify each patient by using this patient file. Dates and authors of all source data entry and changes must be clearly identifiable.

Documents and data to be considered source data will be identified and agreed with the investigator in advance of the first screening visit. The location of all source data will be documented and filed in the Investigator Site File (source data location form).

Electronic patient files will be printed whenever the monitor performs source data verification. Printouts must be signed and dated by the investigator, countersigned by the monitor, and filled at the center as required for other source data documents.

21.3 Monitoring

The extent and details of monitoring including source data verification will be specified in the monitoring plan.

The trial center must not enroll any patient before the initiation visit was performed and final eligibility of the center is confirmed by the monitor and Sponsor. During the trial, further monitoring visits will be performed according to ICH GCP, the sponsor's designee's or local CRO's standard operating procedures, and local regulations. eCRFs will be reviewed against source data for adherence to the trial protocol and ICH GCP, as well as for completeness, accuracy, and consistency of data. Additionally, the monitor will check the progress of enrolment, and will ensure that the IMP is being stored, dispensed and accounted for according to specifications. Key trial personnel must be available to assist the monitor during these visits.

The investigators must permit the monitor`s access to the patient's medical records and all applicable source documents. Throughout the trial, all data captured in the eCRF will only be identified by patient number. The data will be blinded correspondingly in all data analyses.

It is the investigators' obligation to assure documentation of all relevant data in the patient's file, such as medical history and concomitant diseases, date of trial enrolment, visit dates, results of examinations, administrations of IMP and any concomitant medication, and AEs.

21.4 Audits and inspections

During the trial, audits may be performed by independent auditors. Audits of clinical research activities will be performed in accordance with corresponding standard operating procedures to ensure compliance with the principles of GCP.

Regulatory authorities may wish to conduct an inspection. If an inspection is requested, the investigator must inform the sponsor or sponsor's designee immediately.

The investigator must allow auditors or inspectors access to source data and documents and will answer any questions.

21.5 Data management procedures

All data management activities will be conducted by the sponsor's designee following their standard operating procedures.

Details on data handling will be described in the data management plan. Data entered into the eCRF will be validated through online edit checks and offline checks run by the data manager according to the data validation plan. For all identified discrepancies, the data manager will raise a query in the electronic data capture application. The appropriate investigational personnel will

answer the queries in the eCRF, which will be audit trailed by the electronic data capture application.

The sponsor's designee will handle the data cleaning process, query process, and coding.

For the main analysis, the respective database will be locked when it is considered complete and accurate and after all changes following the data review meeting (if applicable) are included (i.e. all data cleaning activities performed). All changes will be tracked (audit trail). Sponsor approval prior to database lock is mandatory.

21.6 Trial report and publications

The results of the main treatment period will be summarized in a clinical trial report according to the ICH E3 Note for guidance on structure and content of clinical trial reports. Results of the extended treatment period will be reported in an addendum to the clinical trial report.

Regular safety update reports will be submitted to investigators as well as to regulatory authorities and IECs, as appropriate, within the timeframes defined per national regulation or by the IEC.

The preparation and submission of abstracts or manuscripts including the trial results will be coordinated by the steering committee. The publication or presentation of any trial results shall comply with all applicable privacy laws.

22 Trial periods

Cohort 1:

Actual start:	February 2019 (first patient in)
Actual recruitment period:	8 months
Actual end main treatment period:	April 2020 (main part: last patient out)
Estimated end extended treatment period:	December 2029 (last patient EoS visit)

Cohort 2 (Planned):

Estimated start:	October 2020 (first patient in)
Estimated recruitment period:	3 months
Estimated interim analysis:	March 2021 (main part: last patient completing Week 12)
Estimated end main treatment period:	May 2021 (main part: last patient out)
Estimated end extended treatment period:	December 2029 (last patient EoS visit)

The end of the trial is defined as last patient visit, i.e. the EoS visit, in any participating center.

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24 Approval and signatures

Protocol agreed to by sponsor:

ANDREAS HUEHLER

Sponsor's signatory name (print)

Sponsor's signatory signature

28-AUG-2020

Date

Protocol agreed to by coordinating investigator:

Robert J. Fox

Coordinating investigator name (print)

Coordinating investigator signature

31-Aug-2020

Date

Principal investigator agreement page for the protocol

I agree:

- To assume responsibility for the proper conduct of the clinical trial at this site, and to conduct the trial in compliance with national law, the valid version of the Declaration of Helsinki, the GCP-guidelines, the present trial protocol including its amendments, and with any other trial conduct procedures provided by the sponsor or authorized representatives.
- Not to implement any deviations from or changes to the protocol (including protocol amendments) without agreement from the sponsor and prior review and favorable opinion from the ethics committee and approval from the competent authority, if applicable, except where necessary to eliminate an immediate hazard to the patient(s), or for administrative aspects of the clinical trial (where permitted by all applicable regulatory requirements).
- That I am familiar with the appropriate use of the investigational medicinal product as described in this protocol and any other information provided by the sponsor including, but not limited to, the current investigator's brochure or equivalent document provided by the sponsor.
- To ensure that all persons assisting me with the clinical trial are adequately informed about the investigational medicinal product and of their trial-related duties and functions.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply details about the investigator's ownership interest in the sponsor or the trial product, and more generally about his/her financial ties with the sponsor. The sponsor will use and disclose the information solely for the purpose of complying with regulatory requirements.

_____

Principal investigator name (print)

_____ _____

Principal investigator signature Date

25 Appendices

Appendix 1 Expanded Disability Status Scale and Neurostatus form

A-Table 1: Expanded Disability Status Scale (EDSS)

Score	Description
0.0	Normal neurological exam – (all Grade 0 in Functional Systems [FS*])
1.0	No disability, minimal signs in one FS (i.e., Grade 1)
1.5	No disability, minimal signs in more than one FS (more than one Grade 1)
2.0	Minimal disability in one FS (one FS Grade 2, others 0 or 1)
2.5	Mild disability in one FS or minimal disability in two FS (two FS Grade 2, others 0 or 1)
3.0	Moderate disability in one FS (one FS grade 3, others 0 or 1) though fully ambulatory; or mild disability in three or four FS (three / four FS grade 2, others 0 or 1) though fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS (one FS grade 3) and mild disability in one or two FS (one / two FS grade 2) and others 0 or 1; or fully ambulatory with two FS grade 3 (others 0 or 1); or fully ambulatory with five FS grade 2 (others 0 or 1)
4.0	Ambulatory without aid or rest for ≥500 meters; up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps
4.5	Ambulatory without aid or rest for ≥300 meters; up and about much of the day, characterized by relatively severe disability usually consisting of one FS grade 4 and combination of lesser grades exceeding limits of previous steps
5.0	Ambulatory without aid or rest for ≥ 200 meters (usual FS equivalents include at least one FS grade 5, or combinations of lesser grades usually exceeding specifications for step
5.5	Ambulatory without aid or rest for ≥ 100 meters
6.0	Unilateral assistance (cane or crutch) required to walk at least 100 meters with or without resting (see chapter 8, ambulation)
6.5	Constant bilateral assistance (canes or crutches) required to walk at least 20 meters without resting
7.0	Unable to walk 5 meters even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 hours a day
7.5	unable to take more than a few steps; restricted to wheelchair; may need some help in transferring and in wheeling self
8.0	Essentially restricted to bed or chair or pushed in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally, has effective use of arms
8.5	Essentially restricted to bed much of day. Has some effective use of arms retains some self-care functions
9.0	Confined to bed. Can still communicate and eat
9.5	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow
10.0	Death due to MS

Note: EDSS steps of 4 and below refer to patients who are fully ambulatory (able to walk 500 m without aid or rest), and the precise steps are defined by the Functional System score(s). EDSS steps from 4.5 up are based entirely on ambulation capabilities.

For the Functional System Visual Function Grades, the following conversions should be made for the calculation of the EDSS: 6 = 4, 5 = 3, 4 = 3, 3 = 2, 2 = 2, 1 = 1, and 0 = 0.

*An Functional System Mental Function Grade of 1 does not count towards EDSS.

A-Table 2: Neurostatus form

neurostatus scoring

Scoring Sheet for a standardised, quantified neurological examination and assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale in Multiple Sclerosis

STUDY NAME P2-IMU-838-MS

PERSONAL INFORMATION

Patient	
Date of Birth (04-Jun-1980)	– – –
Centre Nr/Country	
Name of EDSS rater	
Date of Examination	– – – 2 0

SYNOPSIS

1. Visual	[1]	Ambulation Score	
2. Brainstem			
3. Pyramidal		EDSS Step	
4. Cerebellar			
5. Sensory			
6. Bowel/Bladder	[1]	Signature	
7. Cerebral			

1. VISUAL (OPTIC) FUNCTIONS

OPTIC FUNCTIONS	OD	OS
Visual acuity ☐ CC ☐ SC		
Visual fields		

Scotoma		
* Disc pallor		
FUNCTIONAL SYSTEM SCORE	→	[1]

2. BRAINSTEM FUNCTIONS

CRANIAL NERVE EXAMINATION	
Extraocular movements (EOM) impairment	
Nystagmus	
Trigeminal damage	
Facial weakness	

Hearing loss	
Dysarthria	
Dysphagia	
Other cranial nerve functions	
FUNCTIONAL SYSTEM SCORE	

3. PYRAMIDAL FUNCTIONS

REFLEXES	R	><	L
Biceps			
Triceps			
Brachioradialis			
Knee			
Ankle			
Plantar response			
Cutaneous reflexes			
* Palmomental reflex			

LIMB STRENGTH	R	L
Deltoid		
Biceps		
Triceps		
Wrist/finger flexors		
Wrist/finger extensors		
Hip flexors		
Knee flexors		

Knee extensors		
Plantar flexion (feet/toes)		
Dorsiflexion (feet/toes)		
* Position test UE, pronation		
* Position test UE, downward drift		
* Position test LE, sinking		
* Able to lift only one leg at a time (grade in °)	°	°
* Walking on heels		
* Walking on toes		
* Hopping on one foot		
SPASTICITY		
Arms		
Legs		
Gait		
OVERALL MOTOR PERFORMANCE		
FUNCTIONAL SYSTEM SCORE		

CC = corrected
SC = without correction
* = optional part of the examination
[1] = converted FS Score

4. CEREBELLAR FUNCTIONS

CEREBELLAR EXAMINATION			Rapid alternating movements UE impairment		
Head tremor			Rapid alternating movements LE impairment		
Truncal ataxia			Tandem walking		
	R	L	Gait ataxia		
Tremor/dysmetria UE			Romberg test		
Tremor/dysmetria LE			Other, e. g. rebound		
			FUNCTIONAL SYSTEM SCORE		

5. SENSORY FUNCTIONS

SENSORY EXAMINATION	R	L	Position sense UE		
Superficial sensation UE			Position sense LE		
Superficial sensation trunk			* Lhermitte's sign		
Superficial sensation LE			* Paraesthesiae UE		
Vibration sense UE			* Paraesthesiae trunk		
Vibration sense LE			* Paraesthesiae LE		
			FUNCTIONAL SYSTEM SCORE		

6. BOWEL/ BLADDER FUNCTIONS

Urinary hesitancy/retention		Bowel dysfunction	
Urinary urgency/incontinence		* Sexual dysfunction	
Bladder catheterisation		FUNCTIONAL SYSTEM SCORE	→ [1]

7. CEREBRAL FUNCTIONS

MENTAL STATUS EXAMINATION		Decrease in mentation	
° Depression		+ Fatigue	
° Euphoria		FUNCTIONAL SYSTEM SCORE	

AMBULATION

Distance reported by patient (in meters)		Assistance	
Time reported by patient (in minutes)		Distance measured (in meters)	
		AMBULATION SCORE	

* = optional part of the examination
[1] = converted FS Score
° Depression and Euphoria are not taken into consideration for FS and EDSS calculation.
+ Because fatigue is difficult to evaluate objectively, in some studies it does not contribute to the Cerebral FS score or EDSS step. Please adhere to the study's specific instructions.

UE = upper extremities
LE = lower extremities

Standardised Neurological Examination and Assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale
Slightly modified from J.F. Kurtzke, Neurology 1983:33,1444-52

Appendix 2 Treatment satisfaction questionnaire for medication

TSQM *(Version 1.4)*

Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication *over the last two to three weeks, or since you last used it.* For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

4. As a result of taking this medication, do you experience any side effects at all?

☐1 Yes
☐0 No (if No, then please skip to Question 9)

[Clinical Trial Version] 1

5. How bothersome are the side effects of the medication you take to treat your condition?

☐1 Extremely Bothersome
☐2 Very Bothersome
☐3 Somewhat Bothersome
☐4 A Little Bothersome
☐5 Not at All Bothersome

6. To what extent do the side effects interfere with your physical health and ability to function (i.e., strength, energy levels, etc.)?

☐1 A Great Deal
☐2 Quite a Bit
☐3 Somewhat
☐4 Minimally
☐5 Not at All

7. To what extent do the side effects interfere with your mental function (i.e., ability to think clearly, stay awake, etc.)?

☐1 A Great Deal
☐2 Quite a Bit
☐3 Somewhat
☐4 Minimally
☐5 Not at All

8. To what degree have medication side effects affected your overall satisfaction with the medication?

☐1 A Great Deal
☐2 Quite a Bit
☐3 Somewhat
☐4 Minimally
☐5 Not at All

9. How easy or difficult is it to use the medication in its current form?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

10. How easy or difficult is it to plan when you will use the medication each time?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

11. How convenient or inconvenient is it to take the medication as instructed?

☐1 Extremely Inconvenient
☐2 Very Inconvenient
☐3 Inconvenient
☐4 Somewhat Convenient
☐5 Convenient
☐6 Very Convenient
☐7 Extremely Convenient

12. Overall, how confident are you that taking this medication is a good thing for you?

☐1 Not at All Confident
☐2 A Little Confident
☐3 Somewhat Confident
☐4 Very Confident
☐5 Extremely Confident

13. How certain are you that the good things about your medication outweigh the bad things?

☐1 Not at All Certain
☐2 A Little Certain
☐3 Somewhat Certain
☐4 Very Certain
☐5 Extremely Certain

14. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

Appendix 3 Dose response Cohort 2 sub-trial *(not valid in Romania)*

1. Background and rationale

In the Cohort 1 main analysis of this trial the primary and key secondary endpoints have been met with high statistical significance i.e. both IMU-838 doses statistically significantly reduced the number of CUA MRI lesions up to Week 24 as compared to placebo. The reduction was 62% with 45 mg IMU-838 ($p = 0.0002$, 1-sided, primary endpoint) and 70% with 30 mg IMU-838 ($p < 0.0001$, 1-sided, key secondary endpoint). All other secondary endpoints, including other MRI parameters, clinical endpoints such as relapses and biomarkers such as neurofilament light chain, also provided a noticeable and numerical benefit for IMU-838 as compared to placebo. IMU-838 in this trial was safe and well-tolerated in patients with RRMS. The rate of TEAEs was similar in IMU-838 and placebo-treated patients (30 mg: 45.1%, 45 mg: 40.6%, placebo: 43.5%). Serious TEAEs were rare and only observed in 3 out of 140 IMU-838-treated patients, and in 1 out of 69 placebo-treated patients. The rate of treatment withdrawals in the 24-week blinded treatment period was only 4.3% in the pooled IMU-838 treatment arms versus 7.2% in the placebo group.

Based on these results both doses, 30 and 45 mg/day IMU-838, appear to be equally safe and effective in patients with RRMS. Although there was no safety signal in the Cohort 1 main analysis for either doses, the lowest effective dose 30 mg/day IMU-838 may be proposed to be investigated in further trials in RRMS, including the planned Phase 3 trial. However, and given the relative equal performance of the 2 doses in Cohort 1 and to allow for pharmacodynamic

modeling of the dose-response relationship, data from a lower dose in the effective dose range will be required. The objective of the Cohort 2 sub-trial is thus to obtain exploratory data on the dose response of IMU-838 by evaluating a lower IMU-838 dose i.e. 10 mg/day to provide additional data for pharmacodynamic modelling.

The 10 mg IMU-838 dose was selected since it is more than 50% lower than the lowest effective dose of Cohort 1 (30 mg IMU 838) and avoids undesired overlap in serum trough levels for pharmacodynamic modelling of the pooled Cohort 1 and 2 data.

The 10 mg/day dose is expected to show noticeable efficacy in the Cohort 2 sub-study as an interim analysis of the ongoing Trial P2-IMU-838-UC in patients with ulcerative colitis, confirmed that the 10 mg dose lies within the potential effective dose range of IMU-838 i.e. this interim analysis showed that none of the doses used (10 mg, 30 mg, or 45 mg IMU-838) was either likely ineffective or intolerable expanding the expected effective dose range of IMU-838 in immunological diseases. In summary, the dose of 10 mg/day IMU-838 is expected to be an effective dose in this Cohort 2 sub-trial. A small placebo arm is included to provide blinding of patients and to relate Cohort 2 treatment effects.

Assessments and procedures will mostly follow those described for the main treatment period in the Cohort 1 main trial. However, some assessments not necessary for pharmacodynamic modelling from Cohort 2 data will not be performed as well as few new exploratory biomarker data are added. Additionally, only MRI machines with a field strength of 1.5 Tesla will be allowed to provide more homogeneous MRI data for pharmacodynamic modelling. The Cohort 1 main trial allowed MRI assessments of 1.5 and 3 Tesla. As there was a strong imbalance of cases between 1.5 Tesla and 3 Tesla, the uncertainty of statistical estimators for adjustment of means for the 3 Tesla MRI cases was very high.

In addition, an unblinded interim analysis of selected MRI data is planned after all Cohort 2 patients have completed Week 12 assessments. In the Cohort 1 main analysis a recognizable reduction of the number of CUA and Gd+ lesions by IMU-838 as compared to placebo was already observed at Week 12. This interim analysis will therefore provide an early assessment of dose-response of the 10 mg/day dose and will facilitate expeditious regulatory discussions for Phase 3 execution. The interim analysis after Week 12 would be performed without revealing individual treatment assignments to the Sponsor, however the interim analysis will provide very selected group-level MRI data. As all or almost all Cohort 2 patients may have already completed the final Week 24 assessment of the main treatment period of Cohort 2 when the interim analysis is performed, the impact for the conduct of the Cohort 2 sub-trial may be minimal, if any.

PBMC-based pharmacodynamic biomarkers, PRO questionnaires (TSQM), coagulation assessments, miR-122, JCV-DNA, and genotyping parameters are not necessary for

pharmacodynamic modelling and were already assessed in the Cohort 1 main trial. Thus, such assessments are unnecessary for the objectives of Cohort 2 and will not be performed in this Cohort 2 sub-trial. Additional assessments in Cohort 2 that were not performed in the Cohort 1 include fibroblast growth factor 19 (FGF-19), 7α-Hydroxy-4-cholesten-3-one (C4), and high-density lipoprotein cholesterol as indicated in Table 2.

7α-Hydroxy-4-cholesten-3-one (C4) is an intermediate in the biochemical synthesis of bile acids from cholesterol. The FGF-19 is a protein that in humans functions as a hormone, regulating bile acid synthesis. High-density lipoprotein (HDL) cholesterol is a commonly performed surrogate value for hepatic reverse cholesterol transport. Change in serum C4, FGF-19 and HDL cholesterol concentrations may be indicative for activation of certain nuclear receptors by medications.

2. Trial design

2.1 Overall trial design

This is a double-blind, placebo-controlled, randomized, parallel-group sub-trial of P2-IMU-838-MS to assess the efficacy and safety of once-daily oral 10 mg/day IMU-838 compared to placebo in patients with RRMS and evidence of active disease.

The design generally follows the design of the main trial. However, only MRI machines with a field strength of 1.5 Tesla will be allowed (the main trial allowed ≥1.5 Tesla, for reasons see Section 1 of this Appendix). An overview is given in Figure 2 below. Screening (12.2) and eligibility (Section 9) will be the same as in the Cohort 1 main trial.

Before any clinical activities for the sub-trial are performed, patients will be informed by the investigator (or authorized designee, see Section 18) about this trial and the risk profile of IMU-838 and patients will have to sign an informed consent form specific to this Cohort 2 sub-trial.

Main treatment period

Patients in the Cohort 2 sub-trial main treatment part will be randomized 1:4 to placebo and 10 mg IMU-838 for 24 weeks. All patients will receive half the assigned dose during the first 7 days of the main treatment period (1 tablet per day) and the full assigned dose from Day 7 onwards (2 tablets once daily). Clinic visits after Day 0 during the double-blind Cohort 2 main treatment period will be scheduled at Day 7, and at Weeks 6, 12, 18 and 24, with MRI assessments at Weeks 6, 12, 18 and 24. At Week 24 (EoMT), patients will have the option to continue into the extended treatment period if they meet respective eligibility criteria as described in Sections 9.2 and 9.3 of this protocol. An unblinded interim analysis evaluating selected MRI parameters will be performed at Week 12 (see Section 2.3 below).

Extended treatment period

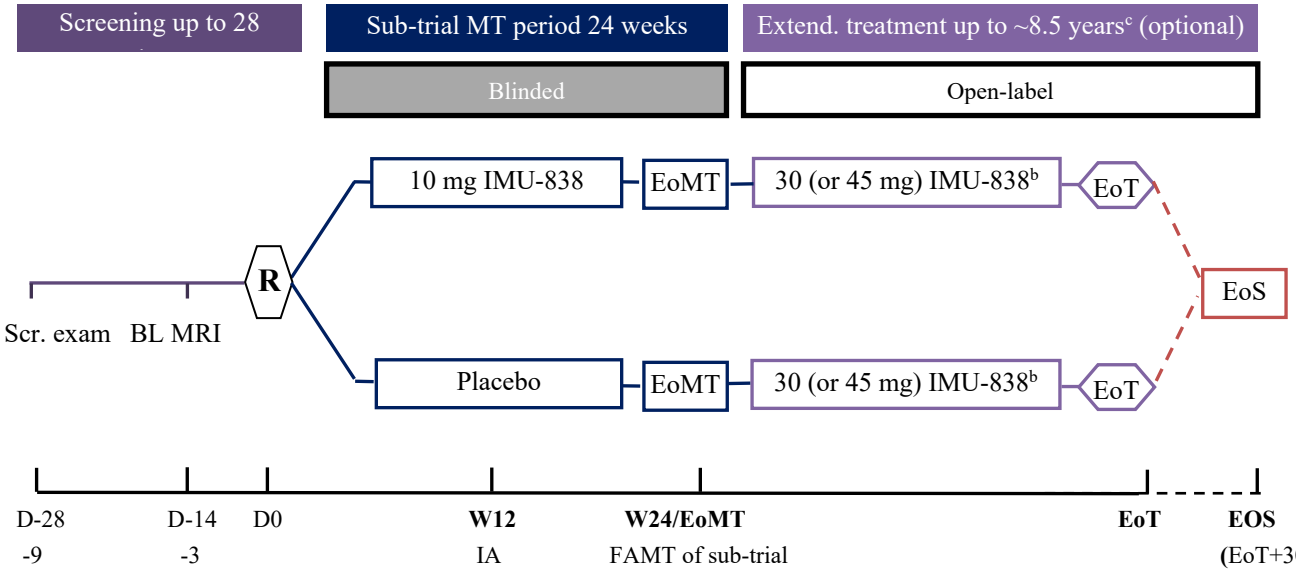
Treatment during the extended period will be open label. The recommended dose for the extended treatment period will be 30 mg/day. However, based on discussion between investigator and patient 45 mg/day IMU-838/day may also be used as this dose was also found to be safe and effective in the Cohort 1 main analysis. Switching between open-label doses will be allowed in the extended treatment period, as described for patients in Cohort 1. Although the treatment in the extended treatment period will be always open, the treatment assignment during the main treatment period for patients and investigators will be kept blinded until after database lock of the main treatment period of the sub-trial. Identical to the start of the main treatment period, all patients will receive half the assigned dose during the first 7 days of the extended treatment period and will then continue with the full assigned dose.

The extended treatment period will be terminated for patients in the Cohort 2 sub-trial at the day the last patient of the Cohort 1 main trial has completed the respective extended treatment period, prematurely or as scheduled.

End-of-study visit

All patients discontinuing treatment, as scheduled or prematurely, will undergo an EoS visit 30 days (+14 days) after last IMP administration.

Figure 2: Trial flow chart - Cohort 2 sub-trial



[a] Can be interrupted/extended, if the baseline MRI must be repeated due to poor quality (to be done as soon as possible). If results of the central MRI assessment are not available in time for randomization, the screening period can be extended by up to 7 days, if needed.

[b] 30 mg/day IMU-838 is recommended. However, based on discussion between investigator and patient 45 mg/day IMU-838/day may also be used. Switching between open-label doses will be allowed.

[c] The extended treatment period will be terminated for patients in the Cohort 2 sub-trial, at the day the last patient of the Cohort 1 main trial has completed, prematurely or as scheduled, the extended treatment period.

BL = baseline, D = day, EoMT = end-of-main treatment, EoS = end-of-study, EoT = end-of-treatment, exam = examination, FAMT = final analysis of main treatment period, IA = interim analysis, MRI = magnetic resonance imaging, MT =main treatment, R = randomization, Scr. = screening, W = Week.

Investigators and trial sites: centers who participated in the Cohort 1 main trial from Bulgaria, Ukraine, and Poland, that use an MRI machine with a field strength of 1.5 Tesla.

Assessments and procedures not specifically described in this Appendix will be done as described for the main trial.

2.2 Treatments

Test product

Main treatment period: tablets with 5 mg; administration as in the main trial (Section 11.1) i.e. 1 tablet once daily (Days 0 to 6) and 2 tablets once daily (Days 7 to EoM).

Extended treatment period: 1 tablet once daily, i.e. 15 mg/day (or 22.5 mg/day) IMU 838 for Days 0 to 6, and 2 tablets once daily Day 7 to EoT.

Reference product *(only applicable during main treatment period)*
Matching placebo, once-daily oral administration of 1 or 2 tablets, as described for the test product and Section 11.1

Prior and concomitant medications; precautions and restrictions
Will be applied as in main trial (Section 11.3)

2.3 Randomization, blinding and unblinding procedures

Randomization will be done either by a voice-interactive system or manually by an unblinded designee. At randomization, all IMP kits for the entire 24-week main treatment duration will be assigned to each patient; however IMP kits will be handed out to patients only during visits as outlined in Table 2. Since only 1.5 Tesla MRI machines will be used, stratification of randomization for MRI field strength is not necessary and stratification will only consider number of Gd+ lesions in baseline MRI (0 Gd+ lesion; ≥1 Gd+ lesion).

Other procedures will be applied as in the main study (Section 10), however there will be no re-randomization at the start of the extended treatment period as the extended treatment period of the Cohort 2 sub-trial will be open right from the start of the extended treatment period (while in Cohort 1 it was blinded until the main results for the main treatment were available).

Blinding during the interim analysis of the main treatment period

An interim analysis will be performed after all Cohort 2 patients have completed the Week 12 assessments. Care will be taken to maintain the blind regarding individual treatment assignments for the Sponsor, patients, investigators and other study personnel during this analysis to avoid introducing any biases. This will include that only very selected group-level data are provided to the Sponsor, that any reference to individual patients or of potentially unblinding information in footnotes and listing will be avoided and that investigators will not be informed about the data of the interim analysis.

After all patients have completed their Week 12 assessments the respective data base will be locked, data unblinded and analyzed.

Access to interim individual patient data will be restricted to an independent data manager and an independent biostatistician performing the interim analysis. The following selected data will be analyzed and respective group level averages without minimum and maximum values will be made available to the Sponsor:

- cumulative CUA MRI lesions until Week 12
- cumulative Gd+ lesions until Week 12
- number of patients without CUA MRI lesions until Week 12

- number of patients without Gd+ lesions until Week 12

In order to provide sufficient data points in the placebo arm, Cohort 1 placebo patients from the same sites that contributed to the Cohort 2 Week 12 data and investigated using 1.5 Tesla MRI examinations will be allowed to enrich the Cohort 2 placebo arm. In addition, summary data from Cohort 1 30 mg/day and 45 mg/day data may be shown as comparison to Cohort 2 data from 10 mg/day IMU-838, however the same restriction for sites and 1.5 Tesla MRI as for placebo will apply. Details will be described in the SAP for Cohort 2. To minimize bias, the SAP for the interim analysis will be finalized before any data will be analyzed.

Aggregate data on accrual and drop-out rates, and reasons for ineligibility and discontinuation will also be made available for the Sponsor.

2.4 Trial patients

Number of patients (total and for each treatment) planned

Approximately 60 patients are planned to be randomized 1:4 to treatment with placebo or 10 mg/day (12:48 patients) in the main treatment period.

No formal sample size calculation was performed for this sub-trial but N = 60 randomized patients are considered sufficient for a robust estimation of the dose response and pharmacodynamic modelling.

The maximum numbers of Cohort 2 patients randomized will be 30 per center and 50 per country.

Eligibility criteria and withdrawal of patients

For the main treatment and extended treatment periods eligibility will be applied as in the main study (Sections 9 and 17).

2.5 Objectives and endpoints

Objective

The objective of this sub-trial is to obtain more efficacy and safety data of IMU-838 in patients with RRMS and to allow pharmacodynamic modelling of the dose response.

Endpoints

Efficacy

- Between-treatment differences in the cumulative number of CUA MRI and Gd+ lesions up to Week 24 (will be of primary interest).
- Between-treatment differences in the following MRI parameters:
  - Mean number of CUA lesions at Weeks 6, 12, 18 and 24
  - Cumulative number of CUA MRI lesions up to Weeks 6, 12, 18 and 24

- T2-lesion load at Weeks 6, 12, 18 and 24 compared to Baseline
- T1-lesion load at Weeks 6, 12, 18 and 24 compared to Baseline
- Cumulative number of new Gd+ lesions up to Weeks 6, 12, 18 and 24
- Cumulative number of new T2 lesions up to Weeks 6, 12, 18 and 24
- Cumulative number of new T1 lesions up to Weeks 6, 12, 18 and 24
- Proportion of patients without new Gd+ lesions over 24 weeks
- Proportion of patients without new or enlarging T2-weighted lesions over 24 weeks
- Correlation of MRI-based assessments with quartiles of IMU-838 trough levels at Week 24

- Clinical endpoints:
  - Number of relapses in each treatment arm
  - Change of EDSS from Baseline to Weeks 12 and 24
- Biomarkers:
  - Changes from Baseline in serum neurofilament at Week 24
  - Changes in serum C4 (7α-hydroxy-4-cholesten-3-one)
  - Changes in serum fibroblast growth factor 19 (FGF-19)

Safety

- AEs, serious AEs and clinically significant laboratory abnormalities (as assessed by the investigator)
- AEs of special interest:
  - Red blood cell urine positive, at least of moderate intensity
  - Hematuria
  - Retroperitoneal colicky pain with suspected or confirmed nephrolithiasis
- Proportion of patients treated with 10 mg/day as compared to placebo who experienced at least one of the following AEs:
  - Neutropenia
  - Lymphopenia
  - Diarrhea
  - Alopecia
  - Hemorrhage

- Abnormalities in alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, and total bilirubin with both elevations >1.5 x ULN and ≥35% elevated compared to Baseline

- ECG, physical examination, and vital signs
- Time to treatment discontinuation for any reason
- Rate of treatment discontinuations up to Week 24

Pharmacokinetics

- Population PK at Week 6 (3-10 hours post-dose)
- Plasma trough levels of IMU-838 at Days 7, and Weeks 6, 12, 18, and 24

2.6 Study schedule

A schedule of assessments of the main treatment part for the Cohort 2 sub-trial is provided in Table 2.

The assessment and procedures for patients who will continue into the extended period will follow those describe for the Cohort 1 main trial (Table 1). However, the extended treatment period will be terminated for patients in the Cohort 2 sub-trial, at the day the last patient of the Cohort 1 main trial has completed or discontinued the extended treatment period. The extended treatment period in this sub-trial will thus be shorter and the EoT will be before V46 (W516) as indicated in Table 1.

For more details on procedures (except for FGF-19 and C4) to be performed at the visits described in Table 2 please refer to the main trial (Section 12).

If a patient prematurely discontinues this Cohort 2 sub-trial before Week 24 (for possible reasons, please see Section 17), all assessments scheduled for the EoMT visit should be performed. All patients who prematurely discontinue the Cohort 2 sub-trial will be encouraged to complete the EoMT visit, and the EoS assessments at 30 days (+14 days) after the last IMP intake.

Table 2: Schedule of assessments - Cohort 2 sub-trial (main treatment period)

	Screening		Blinded treatment						Unscheduled visit		EoS
		BL MRI	Main treatment (MT) period						due to MS-related symptoms	due to safety	(end of study visit)
	S1[a]	S2[k]	V0	V1	V2	V3	V4	V5/ EoMT			
	D-28 - D-9	D-14 - D-3	D0	D7 ±1 d	W6 -7/+4 d	W12 ±7 d	W18 ±7 d	W24 ±7 d			30 d after last IMP +14 d
Assessments											
Informed consent	•										
Demographics	•										
In-/exclusion criteria	•		•					(•)[j]			
Randomization			•								
Medical history[b]	•										
Previous therapy	•										
Concomitant medications/procedures	•	•	•	•	•	•	•	•	•	•	•
MS disease history	•										
Physical examination	•		•					•	•	•	•
New MS related neurological symptoms (treating physician)	•		•	•	•	•	•	•	•		
EDSS (evaluating physician)	•		•	(•)[m]	(•)[m]	•	(•)[m]	•	(•)[m]		
MS relapse (treating physician)			•	(•)[m]	(•)[m]	•	(•)[m]	•	(•)[m]		
MRI scan		•			•	•	•	•[e]			
Central MRI quality & eligibility assessment as well as BL stratification variables		•									
Central MRI assessment of efficacy variables					•	•	•	•			
Laboratory assessments											
Central screening labs, incl. blood pregnancy testf	•										
Local screening lab (Tbc-IGRA)	•										
Blood biochemistry (including HDL cholesterol)			•	•	•	•	•	•	•	•	•
Hematology			•	•	•	•	•	•	•	•	•

continued

Table 2: Schedule of assessments - Cohort 2 sub-trial (main treatment period) *(continued)*

	Screening		Blinded treatment						Unscheduled visit		EoS
		BL MRI	Main treatment (MT) period						due to MS-related symp-toms	due to safety	(end of study visit)
	S1[a]	S2[k]	V0	V1	V2	V3	V4	V5/ EoMT			
	D-28 - D-9	D-14 - D-3	D0	D7	W6	W12	W18	W24			30 d after last IMP
Assessments				±1 d	-7/+4 d	±7 d	±7 d	±7 d			+14 d
Urinalysis			•	•	•	•	•	•	•	•	•
IMU-838 trough level[g]			•	•	•	•	•	•			•[p]
Population PK[g]					•[l]						
C4[s]			•	•	•	•	•	•			•[p]
Local urine pregnancy test[d]			•[i]		•	•	•	•			•
Neurofilament[g]			•		•			•			
FGF-19[r]			•		•[q] •[q]			•			
Lab kits used											
Screening lab kit	S										
Trial lab kit			B	B	B	B	B	B	C	C	C
Neurofilament			NFL		2xNFL			NFL			
PK kit			PK	PK	2xPK	PK	PK	PK			PK[p]
Shipment to central lab											
Ambient temperature	•		•	•	•	•	•	•	•	•	•
Dry ice								•[o]			•[n]
Safety											
AE assessment	•	•	•	•	•	•	•	•	•	•	•
12-lead ECG	•				•			•		•	
Vital signs	•[c]		•[c]	•[c]		•[c]		•[c]			•[c]
IMP											
IMP administration[h]											
IMP dispensing			•		•	•	•	•			
No. of bottles disp.			1		1-2[t]	1-2[t]	1-2[t]	3			
IMP accountability								•			

Assessments in brackets (•) indicate assessments which must not always be performed. Refer to the respective footnote.

[a] Within 28 days from Baseline (Day 0). If the baseline MRI is repeated, the screening period maybe extended. However, patients must be randomized within 14 days of the repeated baseline MRI. Screening Visit 1 assessments will be valid for up to 60 days until the day of randomization, but will have to be repeated if exceeding 60 days. If results of the baseline MRI assessments are not available within 14 days (either after the first or, if applicable, after the repeated MRI) randomization can be delayed by up to 7 days, which may also result in an extension of the screening period.

[b] Including the history of autoimmune diseases (other than MS).

[c] Including height (only at Screening), respiratory rate, weight, blood pressure, pulse rate, and body temperature.

[d] Any positive local urine pregnancy test has to be followed up with a confirmatory local blood pregnancy test.
[e] Can be repeated if initial MRI scan is not at least partially assessable.
[f] Serum pregnancy test at central laboratory.
[g] Samples to be stored at -20°C until next scheduled dry-ice shipment to central laboratory.
[h] During the first week of treatment: 1 tablet once daily; other weeks: 2 tablets once daily.
[i] The result of this local pregnancy test must be available and negative before the first IMP can be taken.
[j] Only for patients who continue into the extended treatment phase.
[k] If the central reader evaluates the quality of the baseline MRI as not sufficient, the MRI must be repeated as soon as possible.
[l] Taken at 3 to 10 hours post-dose (in addition to the sample which is collected pre-dose at the same day for IMU-838 trough values).
[m] If, based on new neurological symptoms of the patient, the treating physician suspects that the patient may have an MS relapse (as defined in this protocol), an EDSS assessment by the evaluating physician and an assessment of MS relapse by the treating physician (based on the EDSS) must be performed at this visit.
[n] The sample can be stored at -20°C for up to 1 year and dry ice shipment can be combined with another dry ice shipment. However, the last dry ice shipment should be done when the last Cohort 2 patient has completed the MT period.
[o] The dry ice shipment should be generally done immediately after Week 24 visit. However, it may be delayed by up to 4 weeks if the dry ice shipment can be combined with the dry ice shipment for another patient at the same site.
[p] To be performed only up to the time of last patient last visit of the main treatment period in the Cohort 2 sub-trial (Week 12). Investigators will be notified immediately.
[q] Taken pre-dose and at 3 to 6 hours post-dose.
[r] Will be measured out of neurofilament lab kit (NFL lab kit), requires second NFL kit at Week 6 at 3 to 6 hours post-dose.
[s] Will be measured out of IMU-838 trough level samples (PK lab kit).
[t] Depending on amount of tablets patients still have from the previous visit.

AE = adverse event, BL = baseline, C4 = 7α-Hydroxy-4-cholesten-3-one, D = day, disp. = dispensed, DNA = deoxyribonucleic acid, ECG = electrocardiogram, EDSS = Expanded Disability Status Scale, EoMT = end-of-main treatment, EoS = end-of-study, EoT = end-of-treatment, ET = extended treatment, FGF = fibroblast growth factor, HDL-high density lipoprotein, IMP = investigational medicinal product, incl. = including, MRI = magnetic resonance imaging, MS = multiple sclerosis, MT = main treatment, No = number, PD = pharmacodynamic, PK= pharmacokinetic, S = screening, Tbc-IGRA = Tuberculosis interferon gamma release assay, V = Visit; W = Week.

2.7 Efficacy and safety assessments

Details on efficacy and safety assessments are described in Sections 14 and 15.

MRI assessments will be done using an MRI machine with a field strength of 1.5 Tesla. 3 Tesla machines as in the main trial are not allowed. For this reason, the Cohort 2 will only allow inclusion and assessments of patients at sites using 1.5 Tesla MRI.

The assessments performed will mostly include those described for the Cohort 1 main trial with few exceptions (for details see Section 1 of this Appendix).

3. Biostatistical methods and reporting

The Cohort 2 sub-trial will be analyzed after the last patient has terminated the sub-trial and the data base for the sub-trial has been locked (for data collection, monitoring and quality assurance see Section 21. However, for data collection during the Cohort 2 main treatment period no eCRF but paper CRF will be used. For the extended treatment period an eCRF, as in the Cohort 1 main trial, will be used.

All data will be analyzed descriptively as described in an SAP. The primary analysis set will be the FAS (for definition see Section 16.2). No formal statistical testing will be performed.

The cumulative number of CUA and cumulative number of new Gd+ lesions up to Week 24 will be analyzed with a negative binomial regression model with logarithmic link function with treatment group, Baseline volume of T2 lesions, and number of Gd+ lesions at Baseline as independent factor.

The main analysis of Cohort 2 will be done using Cohort 2 data, however an additional analysis of pooled Cohort 1 and 2 data will be performed. In order to allow pooling of data with an identical patient population, Cohort 1 placebo patients from the same sites that contributed to the Cohort 2 Week 12 data and investigated using 1.5 Tesla MRI examinations will be allowed to enrich the Cohort 2 placebo arm. In addition, Cohort 1 data of 30 mg/day and 45mg/day may be listed as comparison to Cohort 2 data of 10 mg/day IMU-838, however the same restriction for sites and 1.5 Tesla MRI as for placebo will apply. Details will be described in the SAP for Cohort 2.

All safety analyses will be done descriptively. Some limited pooled safety assessments of Cohorts 1 and 2 will also be provided.

The results of the Cohort 2 sub-study will be summarized in an addendum to the clinical trial report.