Immunic THERAPEUTICS

STUDY PROTOCOL

A phase 2, multicenter, randomized, double-blind, placebo-controlled, dose-finding study to evaluate the efficacy and safety of IMU-838 for induction and maintenance therapy in moderate-to-severe ulcerative colitis

CALDOSE-1

EudraCT No: 2017-003703-22
IND No.: 134114

Protocol no.:	P2-IMU-838-UC
Sponsor:	Immunic AG Lochhamer Schlag 21 82166 Graefelfing, Germany
Coordinating investigator:	Prof. Geert D'Haens Executive Director, Inflammatory Bowel Disease Centre Academic Medical Centre University of Amsterdam Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands
Protocol version and date:	Final 6.0, 14-Dec-2021
Previous protocol versions and date:	Final 5.0, 26-Feb-2021
	Final 4.0, 17-Sep-2019
	Final 3.1 (UK), 23-Jan-2018
	Final 3.1 (PL), 01-Jun-2017
	Final 3.0, 21-Nov-2017
	Final 2.0, 24-Oct-2017
	Final 1.0, 16-Oct-2017

REVISION CHRONOLOGY

- Original version: Version 1.0, dated 16-Oct-2017
- Version 2.0, dated 24-Oct-2017

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

  - Title page: 'This version includes the following amendments' was replaced by 'Previous protocol versions and date.'
  - In the Schedule of assessments - induction phase (Table 1) a cross for 'IMU-838 trough levels' was included at Day 0, which was erroneously missing in protocol Version 1.0.
  - In the Schedule of assessments - open-label treatment arm (Table 3), 'Collection of endoscopic assessments if available from clinical routine' was replaced by 'Collection of endoscopic results if performed during clinical routine.
  - Section 14.3: IP-10 (IFNγ induced protein) was deleted from the list of cytokines which will be assessed.
- Version 3.0, dated 21-Nov-2017

  The following changes were included in Version 3.0 compared with Version 2.0:

  - Thresholds for neutrophil count and platelet count in Inclusion Criterion 6 specified in cells/L in addition to cell/µL or cell/mm³, respectively.
  - In Table 1 drug accountability at D7 and W2 deleted.
  - In Table 4 and Section 14.1 time windows for PK sampling time points included i.e. ±15 minutes for each time point from 1 to 6 hours post-dose, and ±1 hour for the 24-, 48-, and 72-hour time point.
  - Table 5 and Section 12.10 time window for EoS visit added (-3 days/+4 weeks).
  - In Section 2 and 6 responsibilities clarified: for LKF 'biomarker' added; IMGM 'genotyping and assessment of miR-122' (no biomarkers as specified previously in Section 2), in Section 6 for Nuvisan packaging of IMP added.
  - Section 11.1.3: Label specification modified:

    'The labels will contain at least the following information: route of administration, study code, randomization number, batch number, expiry date, as well as the following instructions for use: for clinical study use only, keep out of the reach of children, do not store above +25°C, return all unused study medication.'

    Changed to:

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

- Section 11.1.4: New storage condition added due to new stability data

  'Study medication must be stored at or below +25°C (77 F) in a dry place, protected from direct sun light.'

  replaced by

  'In stability studies, the medicinal product was stable at ambient (25°C/60% relative humidity) and at accelerated storage conditions (40°C/75% relative humidity). Thus, IMU-838 does not require any special storage conditions. However, the tablets in general should be protected from direct sun light, moisture, freezing, and excessive heat (excessive heat is customarily defined as any temperature above 40°C [104 F]). It should also be advised to keep the bottle tightly closed in order to protect from moisture.'

- Section 12.5: 'The Start$_{OLE}$ visit must be performed within 4 weeks of the last dose of the blinded treatment during the induction or maintenance phase.' changed to 'The Start$_{OLE}$ visit must be performed within 30 days of the last dose of the blinded treatment during the induction or maintenance phase' as specified in Table 4.
- Section 15.2.2: Lab Kits A and B, Biochemistry: '..magnesium chloride (MgCl),..' changed to …'magnesium (Mg), chloride (Cl),..'
- Inconsistencies in and between Section 15.2.5 and Section 15.2.6 clarified i.e. in Section 15.2.5 'The HBcAg assay will be a combined immunoglobulin G (IgG) and IgM test' changed to 'The HBcAb assay will be a combined immunoglobulin G (IgG) and IgM test', and in Section 15.2.6 under serology 'HCV' added.

- Version 4.0, dated 17-Sep-2019

  The following changes were included in Version 4.0 compared with Version 3.0:

  - According to the independent DRC, the interim analysis did not show that any of the IMU-838 doses used in Enrollment Period 1 were likely ineffective and/or intolerable. Thus all 3 IMU-838 doses will be continued in Enrollment Period 2. Initially it was planned that Enrollment Period 2 would include only up to 2 doses of IMU-838 and placebo, excluding likely ineffective and/or intolerable doses based on the interim analysis at end of Enrollment Period 1. Enrollment Period 2 will now include approximately further 180 patients randomized 1:1:1:1 to oral 10 mg/day, 30 mg/day, 45 mg/day IMU-838, or placebo (about 45 patients each) instead of the 135 patients planned if 2 IMU-838 doses or 150 patients if 1 IMU-838 dose would have been

continued. In total, approximately 240 patients will be randomized into this trial in both, Enrollment Periods 1 and 2. The sample size calculation per se is not changed as for the primary endpoint analysis, on which the sample size calculation was based on, 2 IMU-838 dose groups will be pooled and compared to the placebo groups, as already foreseen in the previous protocol versions. However, as Enrollment Period 2 will now include 3 IMU-838 treatment arms instead of the maximum planned 2 groups, an additional 45 need to be enrolled to ensure that 60 patients per treatment groups will be available for the primary analysis as stipulated in the sample size calculation (see Section 16.1). The following sections were adjusted accordingly:

- Section 1: paragraph added to briefly describe conclusion of the interim analysis and consequences, primary and first secondary efficacy endpoint modified (see below), sample size adjusted (see below), 'As recruitment in Enrollment Period 1 is ongoing during the interim analysis, Enrollment Period 1 will most likely include a few more patients than the scheduled approximately 60 patients' was deleted, Figure 1 (Study flow chart) 4 treatment arms in Enrollment Period 2 included (instead of the possibility of 2 or 3 arms)
- Section 7.2 (Study endpoints):
  - Primary endpoint. The following was adjusted:

    All patients (both, Enrollment Period 1 and Enrollment Period 2 patients) who were randomized to ~~the active dose(s) selected for Enrollment Period 2~~ will be used …

    Replaced by

    All patients (both, Enrollment Period 1 and Enrollment Period 2 patients) who were randomized to **30 mg/day and 45 mg/day** IMU-838 will be used…..
  - First secondary endpoint adjusted as follows:

    • ~~If 2 IMU-838 doses are continued in Enrollment Period 2:~~ proportion of patients with both symptomatic remission and endoscopic healing at Week 10 ~~for the following comparisons:~~

    o ~~the higher active dose versus placebo~~

    o ~~the lower active dose versus placebo~~

    o ~~the lower versus the higher active dose.~~

    Replaced by

    • Proportion of patients with both symptomatic remission and endoscopic healing at Week 10 (**all individual IMU-838 doses will be compared with one another and to placebo**).

- Section 8.1.3 (Induction phase):
  - Paragraph added to briefly describe conclusion of the interim analysis and consequences.
  - The following was added: 'In total, approximately 240 patients will be randomized in both Enrollment Periods 1 and 2.'
  - Paragraphs on Enrollment Period 2 adjusted accordingly.
  - 'There will be no recruitment stop during the interim analysis. Recruitment into Enrollment Period 1 will continue until results of the interim analysis will be available and Enrollment Period 2 will be started' deleted.
- Section 8.2 (Study design rationale): Paragraph added to briefly describe conclusion of the interim analysis and consequences.
- Section 9.1 (Sample size):
  - Sample size for Enrollment Period 2 adjusted from 135 patients, planned if 2 IMU-838 doses were continued, or 150 patients, planned if 1 IMU-838 dose were continued, to 180 patients. The sample size calculation per se was, however, not changed (see above).
  - Included that the 30 mg/day and 45 mg/day groups will be pooled for the primary endpoint analysis.
  - The following was deleted: 'Since enrollment is not stopped during interim analysis, a small "over-enrollment" of Enrollment Period 1 may occur. However, patient targets for Enrollment Period 2 will only consider the time period following implementation of recommendations from the interim analysis.'
- Section 11.1.5 (Treatment dose, dose selection, and administration):
  - Table 6 (Doses administered): Dosing in Enrollment Period 2 adjusted.
  - The following was included at the end of this section: 'However, from the interim results the DRC concluded that none of the IMU-838 doses used in Enrollment Period 1 were likely ineffective and/or intolerable and the Steering Committee recommend continuing all 3 IMU-838 doses in Enrollment Period 2. These recommendations were accepted and implemented by the sponsor and thus Enrollment Period 2 will include all 3 IMU-838 doses.'
- Section 16.1 (Sample size calculation):
  - The possibility that 2 doses will be combined for the primary endpoint analysis was already implemented in the previous protocol. Now wording slightly modified to include that these 2 doses will be the 30 mg/day and 45 mg/day IMU-838.

- The possibility that only 1 IMU-838 dose will be continued in Enrollment Period 2 was deleted.

– Section 16.4 (Primary efficacy analysis): adjusted and specified that the 30 mg/day and 45 mg/day IMU-838 will be pooled for the primary endpoint analysis and compared with placebo

– Section 16.5 (Interim analysis): Wording slightly adjusted.

- Section 1 (Summary and flow chart) and Section 6 (Investigators, study administrative structure, and study committees):

– Additional countries in which the trial will be performed added i.e. Albania, Belarus, Bosnia-Herzegovina, North Macedonia, Norway, and Turkey.

– Number of centers updated from '80 to 90' to 115

- Section 1 (Summary and flow chart) and Section 8.1.3 (Induction phase):

To avoid confusion the following was changed:

Section 1:

'All patients will receive their full dose they are randomized to starting from ~~Week 2~~.'

replaced by 'All patients will receive their full dose they are randomized to starting from **Day 7**.'

Section 8.1.3:

'Patients will be dosed with their full assigned dose starting ~~Week 2~~ of the induction phase and thereafter' replaced by 'Patients will be dosed with their full assigned dose starting **Day 7** of the induction phase and thereafter.'

- Section 1 (Summary and flow chart) and Section 9.2 (Inclusion Criteria 4):

Additional requirement for active disease added in Inclusion Criterion 4 (Mayo rectal bleeding score of ≥1).

4. Active symptoms defined as a Mayo stool frequency score of ≥2 and a modified Mayo endoscopy subscore of ≥2 at the screening flexible sigmoidoscopy (endoscopy assessed by an independent central reader blinded to screening center and patient information)

replaced by

4. Active disease defined as

   a. Mayo stool frequency score of ≥2 **at Screening Visit 1**
   b. Mayo rectal bleeding score of ≥1 at Screening Visit 1

c. modified Mayo endoscopy subscore of ≥2 at the screening flexible sigmoidoscopy (endoscopy assessed by an independent central reader blinded to screening center and patient information)

- Section 1 (Summary and flow chart) and Section 9.3 (Exclusion Criterion 27), Section 11.2.2 (Other prohibited and restricted medications), Appendix 1:

  Sections adapted to current version of IB and specified that care should be exercised when using medications that are substrates of the BCRP transport system, especially when the elimination of the medication depends on the BCRP transport system. Added that patients should be closely monitored for signs and symptoms of excessive exposure to these medications and that the dosing of these medications should be carefully considered. In addition, specified that statins should be lowered to the lowest possible dose and doses of rosuvastatin are not allowed to exceed 10 mg daily (during screening and entire study).

- Section 1 (Summary and flow chart) and Section 9.3 (Exclusion Criterion 13), and Section 15.2.2:

  'Creatinine clearance' corrected to 'estimated glomerular filtration rate'.

- Section 1 (Summary and flow chart) and Section 9.3 (Exclusion Criterion 9), 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 is only considered HIV positive when both tests are positive.

- Section 1 (Summary and flow chart) and Section 9.3 (Exclusion Criteria for open-label extension arm 1 and 2):

  1. Any ongoing, clinically significant ~~(as assessed by the investigator)~~ treatment-emergent (started during the IMU-838 treatment in the blinded treatment arms) adverse event (AE) or laboratory abnormality (including blood chemistry and urinalysis)*
  2. Significant treatment or study non-compliance during induction and/or maintenance phase (as assessed by the investigator), and/or inability or unwillingness to follow instructions by study personnel

  replaced by

  1. Any ongoing, clinically significant treatment-emergent (started during the IMU-838 treatment in the blinded treatment arms) adverse event (AE) or laboratory abnormality (including blood chemistry and urinalysis) **as assessed by the investigator***

2. Significant treatment or study non-compliance during induction and/or maintenance phase (as assessed by the investigator), and/or inability or unwillingness to follow instructions by study personnel **as assessed by the investigator**

- Section 8.1.3 (Induction phase), Section 10.3 (Maintenance of blinding during interim or exploratory analyses), Section 16.4 (Primary efficacy analysis) and 16.5 (Interim analysis):

  Time of interim analysis adjusted to what was specified in the SAP for the interim analysis, i.e. that the interim analysis will be conducted when in Enrollment Period 1 approximately 60 patients have been randomized and had received at least 1 dose of IMP instead of 'after approximately 60 patients had completed their W10/EoI assessments.' The respective footnotes (i.e. This includes all patients who had completed Week 10 and those who prematurely discontinue the induction phase at Week 6 or between Week 6 and Week 10, for whom the Week 10/EOI assessment were performed at time of discontinuation) were deleted where applicable.

- Section 1 (Summary and flow chart) and Section 23 (Study periods):
  - Start of trial updated from January 2018 to March 2018
  - Estimated end of maintenance phase changed from January 2021 to June 2022 and recruitment period extended from 24 months to 40 months.

- Table 1 (Schedule of assessments - induction phase):
  - Screening visits identified as S1 and S2
  - for S1 the following footnote added: 'Within 30 days of D0. If there is a delay in assessments from Screening Visit 1 or assessments need to be repeated due to technical difficulties, assessments from Screening Visit 1 are valid for up to 60 days between Screening Visit 1 and randomization. If 60 days are exceeded, Screening Visit 1-assessments must be repeated. Note that tests can solely be repeated if tests are inconclusive or had technical problems. A re-screening of patients is not allowed (if not requested or approved by the sponsor).'

- Table 1 (Schedule of assessments - induction phase) and Section 13.2:

  Assessment of Mayo stool frequency score and Mayo rectal bleeding score added at Screening Visit 1 to allow correct calculation of Inclusion Criteria 4.

- Table 1, Table 2, Table 3, Table 4, and Table 5 (Schedule of assessments):

  Hematology added i.e. 'Clinical biochemistry' replaced by 'Clinical biochemistry and hematology' and 'CBC with differential' deleted to be consistent with the respective lab kits.

- Section 2 (Addresses and responsibilities) and Section 6 (Investigators, study administrative structure, and study committees):
  - outside vendors were added for HIV testing based on the Nucleic Acid Amplification Technology, population PK modelling, eCRF, and emergency unblinding by phone
  - contact details were updated for IMGM Laboratories and Chiltern International Laboratories (now Covance)
  - services provided by Nuvisan were updated
- Section 10.2 (Emergency unblinding):

  Added that emergency unblinding may be performed by an emergency phone service, in case the web-based system cannot be accessed for any reason.
- Section 10.3 (Maintenance of blinding during interim or exploratory analyses), Section 16.3 (Statistical analyses), Section 16.7 (Explorative analysis of maintenance phase) and Section 23 (Study report and publications):

  Because it was decided not to disclose any group level data of the interim analysis after Enrollment Period 1 or of the exploratory analysis of the maintenance phase to the Steering Committee the following was deleted in Section 10.3:

  'However, the following selected data from the interim analysis (only group level averages without minimum and maximum values) could be made available to members of the Steering Committee, following the DRC recommendations to support their decision on dose continuation:

  For the interim analysis of the induction phase following Enrollment Period 1

  Percentage of patients with symptomatic response and symptomatic remission at Week 10

  Percentage of patients with endoscopic healing at Week 10

  Percentage of patients with any AE

  Mean CRP and mean fCP in stool

  For the exploratory analysis of the maintenance phase following data base lock for the final analysis of the induction phase

  Proportion of patients in symptomatic remission by visit up to Week 50

  Proportion of patients without symptomatic UC relapse until Week 50

  Proportion of patients with endoscopic healing at Week 50

  Mean CRP and mean fCP in stool'

  In addition, as group level data are no longer disclosed it was considered appropriate not to finalize all SAPs before the interim analysis. The SAP for the induction phase

that describes the primary endpoint analysis, however, was finalized before the interim analysis as scheduled. The following was changed:

Section 10.3:

'To minimize bias, the statistical analysis plan (SAP) for all scheduled analyses i.e. including the interim analysis, ~~explorative data analysis, final analysis induction phase, final analysis maintenance phase, and analyses for open-label phase~~ will be finalized before any data will be analyzed i.e. before the interim analysis.'

replaced by

'To minimize bias, the statistical analysis plan (SAP) for the induction period **(which includes the primary endpoint of the study**) will be finalized before any data will be analyzed in the interim analysis.'

Section 16.3:

'A detailed description of the statistical analyses for all scheduled analyses (i.e. interim analysis, explorative analysis of maintenance phase, final analysis induction phase, final analysis maintenance phase, and analyses for the open-label phase) will be provided in an SAP ~~and will be finalized before any data will be analyzed, i.e. before the interim analysis.~~'

replaced by

'A detailed description of the statistical analyses for all scheduled analyses (i.e. interim analysis, explorative analysis of maintenance phase, final analysis induction phase, final analysis maintenance phase, and analyses for the open-label phase) will be provided in SAPs. **To minimize bias, the SAP for the induction period (which includes the primary endpoint of the study) will be finalized before any data will be analyzed in the interim analysis.**

Section 16.7: In 'A detailed description of the analyses will be provided in the corresponding SAP which will be finalized before the interim analysis of the induction phase' the following was deleted ' which will be finalized before the interim analysis of the induction phase.'

Section 22: Because no groups level data will be disclosed no abbreviated report will be done for the interim analysis and was thus deleted in the respective paragraph.

- Section 12.2 (Screening):

  Added that assessments from Screening Visit 1 are valid for 60 days i.e. 'Only patients who have passed all eligibility criteria at Screening Visit 1 should be continued into Screening Visit 2 (endoscopy). If there is a delay in assessments from Screening Visit 1 or assessments need to be repeated due to technical difficulties, assessments from Screening Visit 1 are valid for up to 60 days between Screening Visit 1 and

randomization. If 60 days are exceeded, Screening Visit 1-assessments must be repeated. Note that tests can solely be repeated if tests are inconclusive or had technical problems. A re-screening of patients is not allowed (if not requested or approved by the sponsor).'

- Section 15.1.1.1 (Adverse events):

  Clarified that overdosing will not be considered an AE but must be documented as protocol deviation i.e.

  'Overdose which is defined as more than twice the full randomized dose will also be considered AEs.'

  replaced by

  '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 Section 15.1.1.2)**.'

- Section 15.1.1.3 (Serious adverse events):

  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 15.2.2 (Blood chemistry, hematology, and coagulation):

  Clarified that coagulation parameters are part of Lab Kit A.

- Section 15.2.4 (miR-122 expression):

  '~~The exploratory biomarker~~ miR-122…' changed to 'Micro RNA 122 is…'

- Section 15.2.6 (Screening laboratory):

  Under biochemistry 'total bilirubin' deleted as it was listed 2 times; eGFR (CKD-EPI) added as needed for eligibilty criteria.

- Section 17 (Patient withdrawal from study participation):
  - To clarify that the listed reasons for withdrawal represent stopping rules for a patient, the following was added before the withdrawal reasons: 'Patients must be withdrawn from the study for any of the following reasons.'
  - For liver enzyme stopping rules, reference to Section 11.5.2 added

- Country-specific amendments included (applicable only for the respective country(ies)):
  - Poland and UK:
    - Sections 1 (Summary and flow chart) and 9.2 (Inclusion Criterion 8):

      Inclusion criterion 8 was extended to include

- that female partners of childbearing potential of sexually active male study participants need adequate contraception as outlined in inclusion criterion 7, and
- that male participants whose partners are pregnant must use condoms while taking study medication to avoid exposure of the fetus to study medication *(Poland only)*

▪ Section 11.4 (Precautions and restrictions) was modified to reflect the changes made to Inclusion Criterion 8 as described above.

UK only

▪ Sections 1 (Summary and flow chart), Table 3 (Schedule of assessments - open-label treatment arm), Table 4 (Schedule of assessments - open-label treatment arm for PK population at designated PK centers), Sections 8.1.5 (Open-label treatment extension), 12.5 (Open-label treatment arm), and 23 (Study periods): The open-label extension treatment period was restricted to a maximum of 3 years. The maximum study duration was changed accordingly from 10 years to 4 years with a maximum open-label extension period of 3 years. Because the available data at the interim analysis were limited, the DRC did not make a recommendation whether the extended treatment period may be prolonged as specified in protocol Version 3.1 (UK). Now specified that the steering committee will make a recommendation after one of their future regular safety assessments on a potential prolongation when more safety data from the ongoing open-label treatment extension is available.

o Editorial changes throughout

- Version 5.0, dated 26-Feb-2021

The following changes were included in Version 5.0 compared with Version 4.0:

o Cover page and Section 2: The Sponsor address was updated.

o Section 1 (principal investigators and study centers) and Section 6: Involved countries were summarized as “countries in Western and Eastern Europe and the United States in America”.

o Section 1 (pharmacokinetic period), Section 8.1.6, and Section 14.1 were revised to clarify that the pharmacokinetic period that is scheduled at the start of the OLE period may be performed not only after completion of the maintenance phase but also after the induction or extended induction phase. Respective text in Section 9.1 was deleted as not considered necessary in this section.

- Section 1, Table 1, and Section 12.2: Clarified that assessments at Screening Visit 2 may be repeated in case of technical problems within the times indicated for repetition of Screening Visit 1 assessments.
- Exclusion criterion 9 (Section 1 and Section 9.3) and Section 15.2.5: It was clarified that **any** HIV, HBV, or HCV antigen or antibody screening test that shows reactive or borderline results (not as previously only a positive HIV-Ag/Ab test) will be confirmed via NAAT. If no virus specific nucleic acid is detected, and the clinical history of the patients, other laboratory examinations, and current clinical pictures also exclude a concurrent infection, the patient will not be excluded from the study.
- Section 1, Section 11.2.2, and Appendix 1: Restricted medications were updated.
- Section 2 and Section 6: The previous eCRF provider was replaced by ANJU Life Sciences Software.
- Section 10.2 and Section 10.5: Deleted that the interactive web-based response system is situated within the eCRF.
- Section 15.2: Added that clinically significantly abnormal values must be reported as an AE unless there are circumstances unrelated to a disease or the medication that likely explain the abnormal value.

- Version 6.0, dated 14-Dec-2021

  The following changes were included in Version 6.0 compared with Version 5.0:

  - Section 1 and Section 23: Study end, study duration, actual start and recruitment period adjusted; maximum treatment duration in UK (blinded and open-label treatment combined) corrected from 3 to 4 years, as mentioned in other sections
  - Section 1 and Section 6: Number of participating centers updated
  - Added that patients in the open-label treatment extension may be transferred to a separate long-term follow-up trial or to commercial vidofludimus calcium (if applicable and patients have access). In this case the CALDOSE-1 trial will only be closed once all remaining patients in the open-label treatment extension have been transferred to the follow-up trial or commercial vidofludimus calcium. No EoS visit is required for patients transferring to the long-term follow-up study or commercially available vidofludimus calcium. The following sections were changed accordingly:
    - Section 1 (Study duration, Methodology)
    - Sections 8.1.1, 8.1.5, 12.5, 12.8, 12.10, and 23
    - Section 12.9 newly added
    - Figure 1, Table 3, Table 4, Table 5

- The visit schedule in the open-label treatment extension after 50 weeks of overall study treatment was changed from a 10-week schedule to a 24-week schedule. Visit numbering will be kept unchanged. The time window for the OLE visits was expanded from ±7 days to ±14 days. The following sections were changed accordingly:
  - Section 1 (Methodology)
  - Table 3 and Table 4
  - Sections 8.1.5, 11.1.3, and 12.5
- Because of implementation of a new manufacturing process for IMU-838 tablets, a simplified formulation, i.e. IMU-838-RC, was introduced. This formulation contains fewer inactive ingredients. IMU-838-RC will be provided as 30 mg tablets packed in 30 mL polyethylene bottles containing 85 or 100 tablets and may be used only during the open-label treatment extension. After switching, patients must take only 1 instead of 2 tablets during the open-label treatment extension. The following sections were changed accordingly:
  - Section 1 (Treatments)
  - Section 5.2.3 newly added
  - Sections 8.1.5, 11.1.1, 11.1.3, and 11.1.5
  - Table 6
- Sections 1 (Statistical methods), 8.1.5, and 16.5: The possibility to do safety interim analyses during the open-label treatment extension included
- Section 2 and Section 6: List of study personnel updated
- During the open-label treatment extension, compliance will be assessed by the number of bottles dispensed and empty bottles returned (dispensed bottles must be used until empty and then returned; remaining tablets of in-use bottles will not be counted at every trial visit; patients will be advised accordingly). This differs for the EoOLE visit and in case of an interim safety analysis at which remaining tablets in in-use bottles will be counted at the last visit before the interim analysis. Patients will be advised to bring all IMP (including full, in-use, and empty bottles) to all visits; the empty bottles will be kept, the in-use and full ones will be returned to the patient (together with newly issued ones). The number of bottles dispensed will be up to 5 (previous formulation) or up to 2 (simplified formulation). The following sections were changed accordingly:
  - Sections 11.1.3, 11.1.6, 12.1, Table 3, Table 4
- Sections 8.1.1, 11.1.3, 12.1, and Section 12.11 (newly added): contingency measures in case of pandemic situations introduced

- Section 11.2.1.2 and Appendix 1 updated i.e. 'tofacitinib' replaced by 'Janus kinase inhibitors approved for the treatment of IBD (e.g. tofacitinib)';
- Section 11.2.2 and Appendix 1 updated: 'DHODH' deleted (Section 11.2.2) as mentioned in Section 11.2.1.2; 'Sphingosine-1-receptor (S1P) modulators (including, but not limited to fingolimod, siponimod, and ozanimod), monomethyl fumarate, and diroximel fumarate' added: in Appendix 1: 'methotrexate up to 17.5 mg/week' deleted as restricted medication as methotrexate is prohibited during all phases of the study
- Section 15.1.5: name of 'SCRATCH Pharmacovigilance GmbH' updated and 'Chiltern' replaced by 'sponsor's designee'
- Sections 15.1.5 and 15.1.7: clarified that SAEs and pregnancies must be reported **no later than** within 24 hours to the sponsor
- Section 15.2.3: uric acid was deleted from the urinalysis assessments (Lab Kits A, B, and C). The values of urine uric acid have been found to be highly variable and depend to a high degree on urine volumes and fluid intake by the study participants. It was seen that serum uric acid provides a much more reliable picture of the uric acid homeostasis and potential for changes caused by IMU-838. For this reason, the urine uric acid has been removed and the assessment will further focus on serum uric acid.
- Section 17, the following reasons for withdrawal were added:
  - Transfer to another long-term follow-up study
  - Transfer to commercial vidofludimus calcium
  - The patient has fully completed this study
- Section 19.1, the following reasons to halt or terminate the study were added:
  - All patients have been transferred to a long-term follow-up trial or to commercial supply of vidofludimus calcium
  - All patients have completed the full duration of this study
- Section 19.2, the following reasons to close a center were added:
  - All patients of this trial center have completed the full duration of this trial, have been transferred or have otherwise withdrawn from this study, and investigators have stated in writing that they will provide answers to queries after trial site closure
- Appendix 1: reason why BCRP substrates with a narrow therapeutic window are restricted added; updated according to Sections 11.2.1.2 and 11.2.2;
- Editorial changes

1 Summary and flow chart

Study code
P2-IMU-838-UC

Title of the study
A phase 2, multicenter, randomized, double-blind, placebo-controlled, dose-finding study to evaluate the efficacy and safety of IMU-838 for induction and maintenance therapy in moderate-to-severe ulcerative colitis (CALDOSE-1)

Principal investigators and study centers
133 centers were initiated in a variety of countries in Western and Eastern Europe and the United States of America.

Coordinating investigator(s): Prof. Geert D'Haens, University of Amsterdam, The Netherlands

Clinical phase: 2

Study duration

Actual start:	25-Jun-2018 (first patient in)
Estimated end main maintenance phase:	Oct 2022 (main part: last patient out)
Open-label treatment:	Not defined, but maximum treatment duration in this trial limited to a maximum of 10 years (including all phases of the trial; *in UK: maximum of 4 years*). Patients may also be transferred to a follow-up trial or to commercially available vidofludimus calcium, if applicable for patients with access
Actual recruitment period:	~41 months (24-Apr-2018 to 30-Sep-2021)

Study periods
Screening, induction phase with Enrollment Periods 1 and 2, maintenance phase, pharmacokinetics (PK) period, and open-label treatment extension.

Study objectives
Primary objective

- To determine the optimal dose of IMU-838 to induce symptomatic remission and endoscopic healing in patients with moderate-to-severe ulcerative colitis (UC)

Secondary objectives

- To determine the optimal dose of IMU-838 to maintain clinical benefits in patients with moderate-to-severe UC

- To evaluate the effects of IMU-838 on clinical and endoscopic endpoints in patients with moderate-to-severe UC
- To evaluate the time course of activity and effects of IMU-838
- To evaluate the safety and tolerability of IMU-838 in patients with moderate-to-severe UC
- To evaluate exploratory biomarkers, disease activity biomarkers, and pharmacodynamic (PD) effects of IMU-838
- To evaluate population pharmacokinetics (PK) and plasma trough levels of IMU-838 throughout the induction period
- To evaluate single dose PK at Week 50 for a subpopulation of patients with moderate-to-severe UC receiving 30 mg of IMU-838

Methodology

This is a phase 2, multicenter, double-blind, and placebo-controlled study including a blinded induction and maintenance phase, with double randomization i.e. initial randomization for induction and second randomization for maintenance. The study also includes an option for open-label treatment extension for patients discontinuing from or completing blinded treatment. A subset of patients will undergo a **PK period** at the start of the open-label period to establish a full single dose PK profile. Patients in the open-label treatment extension may also be transferred to another long-term follow-up trial or to commercially available vidofludimus calcium. Once all patients are transferred, the open-label treatment extension in this study will be closed.

Induction phase

Enrollment periods and interim analysis: The induction phase comprises Enrollment Period 1 and Enrollment Period 2 with an interim analysis between the 2 periods. Enrollment Period 1 will include approximately 60 eligible patients randomized 1:1:1:1 to oral 10 mg/day, 30 mg/day, 45 mg/day IMU-838, or placebo (about 15 patients each). Initially it was planned that Enrollment Period 2 would include up to 2 doses of IMU-838 and placebo, excluding likely ineffective and/or intolerable doses based on an interim analysis of safety, PK, biomarker, PD and efficacy data after Enrollment Period 1. Because the interim analysis did not reveal a likely ineffective and/or intolerable dose according to the findings of the unblinded data review committee (DRC), the Steering Committee recommended to continue all 3 IMU-838 doses in Enrollment Period 2. These recommendations were accepted and implemented by the sponsor. Thus, Enrollment Period 2 will include approximately further 180 patients randomized 1:1:1:1 to oral 10 mg/day, 30 mg/day, 45 mg/day IMU-838, or placebo (about 45 patients each).

After randomization, and during the first week of study drug treatment in the induction phase, patients will receive only half of their assigned full dose (in both Enrollment Periods 1 and 2) i.e. 5 mg/day, 15 mg/day, 22.5 mg/day IMU-838, or placebo, respectively. All patients will receive their full dose they are randomized to starting from Day 7.

Initial randomization: Eligible patients will be randomized to receive either IMU-838 (as applicable to the respective enrollment period) or placebo. Randomization will be stratified by prior use of any biologics and current use of corticosteroids. In addition, the proportion of patients who had received previous biologics will be limited to approximately 75% of all included patients.

Study procedures: During the induction phase, safety, exploratory biomarkers, PD, disease activity biomarkers (fecal calprotectin [fCP] and C-reactive protein [CRP]), symptomatic and endoscopic assessments (full and partial Mayo score, and respective subscores), and trough IMU-838 blood levels will be regularly evaluated (see Table 1). The induction phase (both enrollment periods) will be at least 10 weeks, after which patients will undergo a scheduled flexible sigmoidoscopy with biopsy and the full Mayo score (including all subscores) will be assessed.

Treatment after Week 10: Depending on symptomatic assessments patients will be treated as follows:

- Patients who have achieved symptomatic remission at Week 10 will enter the maintenance phase.
- Patients who have achieved symptomatic response but not yet in symptomatic remission will continue into an extended induction phase until Week 22 on the dose they were initially randomized to. If these patients have achieved symptomatic remission at Week 22 they will enter the maintenance phase.
- Patients who do not show symptomatic response at Week 10 or symptomatic remission at Week 22 (if the patient had continued into the extended induction phase) will be discontinued from the blinded treatment but will have the option to enroll in the open-label treatment extension arm from Week 10 or Week 22 onwards.

Maintenance phase

Re-randomization: For maintenance treatment, patients who had received IMU-838 during induction will be re-randomized to 10 mg/day or 30 mg/day IMU-838; patients who had received placebo will be "re-randomized" to placebo treatment (however, their treatment assignment will remain blinded). Randomization will be stratified by the IMU-838 dose received in the induction phase.

Study procedures during the maintenance phase: The maintenance phase will start with patients in symptomatic remission at Week 10 or Week 22. Patients in the maintenance phase will receive study medication until 50 weeks of total treatment (adding up induction, extended induction, and maintenance phase), or until UC relapse, whichever occurs earlier. During the maintenance phase, safety, disease activity biomarkers (fCP and CRP), symptomatic and endoscopic assessment (full and partial Mayo score, and respective subscores), and trough IMU-838 blood levels will be evaluated as outlined in the Schedule of events (Table 2). Patient visits will be scheduled every 4 weeks. At Week 50 (or at time of symptomatic UC relapse, if earlier) a scheduled flexible

sigmoidoscopy with biopsy will be performed and the full Mayo score (including all subscores) will be assessed.

Treatment at the end of the maintenance phase: Depending on the symptomatic status, patients will be treated as follows:

- Patients who have completed all Week 50 procedures (including the scheduled flexible sigmoidoscopy with biopsy) will discontinue maintenance treatment with the option to enroll in the open-label treatment extension arm.
- Patients with a symptomatic UC relapse before Week 50 will be prematurely discontinued. At UC relapse a scheduled flexible sigmoidoscopy with biopsy will be performed and the full Mayo score (including all subscores) will be assessed. Patients who have completed the flexible sigmoidoscopy will have the option to enroll in the open-label treatment extension arm.

Explorative data analysis: An explorative data analysis of the maintenance phase will be performed at the time of the final analysis for the induction phase (i.e. when all patients have completed the induction phase or if applicable extended induction phase).

Open-label treatment extension

Patients eligible for the open-label treatment extension arm will be treated with 30 mg IMU-838, once daily. Visits will be scheduled every 4 weeks for the initial 50 weeks of overall study treatment, and every 24 weeks thereafter. Following the implementation of Protocol Version 6.0 the 10-week schedule, for patients in the open-label extension and with more than 50 weeks of overall treatment, will be changed to a 24-week schedule at the next scheduled visit. Safety, concomitant medication, Mayo patient-reported outcome (PRO)-2 score, fCP, and CRP, will be regularly assessed during clinic visits. No endoscopic assessment will be performed but results from such procedures will be collected when done in the course of routine clinical care.

Treatment for a patient in the open-label extension arm will continue as long as no clinically significant safety issue (as assessed by the investigator) occurs, that is related to study procedures or study treatment, until the patient no longer receives a benefit from study treatment (as assessed by the investigator), until the patient withdraws consent, or until the sponsor terminates the study. In addition, patients in the open-label extension arm may be transferred by the sponsor to a separate and comparable follow-up trial in which they can continue treatment with IMU-838 or, if patients have access, transfer to commercially available vidofludimus calcium. Once all remaining participating patients have been transferred respectively, the CALDOSE-1 study will be closed.

Patients will be allowed to receive a maximum of 10 years *(not applicable for UK, see below)* total combined treatment with study medication in this trial.

For UK the following applies: Patients will be allowed to receive a maximum of 4 years total combined treatment with study medication in this trial. The maximum duration of the open-label treatment extension is 3 years. However, if no safety concerns arise during future regular safety assessments and sufficient safety data are available, the steering committee may recommend extending the overall treatment period including all phases to a maximum of 10 years as per a substantial amendment.

Pharmacokinetic period

Across designated study centers ("PK centers") only, the first 8 patients who completed the induction, extended induction or maintenance phase as scheduled and who will continue into the open-label phase will be included in a PK subpopulation for which a full single-dose PK profile (up to 72 hours post-dose) will be established. These patients will receive their first open-label dose of 30 mg IMU-838 at the Start$_{OLE}$ visit. Blood samples will be collected pre-dose and up to 72 hours post dose (during which period the patient will take no additional dose). On Day 3$_{OLE}$, after the last PK blood sample has been taken, patients will continue their open-label phase with daily dosing as all other patients.

Patient flow during the trial

A chart summarizing the patient flow in this trial is included in Appendix 3. The term Baseline in this study defines any patient assessments done pre-dose at Day 0, or in the case of endoscopy, the screening endoscopy done between Day -14 to Day -3 (see Table 1).

Treatments

Test product

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

Formulation:	Tablets containing a specific polymorph of vidofludimus calcium, manufactured by wet granulation (IMU-838) or roller compaction (IMU-838-RC)
Tablet strengths:	Tablets with 5 mg, 15 mg, and 22.5 mg IMU-838, and 30 mg IMU-838-RC (only open-label extension)

Doses:

Tablets will be taken once daily.

Induction phase (tablet strengths refer to the IMU-838 formulation):

Week 1: 5 mg/day (1 x 5 mg)	Weeks 2-10 or 2-22: 10 mg/day (2 x 5 mg)
Week 1: 15 mg/day (1 x 15 mg)	Weeks 2-10 or 2-22: 30 mg/day (2 x 15 mg)
Week 1: 22.5 mg/day (1 x 22.5 mg)	Weeks 2-10 or 2-22: 45 mg/day (2 x 22.5 mg)

All 3 IMU-838 doses will be used in Enrollment Periods 1 and 2.

Maintenance phase:	10 mg/day (2 x 5 mg IMU-838) 30 mg/day (2 x 15 mg IMU-838)
Open-label arm:	30 mg/day (2 x 15 mg IMU-838 or 1 x 30 mg IMU-838-RC)

Reference product

Placebo tablets

Number of patients (total and for each treatment) planned

Overall about 240 patients will be enrolled: approximately 60 patients during **Enrollment Period 1** (15 patients each) and 180 patients (45 patients each) during **Enrollment Period 2** randomized each 1:1:1:1 to oral 10 mg/day, 30 mg/day, or 45 mg/day IMU-838, or placebo.

Inclusion criteria

Induction phase

1. Male and female patients, aged 18 - 80 years
2. UC diagnosed more than 3 months before Screening (Day -30) as documented in the medical chart
3. Previous treatment failure defined as:
   a. Patient had an inadequate response with, lost response to, or was intolerant to approved or experimental immunomodulators (azathioprine, 6-mercaptopurine, 6-thioguanine, methotrexate, or tofacitinib) or biologics (no more than 2 treatment failures with biologic drugs i.e. anti-tumor necrosis factor α antibodies [infliximab, adalimumab, golimumab and their biosimilars], vedolizumab, or certain experimental antibodies [ustekinumab]); or
   b. Patient had an inadequate response to, was intolerant to, or is corticosteroid dependent (corticosteroid-dependent patients are defined as i) unable to reduce steroids below the equivalent of prednisolone 10 mg/day within 3 months of starting steroids, without recurrent active disease, or ii) who have a relapse within 3 months of stopping steroids.[1])
4. Active disease defined as
   a. Mayo stool frequency score of ≥2 at Screening Visit 1
   b. Mayo rectal bleeding score of ≥1 at Screening Visit 1
   c. modified Mayo endoscopy subscore of ≥2 at the screening flexible sigmoidoscopy (endoscopy assessed by an independent central reader blinded to screening center and patient information)

[1] Dignass A, Eliakim R, Magro F, Maaser C, Chowers Y, Geboes K, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. J Crohns Colitis 2012;6(10):965-90.

5. Endoscopic appearance typical for UC and extending >15 cm from the anal verge as confirmed by an independent central reader (blinded to screening center and patient information)
6. Laboratory values: Neutrophil count >1500 cells/µL (> 1.5 x 10^9/L), platelet count ≥100 000/mm^3 (≥ 100 10^9/L), serum creatinine <1.5 x upper limit of normal (ULN), total bilirubin, alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT) <1.5 x ULN
7. Female patients must
   a. Be of non-child-bearing potential i.e. surgically sterilized (hysterectomy, bilateral salpingectomy, bilateral oophorectomy at least 6 weeks before Screening) or post-menopausal (where postmenopausal is defined as no menses for 12 months without an alternative medical cause), or
   b. If of child-bearing potential, must have a negative pregnancy test at Screening (blood test) and before the first study drug administration (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 2 months before Screening, during treatment with IMU-838, and at least 3 months after the last dose of study therapy

   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 has undergone effective surgical sterilization before the female patient entered the clinical trial and he 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)
8. Male patients must agree not to father a child or to donate sperm starting at Screening and throughout the clinical trial and for 3 months after the last dose of study medication. Male patients must also either
   - 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 IMU-838 and for at least 3 months after the last dose of study medication

For Poland and the UK the following additional requirement apply:

- if male patients have a female partner of childbearing potential, the partner should use a highly effective contraceptive method as outlined in inclusion criterion 7

And additionally, for Poland only:

- if male patients have a pregnant partner, they must use condoms while taking study medication to avoid exposure of the fetus to study medication

9. Ability to understand and comply with study procedures and restrictions
10. The patient is legally competent, has been informed of the nature, the scope and the relevance of the study, voluntarily agrees to participation and the study's provisions and has duly signed the informed consent form

Maintenance phase

1. Symptomatic remission achieved at Week 10 or Week 22 of the induction phase

Open-label treatment extension arm

1. Patient is in the induction phase, had received at least 6 weeks of blinded study treatment and completed the sigmoidoscopy (incl. biopsy) regularly scheduled at Week 10/EoI, and has neither reached symptomatic remission nor symptomatic response

   Or

   Patient is in the extended induction phase, had completed all Week 10 assessments, and has not reached symptomatic remission during or at the end of the extended induction phase,

   Or

   Patient is in the maintenance phase and discontinues from the maintenance phase due to symptomatic UC relapse or other reasons with a flexible sigmoidoscopy performed at discontinuation (if the previous sigmoidoscopy had been performed more than 4 weeks before discontinuation)

   Or

   Patient has completed the maintenance phase as scheduled (including all Week 50 assessments)

Exclusion criteria

Gastrointestinal exclusion criteria

1. Diagnosis of Crohn's disease, inflammatory bowel disease type unclassified, ischemic colitis, microscopic colitis, radiation colitis or diverticular disease-associated colitis
2. Ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine

3. History of colectomy with ileorectal anastomosis or ileal-pouch anal anastomosis or imminent need for colectomy (i.e. colectomy is being planned)
4. Active therapeutically uncontrollable abscess or toxic megacolon
5. Malabsorption or short bowel syndrome
6. History of colorectal cancer or colorectal dysplasia (with the exception of dysplasia in polyps which have been removed)

Infectious disease exclusion criteria

7. *Clostridium difficile* (*C. difficile*) infection
   - Evidence of, or treatment for *C. difficile* infection within 30 days before first randomization
   - Positive *C. difficile* toxin B stool assay during the screening period
8. Treatment for intestinal pathogens other than *C. difficile* within 30 days prior to first randomization
9. Other chronic systemic infections
   - History of chronic systemic infections including but not limited to tuberculosis, human immunodeficiency virus (HIV), hepatitis B or C, within 6 months before Screening
   - Positive interferon-gamma release assay (IGRAs) for *Mycobacterium tuberculosis* at Screening
   - Positive HBsAg (hepatitis B virus surface antigen), HBcAb (hepatitis B core antibody), positive hepatitis C virus and/or HIV-antigen-antibody (HIV-Ag/Ab) test[2] at Screening
10. Any live vaccinations within 30 days prior to study drug administration except for the influenza vaccine

Other medical history and concomitant disease exclusion criteria

11. Known history of nephrolithiasis or underlying condition with a strong association of nephrolithiasis, including hereditary hyperoxaluria or hereditary hyperuricemia
12. Diagnosis or suspected liver function impairment which may cause, as assessed by the investigator, a potential for fluctuating liver function tests during this trial
13. Renal impairment i.e. estimated glomerular filtration rate[3] ≤60 mL/min/1.73m²

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[2] If any HIV, HBV, or HCV antigen or antibody screening test shows reactive or borderline results, a confirmatory Nucleic Acid Amplification Test (NAAT) will automatically be performed for the detection of the virus by using the same blood draw sample. If no virus specific nucleic acid is detected, and the clinical history of the patient, other laboratory examinations, and current clinical pictures also exclude a concurrent infection, the patient will not be excluded from the study.

[3] Calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

14. Serum uric acid levels at Screening >1.2 x ULN (for women >6.8 mg/dL, for men >8.4 mg/dL)
15. History or clinical diagnosis of gout
16. Known or suspected Gilbert syndrome
17. Indirect (unconjugated) bilirubin ≥1.2 x ULN at Screening (i.e. ≥ 1.1 mg/dL)
18. 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

Therapy exclusion criteria

19. Use of any investigational product within 8 weeks or 5 x the respective half-life before first randomization, whatever is longer
20. Use of the following medications within 2 weeks before first randomization:
    a. Tofacitinib
    b. Methotrexate,
    c. Mycophenolate mofetil
    d. Any calcineurin inhibitors (e.g. tacrolimus, cyclosporine, or pimecrolimus)
    e. Oral systemic corticosteroids >20 mg/day prednisolone equivalent including beclomethasone dipropionate (at >5 mg/day) and budesonide (multi-matrix [MMX] at >9 mg/day)
    f. Oral aminosalicylates (e.g. mesalazines) >4 g/day
21. Use of the following medications within 4 weeks before first randomization:
    a. Use of intravenous corticosteroids
    b. Use of thiopurines including azathioprine, mercaptopurine and 6-thioguanine
    c. Use of any rectal and topical aminosalicylates and/or budesonide
22. Use of oral systemic corticosteroids ≤20 mg/day prednisolone equivalent including beclomethasone dipropionate (at ≤5 mg/day) and budesonide (MMX at ≤9 mg/day) unless they have been used for at least 4 weeks before first randomization and at a stable dose for at least 2 weeks before first randomization
23. Oral aminosalicylates (e.g. mesalazines) ≤4 g/day unless they have been used for at least 6 weeks and with a stable dose for at least 3 weeks before first randomization
24. Use of biologics as follows:
    a. anti-tumor necrosis factor α antibodies (infliximab, adalimumab, golimumab, including their biosimilars) within 4 weeks before first randomization
    b. vedolizumab and ustekinumab within 8 weeks before first randomization

25. Use of the DHODH inhibitors leflunomide or teriflunomide within 6 months before first randomization
26. Any use of natalizumab (Tysabri™) within 12 months before first randomization
27. Use of the following concomitant medications is prohibited at Screening 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
    - Rosuvastatin at doses >10 mg/day

General exclusion criteria

28. History of, or current serious, severe, or unstable (acute or progressive) physical or mental illness, or any medical condition, including laboratory anomalies or renal or hepatic impairment, that may require treatment or would put the patient in jeopardy if he/she was to participate in the study
29. Known hypersensitivity to DHODH inhibitors (teriflunomide, leflunomide) or any ingredient of the investigational product
30. Pregnancy or breastfeeding
31. History of drug or alcohol abuse during the past year
32. Concurrent participation in any other clinical trial using an investigational medicinal product or medical device
33. An employee of an investigator or sponsor or an immediate relative of an investigator

Exclusion criteria for open-label treatment extension arm

1. Any ongoing, clinically significant treatment-emergent (started during the IMU-838 treatment in the blinded treatment arms) adverse event (AE) or laboratory abnormality (including blood chemistry and urinalysis) as assessed by the investigator *
2. Significant treatment or study non-compliance during induction and/or maintenance phase (as assessed by the investigator), and/or inability or unwillingness to follow instructions by study personnel as assessed by the investigator
3. Significant protocol deviations during induction and/or maintenance phase that are assessed by the investigator to negatively affect further patient cooperation in this study

* If treatment-emergent AEs are the reason for exclusion from the open-label extension arm, the eligibility can be re-assessed up to 30 days following the last treatment in the blinded treatment arms.

Criteria for evaluation

Primary

Efficacy

Induction phase

- Composite endpoint: Proportion of patients with both, symptomatic remission and endoscopic healing at Week 10

  All patients (both, Enrollment Period 1 and Enrollment Period 2 patients) who were randomized to 30 mg/day and 45 mg/day IMU-838 will be used for the assessment of the primary efficacy endpoint (see Section 16.4 for further information).

Secondary

Efficacy

Induction phase and extended induction phase

- Proportion of patients with both symptomatic remission and endoscopic healing at Week 10 (all individual IMU-838 doses will be compared with one another and to placebo)
- Proportion of patients achieving symptomatic remission during the induction phase (including extended induction phase)
- Time to achieving symptomatic remission within the induction/extended induction phase
- Proportion of patients with clinical response at Week 10
- Proportion of patients with endoscopic healing at Week 10
- Proportion of patients with symptomatic response during the induction phase (including extended induction phase)
- Time course of Mayo scores (full score, partial score, PRO-2 score) over 10 or 22 weeks and changes from Baseline
- Time course of disease activity biomarkers (fCP and CRP)

Maintenance phase

- Proportion of patients in symptomatic remission by visit up to Week 50
- Proportion of patients in durable symptomatic remission up to Week 50
- Time course of Mayo PRO-2 score until Week 50
- Time to symptomatic UC relapse
- Proportion of patients without symptomatic UC relapse until Week 50
- Time course of disease activity biomarkers (fCP and CRP)

- Proportion of patients with endoscopic healing at Week 50
- Proportion of patients with microscopic healing at Week 50
- Corticosteroid-free remission at Week 50 in patients receiving corticosteroids at Baseline

Open-label treatment extension arm

- Proportion of patients with symptom control
- Time course of disease activity biomarkers (fCP and CRP)

Safety

- Incidence and severity of AEs
- Physical examination, body weight, and vital signs*
- Electrocardiogram (12-lead ECG)*
- Safety laboratory: hematology, clinical chemistry including liver function, coagulation parameters, urinalysis
- Micro ribonucleic acid-122 (miR-122) expression (before first dose and 24 hours after first dose)

* *Only induction and maintenance phase.*

Pharmacokinetics

- Plasma trough levels of IMU-838 throughout the induction period
- Population PK analysis
- Full single-dose PK including area under the drug concentration-time curve from time zero to 24 hours (AUC_{0-24h}), AUC_{0-t} (AUC time zero to last measurable concentration), AUC_{0-inf} (AUC time zero to infinity), maximum plasma concentration (C_{max}), time to C_{max} (T_{max}) (in a subset of patients in designated PK centers)

Further exploratory assessments

Induction phase

- Changes from Baseline in biomarker and PD parameters (blood cytokines) during induction up to Week 10
- Correlation of efficacy variables at Week 10 with quartiles of IMU-838 trough levels at Week 2
- Correlation of efficacy variables at Week 10 with biomarker and PD parameters up to Week 6
- If feasible, estimate the relationship between IMU-838 PK and selected safety and efficacy parameters

Statistical methods

The primary endpoint for this study is the composite endpoint proportion of patients with both symptomatic remission and endoscopic healing at Week 10.

All patients (both Enrollment Period 1 and Enrollment Period 2 patients) who were randomized to 30 mg/day and 45 mg/day IMU-838 will be combined and compared with placebo.

A stratified Cochran-Mantel-Haenszel test will be used for the analysis of the primary endpoint in order to adjust for the stratification factors prior use of any biologics and current use of corticosteroids. The primary analysis will be based on the full analysis set.

Sample size calculation is based on the primary endpoint assessed at Week 10 during the final analysis of the induction phase as follows:

With 3 dose groups (30 mg/day and 45 mg/day IMU-838 and placebo) about 49 patients per group are required to show a difference of 16% between the verum group and placebo assuming a placebo remission rate of about 10%, a significance level of 0.097, and a power of 80%. Assuming a drop-out rate of 20%, approximately 60 patients will be required per group.

Underlying assumptions:

Primary endpoint: composite of symptomatic remission and endoscopic healing

Underlying test: Chi square test

Randomization: Enrollment Periods 1 and 2: 1:1:1:1
The sample size is based on a comparison of the 30 mg/day and 45 mg/day IMU-838 treatment groups combined vs placebo.

Power: 80%

Significance level: 0.097, 1-sided

In this early stage development study, a higher α, i.e. 0.1, than the standard 0.025 level is considered appropriate. Due to the interim analysis and to keep the overall α-level to 0.1, this level must be adjusted. A group sequential design with O'Brien-Fleming boundaries will be applied. Accordingly, the sample size calculation is based on a significance level of 0.097, 1-sided.

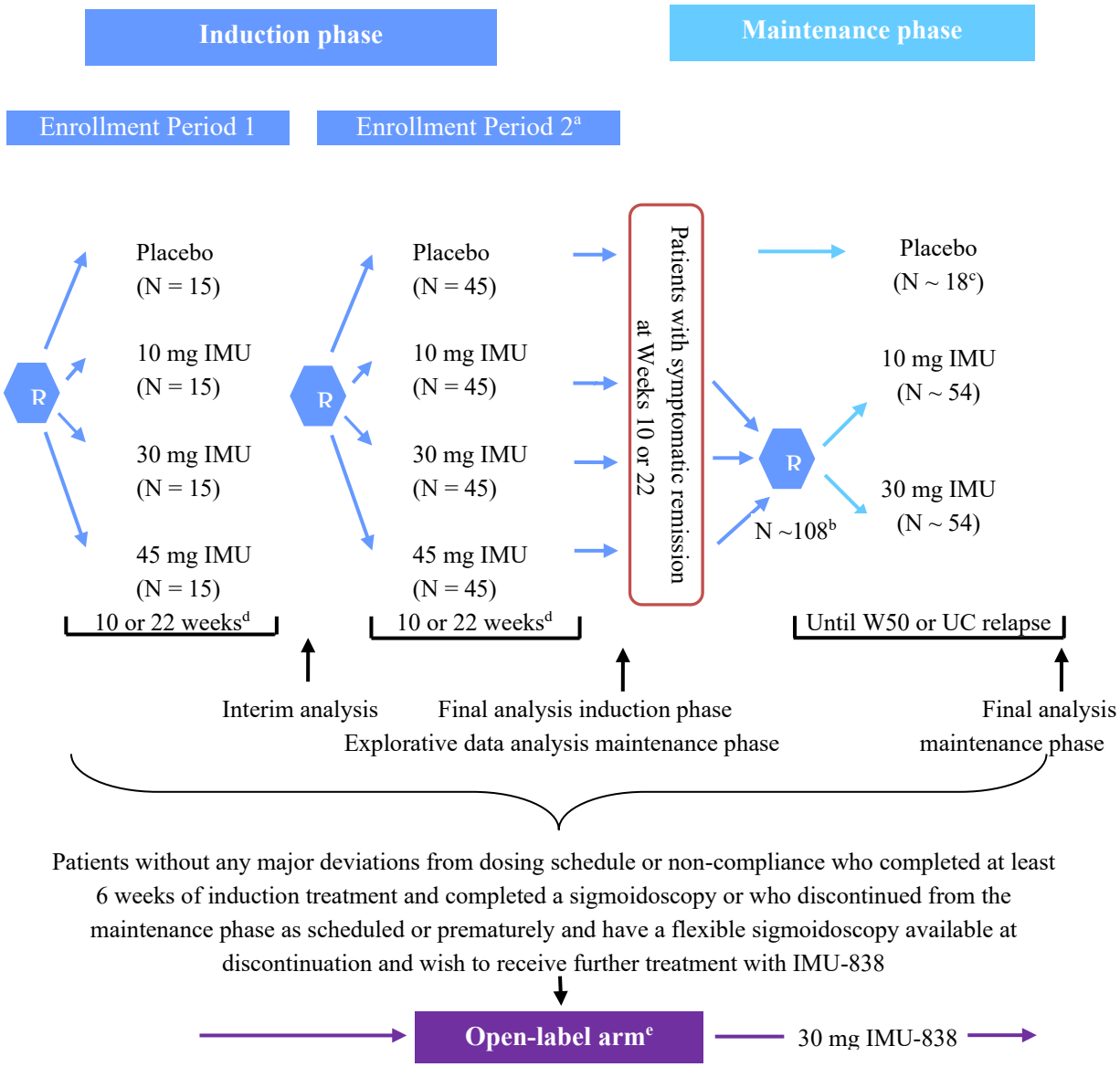
No formal sample size calculation was performed for the sample size of the interim analysis of this small phase 2 study. However, and based on preliminary experiences, 15 patients per group were deemed sufficient to show numerical differences between placebo and verum, and between dose groups.

Interim analyses

During the open-label treatment extension in addition to data review (as outlined in the Steering Committee Charter), safety interim analyses may be performed at the request of the sponsor or the Steering Committee.

Schedules of assessments and flow chart

Figure 1: Study flow chart



[a] Initially it was planned that Enrollment Period 2 would include up to 2 doses of IMU-838 and placebo, excluding likely ineffective and/or intolerable doses based on the results of the interim analysis after Enrollment Period 1. Because the interim analysis did not reveal a likely ineffective and/or intolerable dose according to the unblinded DRC, the Steering Committee recommended to continue all 3 IMU-838 doses in Enrollment Period 2.

[b] Assuming that 60% of IMU-838-treated patients in the induction phase will have a symptomatic remission.

[c] Assuming that 30% of placebo-treated patients in the induction phase will have a symptomatic remission.

[d] Patients who show symptomatic response but no symptomatic remission at Week 10 will continue induction treatment until Week 22. If the patient shows symptomatic remission at Week 22, the patient will continue with maintenance treatment.

[e] If patients are transferred to another long-term follow-up study or to commercially available vidofludimus calcium, the open-label arm will be closed early once all remaining patients are transferred.

DRC = data review committee, IMU = IMU-838, R = randomization, UC = ulcerative colitis, W = Week.

Table 1: Schedule of assessments - induction phase

Assessment	Screen.		Induction phase						Ext. induct.[a]			
	D-30 to -5	D-14 to -3	D0	D1	D7	W2	W6	W10/ EoI[g]	W10	W14	W18	W22/ EoEI
	S1[l]	S2[m]	BL		±1d	±2d	±3d	±3 d	±3d	±7d	±7d	±7d
Signed informed consent	x											
In- and exclusion criteria	x		x[c]									
Physical examination	x		x					x				x
Height	x											
Weight	x		x			x	x	x		x	x	x
Medical + disease history	x											
Concomitant medication	x		x	x	x	x	x	x		x	x	x
Previous UC medication	x		x									
Stool frequency reference value	x											
Partial Mayo score+PRO2			x			x	x	x		x	x	x
Full Mayo score			x					x				
Mayo stool frequency and rectal bleeding score	x[k]											
Randomization			x									
Sigmoidoscopy + biopsy[b]		x						x				
Central reading		x						x				
Geboes score		x						x				
Immunohistochemistry		x						x				
Laboratory assessments												
Central screening labs, incl. blood pregnancy test	x											
Local screening labs, incl. Clostridium toxin and Tbc-IGRA	x											
Blood biochemistry and hematology			x	x	x	x	x	x		x	x	x
Coagulation[d]			x	x		x		x				
Urinalysis			x	x	x	x	x	x		x[e]	x[e]	x
Blood cytokines[d]			x	x		x		x				
Fecal calprotectin			x			x	x	x		x	x	x
Genotyping[d]			x									
IMU-838 trough levels[d]			x	x	x	x[j]	x	x				
IMU-838 plasma conc.[d]						x[j]						
Local urine pregnancy test[f]			x				x	x		x	x	x
mIR-122[d]			x	x								

continued

Table 1: Schedule of assessments - induction phase *(continued)*

Assessment	Screen.		Induction phase						Ext. induct.[a]			
	D-30 to -5	D-14 to -3	D0	D1	D7	W2	W6	W10/EoI[g]	W10	W14	W18	W22/ EoEI
	S1[l]	S2[m]	BL		±1d	±2d	±3d	±3 d	±3d	±7d	±7d	±7d
Lab Kits used												
Screening lab kit	S											
Study lab kit			A	A	B	A	B	A		C	C	B
Genotyping			G									
Fecal calprotectin			FC			FC	FC	FC		FC	FC	FC
mIR-122			BM	BM								
Single PK kit			PK1	PK1	PK1	2xPK1[j]	PK1	PK1				
Biopsy kit		BK						BK				
Shipments to central lab												
Ambient temperature	x		x	x	x	x	x	x		x	x	x
Dry ice								x[i]				
Adverse events	x	x	x	x	x	x	x	x		x	x	x
Vital signs	x		x		x	x	x	x		x	x	x
ECG	x							x				x
Drug accountability							x	x		x	x	x
Dispense of study med.			x				x		x	x	x	
Diary instruction		x										
Patient diary										[h]	[h]	[h]
Diary review			x		x	x	x	x		x	x	x

[a] Extended induction phase: only applicable for patients with symptomatic response but not yet symptomatic remission at Week 10.

[b] Only to be done if all other eligibility criteria assessed at the first screening visit (D-30 to -5) are met. If a full colonoscopy was not performed in the previous year, the screening sigmoidoscopy should be replaced by a full colonoscopy. Includes assessment of histological score.

[c] Before randomization.

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

[e] Urine sediment analysis will only be done when urine dipstick analysis (performed at central laboratory) was positive for RBC.

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

[g] These assessments have to be performed for all patients completing Week 10 and those who prematurely discontinue the induction phase at Week 6 or between Week 6 and Week 10.

[h] Completed only during the 5 days preceding the respective visit.

[i] Samples requiring dry-ice shipment will be collected throughout the induction period, stored at -20°C freezing conditions and then sent to the central laboratory following the Week 10 visit.

[j] At Week 2, IMU-838 plasma levels will be assessed pre-dose (trough level) and 3 to 10 hours post dose (the actual time of the second blood collection can be chosen based on the patient's preference but must be between 3 and 10 hours after dosing).

[k] Will be assessed retrospectively.

[l] Within 30 days of D0. If there is a delay in assessments from Screening Visit 1 or assessments need to be repeated due to technical difficulties, assessments from Screening Visit 1 are valid for up to 60 days between Screening Visit 1 and randomization. If 60 days are exceeded, Screening Visit 1-assessments must be repeated. Note that tests can solely be repeated if tests are inconclusive or had technical problems. A re-screening of patients is not allowed (if not requested or approved by the sponsor).

[m] In case of technical problems, assessments at Screening Visit 2 may be repeated within the times indicated for repetition of Screening Visit 1 assessments.

BL = baseline, conc. = concentration, D = day, ECG =electrocardiogram, EoI = end-of-induction, EoEI = end-of-extended-induction, ext. = extended, IGRA = interferon gammy release assay, incl. = including, induct. = induction phase, lab = laboratory, med.= medication, miR-122 = micro RNA 122, RBC = red blood cells, PK = pharmacokinetics, PRO = patient-reported outcome, RNA = ribonucleic acid, Screen. = screening, Tbc = tuberculosis, UC = ulcerative colitis, W = week.

Table 2: Schedule of assessments - maintenance phase

	Start maintenance phase[a]	Maintenance phase			
		W14, 18[b]	W22[b]	W26, 30, 34, 38, 42, 46	W50/EoM
		±7d (each)	±7d	±7d (each)	±7 d
Inclusion criterion	x				
Physical examination			x		x
Weight		x	x	x	x
Concomitant medication	x	x	x	x	x
Partial Mayo score+PRO-2		x	x	x	x
Full Mayo score					x[d]
Randomization	x				
Sigmoidoscopy + biopsy					x[d]
Central reading					x[d]
Geboes score					x[d]
Laboratory assessments					
Blood biochemistry and hematology		x	x	x	x
Urinalysis		x[e]	x	x[e]	x
Fecal calprotectin		x	x	x	x
Local urine pregnancy test[f]		x	x	x	
Lab kits used					
Study lab kit		C	B	C	B
Fecal calprotectin		FC	FC	FC	FC
Biopsy kit					BK
Shipments to central lab					
Ambient temperature		x	x	x	x
Adverse events		x	x	x	x
Vital signs		x	x	x	x
ECG			x		x
Drug accountability		x	x	x	x
Dispense study medication	x	x	x	x	
Patient diary	[c]	[c]	[c]	[c]	[c]
Diary review		x	x	x	x

[a] At Week 10 following induction phase or Week 22 of extended induction phase, depending on when the patient enters the maintenance phase.
[b] Only if patient has switched to maintenance phase at Week 10.
[c] Completed only during the 5 days preceding the respective visit.
[d] In case of early discontinuation during maintenance phase, the sigmoidoscopy and full Mayo score assessment is to be performed at the time of discontinuation, unless this occurs less than 4 weeks after the last sigmoidoscopy examination.
[e] Urine sediment analysis will only be done when urine dipstick analysis (performed at central laboratory) was positive for RBC.
[f] Any positive local urine pregnancy test has to be followed up with a confirmatory local blood pregnancy test.

AE = adverse event, ECG =electrocardiogram, EoM = end-of-maintenance, lab = laboratory, RBC = red blood cells, PRO = patient-reported outcome, W = week.

Table 3: Schedule of assessments - open-label treatment arm

Assessment	Treatment period		
	Start$_{OLE}$[a]	**Week X$_{OLE}$**[b] ±14d	**EoOLE**[c]
Inclusion and exclusion criteria	x[e]		
Concomitant medication	x[d]	x	x
Mayo PRO-2 score	x[d]	x	x
Laboratory assessments			
Blood biochemistry and hematology	x[d]	x	x
Urinalysis	x[d,f]	x[f]	x[f]
Fecal calprotectin	x[d]		x
Local urine pregnancy test[g]	x[d]	x	x
Lab kits used			
Study lab kit	C[d]	C	C
Fecal calprotectin	FC[d]		FC
Shipments to central lab			
Ambient temperature	x[d]	x	x
Adverse events	x[d]	x	x
Collection of endoscopic results if performed during clinical routine[h]		x	x
Weight	x[d]	x	x
Vital signs	x[d]	x	x
Dispense study medication	x	x	
Drug accountability		x[i]	x

[a] Open-label treatment has to start within 30 days of the last dose of the blinded treatment arms.

[b] Clinic visits will be scheduled every 4 weeks (±7 days) until 50 weeks of total study participation (i.e. induction + extended induction, if applicable, maintenance + open-label part) and every 10 weeks (±7 days) thereafter. The visit schedule in the open-label treatment extension after 50 weeks of overall study treatment is changed from a 10-week schedule to a 24-week (±14 days) schedule after Protocol Version 6.0 comes into force.

[c] Patients can continue treatment as long as there are no clinically significant safety issues (as assessed by the investigator), that are related to study procedures or study treatment, as long as the patient benefits from study treatment (as assessed by the investigator), until the patient withdraws consent, or until the sponsor terminates the study. In addition, if patients will be transferred to a long-term follow-up study or to vidofludimus calcium, the extended treatment period will be closed early once all remaining participants are transferred. Patients will be allowed to be treated with study medication for a maximum of 10 years *(not applicable for UK)* including all periods of the trial. *For the UK the following applies: Patients will be allowed to be treated with open-label study medication for a maximum of 3 years (may be extended, see Section 8.1.5).*

[d] Only to be performed if the open-label treatment starts more than 3 weeks after the last regular study visit.

[e] If continuing treatment-emergent adverse events are the reason for exclusion from the open-label extension arm, the eligibility can be re-assessed up to 4 weeks following the last treatment in the blinded treatment arms.

[f] Urine sediment analysis will only be done when urine dipstick analysis (performed at central laboratory) was positive for RBC.

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

[h] Videotapes will not be collected and not centrally assessed. The investigator's judgment of the endoscopy results will be collected in the eCRF.

[i] During the open-label extension treatment period, dispensed bottles must be used until empty and then returned; remaining tablets of in-use bottles will not be counted at every study visit. Patients will be advised to bring all IMP (including full, in-use and empty bottles) to all visits; the empty bottles will be kept, the in-use and full ones will be returned to the patient (together with newly issued ones). Patients will also be advised to completely use up the tablets in one bottle before starting a new bottle. Only the number of bottles dispensed, and number of empty bottles returned will be counted. Counting of tablets for any in-use bottle will only be performed for any safety interim analysis, as communicated by the sponsor.

IMP = investigational medicinal product, Lab = laboratory, RBC = red blood cells, OLE = open-label extension, PRO = patient-reported outcome, EoOLE = end-of-treatment open-label extension.

Table 4: Schedule of assessments - open-label treatment arm for PK population at designated PK centers

Assessment	Treatment period					
	Start$_{OLE}$[a]	Day 1$_{OLE}$	Day 2$_{OLE}$	Day 3$_{OLE}$	Week X$_{OLE}$[b] ±14d	EoOLE[c]
Inclusion and exclusion criteria	x[e]					
Concomitant medication	x[d]				x	x
Mayo PRO-2 score	x[d]	x	x	x	x	x
Laboratory assessments						
Blood biochemistry and hematol.	x[d]				x	x
Urinalysis	x[d,h]				x[h]	x[h]
Fecal calprotectin	x[d]					x
Dosing with 30 mg IMU-838	x			x[f]	as scheduled	
IMU-838 full PK[i]	x	x	x	x		
Local urine pregnancy test[g]	x[d]				x	x
Lab kits used						
Study lab kit	C[d]				C	C
Fecal calprotectin	FC[d]					FC
Full PK kit	PK2					
Shipments to central lab						
Ambient temperature	x[d]				x	x
Dry ice shipment				x[f]		
Adverse events	x[d]				x	x
Collection of endoscopic results if performed during clinical routine[j]					x	x
Weight	x[d]				x	x
Vital signs	x[d]				x	x
Dispense study medication	x				x	
Drug accountability					x[k]	x

a Open-label treatment has to start within 30 days of the last dose of the blinded treatment arms.

b Clinic visits will be scheduled every 4 weeks (±7 days) until 50 weeks of total study participation (i.e. induction + extended induction, if applicable, maintenance + open-label part) and every 10 weeks (±7 days) thereafter. The visit schedule in the open-label treatment extension after 50 weeks of overall study treatment is changed from a 10-week schedule to a 24-week (±14 days) schedule after Protocol Version 6.0 comes into force.

c Patients can continue treatment as long as there are no clinically significant safety issues (as assessed by the investigator), that are related to study procedures or study treatment, as long as the patient benefits from study treatment (as assessed by the investigator), until the patient withdraws consent, or until the sponsor terminates the study. In addition, if patients will be transferred to a long-term follow-up study or to vidofludimus calcium, the extended treatment period will be closed early once all remaining participants are transferred. Patients will be allowed to be treated with study medication for a maximum of 10 years *(not applicable for UK, see below)* including all periods of the trial. *For UK the following applies: Patients will be allowed to be treated with open-label study medication for a maximum of 3 years (may be extended, see Section 8.1.5).*

d Only to be performed if start of open-label treatment starts more than 3 weeks after the last regular study visit.

e If continuing treatment-emergent adverse events are the reason for exclusion from the open-label extension arm, the eligibility can be re-assessed up to 4 weeks following the last treatment in the blinded treatment arms.

f After last blood sample for full PK has been collected.

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

h Urine sediment analysis will only be done when urine dipstick analysis (performed at central lab) was positive for RBC.

i Blood samples for PK will be collected pre-dose, 1, 2, 3, 4, 5, 6, 24, 48, and 72 hours post-dose (±15 min each for time point from 1 to 6 hours, and ±1 hour each for the 24-, 48-, and 72-hour time point). Samples to be stored at -20°C until next scheduled dry-ice shipment to central laboratory.

j Videotapes will not be collected and not centrally assessed. The investigator's judgment of the endoscopy results will be collected in the eCRF.

[k] During the open-label extension treatment period, dispensed bottles must be used until empty and then returned; remaining tablets of in-use bottles will not be counted at every study visit. Patients will be advised to bring all IMP (including full, in-use and empty bottles) to all visits; the empty bottles will be kept, the in-use and full ones will be returned to the patient (together with newly issued ones). Patients will also be advised to completely use up the tablets in one bottle before starting a new bottle. Only the number of bottles dispensed, and number of empty bottles returned will be counted. Counting of tablets for any in-use bottle will only be performed for any safety interim analysis, as communicated by the sponsor.

IMP= investigational medicinal product, Lab = laboratory, EoOLE = end-of-treatment open-label extension, hematol. = hematology, lab = laboratory, OLE = open-label extension, PK = pharmacokinetics, RBC = red blood cells, PRO = patient-reported outcome.

Table 5: Schedule of assessments - unscheduled visits and end-of-study visit

	Unscheduled visit		EoS[a]
	due to UC exacerbation	due to safety/AE issue	
Physical examination	x	x	x
Weight			x
Concomitant medication	x	x	x
Partial Mayo score+PRO-2	x		
Laboratory assessments			
Blood biochemistry and hematology	x	x	x
Urinalysis	x[b]	x	x
Fecal calprotectin	x		
Local urine pregnancy test[c]			x
Lab kits used			
Study lab kit	C	B	B
Fecal calprotectin	FC		
Shipments to central lab			
Ambient temperature	x	x	x
Adverse events	x	x	x
Vital signs		x	x
ECG		x	x
Patient diary	x[d]		
Drug accountability			x[e]

[a] Should always be done 30 days (-3 days/+4 weeks) after last study treatment (of induction, extended induction, maintenance, or open-label phase, whichever applies). No EoS visit is required for patients transferring to the long-term follow-up study or commercially available vidofludimus calcium.

[b] Urine sediment analysis will only be done when urine dipstick analysis (performed at central laboratory) was positive for RBC.

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

[d] Assessment done retrospectively.

[e] Only to be performed if not done at the last treatment visit.

AE = adverse event, ECG =electrocardiogram, EoS = end-of-study, łab = laboratory, RBC = red blood cells, PRO = patient-reported outcome, UC = ulcerative colitis.

To be considered for patient visits at the study center

- At all visits, patients should arrive at the center in fasted conditions.
- Applies only to induction phase:
    - Patients should arrive at the center without taking their study drug.
    - If patients have inadvertently taken their study drug within 1.5 hours of arriving at the study center, the blood samples for IMU-838 trough levels can still be drawn. If longer than 1.5 hours, the blood levels should not be determined. In either case, this should 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 IMU-838 plasma levels must be scheduled.
- Patients need to bring to the center their study medication and their filled-out diary.
- Visits should be scheduled at the same time in the morning so that visits are all within ±2 hours of the Day 0 visit.
- Patients must be advised at each visit to drink a generous amount of fluid per day to ensure adequate urine flow.

2 Addresses and responsibilities

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IMP labeling, packaging, and distribution	Nuvisan GmbH Wegenerstrasse 13 89231 Neu-Ulm, Germany Phone: +49 731 9840 0 Fax: +49 731 9840 226 Email: bdinfo@nuvisan.com Or
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Distribution	Fisher Clinical Services GmbH Im Wörth 3 79576 Weil am Rhein, Germany *(currently not involved in supply chain, but may be involved in the future)*
Central safety laboratory, biomarker assessment	LKF - Laboratorium für Klinische Forschung GmbH Lise-Meitner-Strasse 25-29 24223 Schwentinental, Germany Phone: +49 4307 8276 0 Fax: +49 4307 8276 79 Email: office@lkf-kiel.de
HIV testing based on Nucleic Acid Amplification Technology	Labor Lademannbogen Lademannbogen 61 22339 Hamburg, Germany Phone: +49 40 53805 0 Fax: +49 40 53805 701 Email: info@labor-lademannbogen.de

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Central endoscopy reading	Clario (formerly Bioclinica, Inc.) 1818 Market St, Suite 2600 Philadelphia, PA 19103, USA Phone: +1 215 972 0420 Fax: +1 215 972 0414 Email: P2-IMU838-UC@bioclinica.com
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Pharmacokinetics (population PK modeling)	PharmaLex Belgium 5 rue Belin 1435 Mont-Saint-Guibert, Belgium Phone: +32 10 46 10 10
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A complete list of study personnel will be available in the trial master file.

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4 Abbreviations and definition of terms

AE	Adverse event
AESI	AEs of special interest
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
AUC	Area under the drug concentration-time curve
$AUC_{0\text{-}24h}$	Area under the drug concentration-time curve from time zero to 24 hours
$AUC_{0\text{-}t}$	Area under the drug concentration-time curve from time zero to last measurable concentration
AUC_{inf}	Area under the drug concentration-time curve from time zero to infinity
BCRP	Breast cancer resistance protein
BSEP	Bile salt export pump
BUN	Blood urea nitrogen
CA	Competent authority
Ca	Calcium
CD	Crohn's Disease
C-diff toxin B	*Clostridium difficile* toxin B
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cl	Chloride
C_{max}	Maximum plasma concentration
CRP	C-reactive protein
CYP	Cytochrome P450
d or D	Day
DHODH	Dihydroorotate dehydrogenase
DRC	Data Review Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
Eo(E)I	End-of-(extended)-induction
EoM	End-of-maintenance
EoOLE	End-of-open-label extension
EoS	End-of-study
FAS	Full analysis set
fCP	Fecal calprotectin

GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV(-Ag/Ab)	Human immunodeficiency virus(-antigen/antibody)
HPF	High powered field
IBD	Inflammatory bowel disease
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
IRB	Institutional review board
IWRS	Interactive web-based response system
K	Potassium
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
miR-122	Micro ribonucleic acid-122
MMX	Multi-matrix
Na	Sodium
OAT1(3)	Organic anion transporters 1(3)
OATP1B1(3)	Organic anion transporting polypeptides 1B1(3)
P	Inorganic phosphate
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PP	Per-protocol set
PRO	Patient-reported outcome
RA	Rheumatoid arthritis
RBC	Red blood cells
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SDV	Source data verification

SUSAR	Suspected unexpected serious adverse reaction
Tbc-IGRA	*Mycobacterium tuberculosis* IFNγ-release assay
TEAE	Treatment-emergent adverse events
Th	T helper (cell)
T_{max}	Time to maximum plasma concentration
TNFα	Tumor necrosis factor α
UC	Ulcerative colitis
ULN	Upper limit of normal
URAT1	Urate anion transporter 1
W	Week
WBC	White blood cell count
Drugs	
4SC-101	Tablet or capsule formulation containing vidofludimus free acid
IMU-838	Tablet formulation containing vidofludimus calcium

Definitions

Baseline	Any assessments done pre-dose at Day 0, or in the case of endoscopy, the screening endoscopy done between Day -14 to Day -3 (see Table 1)
Full Mayo score:	Combined, partial (non-invasive) Mayo score and Mayo endoscopy score
Partial Mayo score:	Non-invasive Mayo subscores, i.e. stool frequency, rectal bleeding, and physician rating of disease activity scores
Mayo PRO-2 score:	Mayo patient-reported outcome score, i.e. stool frequency and rectal bleeding score
Modified Mayo endoscopy score:	The Mayo endoscopy score modified that a value of 1 does not include friability
Symptomatic response:	≥1-point decrease from Baseline in Mayo PRO-2 score
Clinical response:	Decrease from Baseline in the full Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or an absolute subscore for rectal bleeding of 0 or 1

Symptomatic remission:	• Mayo rectal bleeding subscore = 0, and • Mayo stool frequency subscore of 0 or 1
Durable symptomatic remission:	• Symptomatic remission at all but 1 visit from the time the patient first achieved symptomatic remission at the end of induction (i.e. Weeks 10 or 22) until Week 50
Clinical remission:	• Mayo rectal bleeding subscore = 0, and • Mayo stool frequency subscore of 0 or 1, and • Endoscopy subscore 1 or 0 on modified Mayo endoscopy score
Endoscopic healing:	Modified Mayo endoscopy subscore of 0 or 1
Microscopic healing:	Geboes score of ≤3.1
UC relapse (symptomatic):	Re-occurrence of active UC symptoms defined as an ≥2-point increase from the Week 10 value (or Week 22 value if the patient received remission only during the extended induction phase) in Mayo PRO-2 score for 2 consecutive visits, or the need for any treatment escalation as assessed by the investigator after excluding intermittent infections (at the investigator's conclusion).
Symptom control:	Absence of symptomatic UC relapse

Note: In case of inconsistencies between text in the protocol and schedules of assessments (Table 1 through Table 5), the schedules will predominate.

5 Introduction

5.1 Disease background

Ulcerative colitis (UC) is a chronic, relapsing inflammatory bowel disease (IBD) affecting the rectum and colon. The prevalence of IBD continues to increase steadily in Western countries, and newly industrialized countries have a rapidly increasing incidence. [1]

The hallmark of UC is a chronic, uncontrolled inflammation of the intestinal mucosa presumably caused by a dysregulated immune response to bacteria and bacterial products in a susceptible host. This aberrant immune response is mediated by various cytokines and small cell-signaling protein molecules secreted by immune and other cells. The secreted molecules stimulate the proliferation of antigen-specific effector cells and thereby activate the adaptive immune system with a consequent burst of local and systemic inflammation. This upregulation of cytokines may play many roles in the pathophysiology of UC. It is believed that cytokines themselves are directly responsible for mucosal injury and consequent tissue damage. Activated T helper 1 (Th1) cells produce classical proinflammatory cytokines (interferon γ [IFNγ] and tumor necrosis factor α [TNFα]) and interleukin [IL]-2. In addition, Th17 cells seem to be involved leading to enhanced synthesis of Th17 typical cytokines such as IL-17 and IL-23.

The clinical course of UC is characterized by periods of exacerbation and remission. The latter may occur either spontaneously or in response to treatment. Symptoms of an UC flare-up generally involve diarrhea, abdominal pain and cramping, rectal pain and bleeding, fatigue, and urgent bowel movements.

Several treatment options are currently available including anti-inflammatory drugs (e.g. corticosteroids, aminosalicylates), immunosuppressive drugs (e.g. azathioprine 6-mercaptopurine and 6-thioguanine), biologics (e.g. TNFα inhibitors such as infliximab, adalimumab, golimumab, as well as the anti-adhesion molecule vedolizumab), and other drugs to manage specific symptoms (e.g. antibiotics, anti-diarrheal medications, pain relievers, calcineurin inhibitors [cyclosporine, tacrolimus], and iron supplements).

However, some patients respond only poorly to established treatment options or, after an initial response, experience flare-ups, and/or develop intolerable side effects (e.g. major infections with TNFα-inhibitors; myelosuppression, hepatotoxicity and dose-independent nausea, diarrhea, arthralgia and acute pancreatitis with thiopurines). Thus, new treatment options are needed.

5.2 IMU-838

A brief summary of current data is provided below. For more information please refer to the investigator's brochure.

5.2.1 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). Dihydroorotate dehydrogenase 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. Thus, IMU-838-mediated DHODH inhibition selectively affects activated, rapidly proliferating lymphocytes. The metabolic stress secondary to DHODH inhibition leads to a reduction of pro-inflammatory cytokine release including IL-17 (IL-17A and IL-17F) and IFNγ, and to an increased apoptosis in activated lymphocytes.

5.2.2 History

Previously, vidofludimus free acid (SC12267) was 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.

5.2.3 Formulations of IMU-838

Clinical studies up to this point have used the formulation IMU-838 manufactured utilizing wet granulation. A new manufacturing process using roller compaction was developed to allow large scale production of tablets. This necessitated a slightly revised and simplified formulation IMU-838-RC. The ongoing clinical trials will be stepwise transferred to the IMU-838-RC formulation, as well as new clinical trials will now only use the simplified IMU-838-RC formulation.

A bioequivalence study P1-IMU-838-BE was performed between a single oral dose of one IMU-838-RC tablet containing 45 mg vidofludimus (test treatment) and 2 IMU-838 tablets containing 22.5 mg vidofludimus each (reference treatment). The formulation of IMU-838-RC was found to be bioequivalent to the previous IMU-838 formulation regarding the area under the plasma concentration time curve and only a small increase in maximum plasma concentration (C_{max}) was

found. The upper limit of the 90% confidence interval for C_{max} was only slightly above the upper bioequivalence acceptance limit of 125%. This difference is regarded as not clinically relevant.

5.2.4 Non-clinical studies

Pharmacodynamics

As a result of the DHODH inhibition, vidofludimus strongly inhibits activated lymphocytes and reduces the release of pro-inflammatory cytokines and other physiologic effects of activated lymphocytes in *in-vivo* studies. In murine chronic colitis models, vidofludimus improved histological scores of intestinal epithelial damage and inflammatory cell infiltration similar to dexamethasone, and significantly reduced IFNγ and IL-17 in the colon tissue. In a rat arthritis model, vidofludimus effectively suppressed clinical symptoms (total arthritis score) and histopathological signs of arthritis (cellular infiltrate, cartilage erosion).

The permeability through a human intestinal epithelial cell barrier (Caco-2 test) was higher for vidofludimus calcium than vidofludimus free acid. In line, C_{max} and area und the time-concentration curve between zero and infinity (AUC_{inf}) of the calcium salt were 1.7 times higher than the C_{max} and AUC_{inf} of the free acid in rats.

Metabolism of vidofludimus involves primarily cytochrome P450 (CYP)1A1 (about 60%), followed by CYP2C8 (about 20%) and CYP2E1 (about 10%). Vidofludimus was 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 1 and 3 (OAT1 and OAT3), the organic anion transporting polypeptides 1B1 and 1B3 (OATP1B1 and OATP1B3), and the bile salt export pump (BSEP).

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

Toxicology

Main targets of toxicity in rats and dogs included the liver (weight changes, liver enzymes, bile duct hyperplasia) and the thymus (signs of involution, likely due to primary pharmacodynamics of the test compound). Adverse reactions were completely or partly reversible during a recovery period. There was no indication for a remarkable hepatic injury or direct proliferative activity of bile duct epithelium. No signs of preneoplastic lesions were identified. Bile duct hyperplasia is likely a physiological compensation of slightly reduced bile flow upon initiation of treatment, which was possibly caused by BSEP inhibition.

5.2.5 Clinical studies

With the exception of two phase 1 studies performed with IMU-838, all previous clinical studies were performed using vidofludimus free acid (4SC-101).

In 2 of these studies, beneficial effects of 4SC-101 were investigated 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 study in patients with steroid-dependent IBD (Crohn's disease and UC), 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). At the end of the study (after 12 weeks of treatment) more than 50% of the steroid-dependent patients were in remission without any steroid intake. An additional 35% of patients could markedly reduce their steroid threshold dose of disease relapse indicating a strong steroid-sparing effect of 4SC-101. Overall mean steroid intake dropped from about 27 mg/day at Screening to 1.0 mg/day at the end of the study (Week 12).

With respect to safety, 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 studies. At higher 4SC-101 doses (>70 mg/day or single doses of 210 mg) potential drug-related increases in urine red blood cells (RBC) and hematurias were observed (see also Section 8.3).

5.3 Rationale for the study

As outlined above, IMU-838 selectively inhibits pyrimidine synthesis in activated cells. The inhibition of nucleotide synthesis seems to be a promising approach to treat IBD. Purine synthesis inhibitors, like 6-mercaptopurine, azathioprine and 6-thioguanine, are established products for the long-term treatment of IBD. The DHODH inhibitor leflunomide, currently approved for RA, was efficacious in small studies investigating Crohn's Disease (CD), but was associated with diarrhea limiting its use in an IBD patient population.

Based on these data and the pharmacodynamics of vidofludimus, IMU-838 may represent a novel and efficacious oral treatment option for IBD patients. Previous clinical studies with the predecessor drug 4SC-101 confirmed that vidofludimus may be beneficial in patients with steroid-dependent IBD. Thus, Study P2-IMU-838-UC will further evaluate the dose response, as well as efficacy and safety of vidofludimus, using the novel formulation IMU-838, in patients with active, moderate-to-severe UC.

6 Investigators, study administrative structure, and study committees

The study is funded by Immunic AG and included about 133 study centers in a variety of countries in Western and Eastern Europe and the United States of America.

The sponsor, Immunic AG, will be responsible for the overall supervision and administration of the study. Monitoring and project management will be done by Labcorp Drug Development Inc (formerly Covance Clinical and Periapproval Services Ltd), Maidenhead, United Kingdom (a contract research organization - in the following referred to as sponsor's designee). Data management, statistical analysis and report writing will be done by FGK Clinical Research GmbH, München, Germany.

Other vendors used in the study:

- Nuvisan GmbH, Neu Ulm, Germany: labeling, packaging, and distribution of IMP and measurement of IMU-838 in plasma samples
- PharmaLex GmbH, Mont-Saint-Guibert, Belgium: population PK modeling
- LKF - Laboratorium für Klinische Forschung GmbH, Schwentinental, Germany: central clinical safety laboratory and assessment of biomarker
- Labor Lademannbogen, Hamburg, Germany: HIV testing based on Nucleic Acid Amplification Technology
- ESMS Global Limited, London, UK: emergency phone service for unblinding
- Fisher Clinical Services UK Ltd, Horsham, UK: labeling, packaging and distribution of the IMP or Fisher Clinical Services GmbH, Allschwil, Switzerland: labeling and packaging of IMP and Fisher Clinical Services GmbH, Weil am Rhein (Rheinfelden site): distribution of IMP (currently not involved in supply chain, but may be involved in the future)
- Clario (formerly Bioclinica), Philadelphia, PA, USA: central assessment of endoscopic results
- SCRATCH Pharmacovigilance GmbH, Butzbach, Germany: pharmacovigilance services
- IMGM Laboratories GmbH, Martinsried, Germany: genotyping and miR-122 assessment
- Indivumed GmbH, Hamburg, Germany: histological and immunohistochemical assessment
- ANJU Life Sciences Software, Tempe, AZ 85282, USA: electronic case report form (eCRF) and interactive web response system (IWRS)

An independent **data review committee (DRC)** who assessed unblinded safety and efficacy data and was to give recommendation on the dose(s) selection for Enrollment Period 2 (see Section

11.1.5) was appointed. A charter, which includes a detailed description of responsibilities and the procedures on dose selection, was implemented prior to interim data base lock and start of the Enrollment Period 1 interim analysis.

Based on the recommendation of the DRC, a **Steering Committee** including sponsor representatives, the coordinating investigator, and a drug safety officer was to select the dose(s) for Enrollment Period 2 and make potential adjustments to safety procedures, if necessary.

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

7 Study objectives and endpoints

7.1 Study objectives

Primary objective

- To determine the optimal dose of IMU-838 to induce symptomatic remission and endoscopic healing in patients with moderate-to-severe ulcerative colitis (UC)

Secondary objectives

- To determine the optimal dose of IMU-838 to maintain clinical benefits in patients with moderate-to-severe UC
- To evaluate the effects of IMU-838 on clinical and endoscopic endpoints in patients with moderate-to-severe UC
- To evaluate the time course of activity and effects of IMU-838
- To evaluate the safety and tolerability of IMU-838 in patients with moderate-to-severe UC
- To evaluate exploratory biomarkers, disease activity biomarkers, and pharmacodynamic (PD) effects of IMU-838
- To evaluate population pharmacokinetics (PK) and plasma trough levels of IMU-838 throughout the induction period
- To evaluate single dose PK at Week 50 for a subpopulation of patients with moderate-to-severe UC receiving 30 mg of IMU-838

7.2 Study endpoints

Primary

Efficacy

Induction phase

- Composite endpoint: Proportion of patients with both, symptomatic remission and endoscopic healing at Week 10

All patients (both, Enrollment Period 1 and Enrollment Period 2 patients) who were randomized to 30 mg/day and 45 mg/day will be used for the assessment of the primary efficacy endpoint (see Section 16.4 for further information).

Secondary

Efficacy

Induction phase and extended induction phase

- Proportion of patients with both symptomatic remission and endoscopic healing at Week 10 (all individual IMU-838 doses will be compared with one another and to placebo)
- Proportion of patients achieving symptomatic remission during the induction phase (including extended induction phase)
- Time to achieving symptomatic remission within the induction/extended induction phase
- Proportion of patients with clinical response at Week 10
- Proportion of patients with endoscopic healing at Week 10
- Proportion of patients with symptomatic response during the induction phase (including extended induction phase)
- Time course of Mayo scores (full score, partial score, PRO-2 score) over 10 or 22 weeks and changes from Baseline
- Time course of disease activity biomarkers (fCP and CRP)

Maintenance phase

- Proportion of patients in symptomatic remission by visit up to Week 50
- Proportion of patients in durable symptomatic remission up to Week 50
- Time course of Mayo PRO-2 score until Week 50
- Time to symptomatic UC relapse
- Proportion of patients without symptomatic UC relapse until Week 50
- Time course of disease activity biomarkers (fCP and CRP)
- Proportion of patients with endoscopic healing at Week 50
- Proportion of patients with microscopic healing at Week 50

- Corticosteroid-free remission at Week 50 in patients receiving corticosteroids at Baseline

Open-label treatment extension arm

- Proportion of patients with symptom control
- Time course of disease activity biomarkers (fCP and CRP)

Safety

- Incidence and severity of AEs
- Physical examination, body weight, and vital signs*
- Electrocardiogram (12-lead ECG)*
- Safety laboratory: hematology, clinical chemistry including liver function, coagulation parameters, urinalysis
- miR-122 expression (before first dose and 24 hours after first dose)

* *Only induction and maintenance phase.*

Pharmacokinetics

- Plasma trough levels of IMU-838 throughout the induction period
- Population PK analysis
- Full single-dose PK including area under the drug concentration-time curve from time zero to 24 hours ($AUC_{0\text{-}24h}$), $AUC_{0\text{-}t}$ (AUC time zero to last measurable concentration), $AUC_{0\text{-}inf}$ (AUC time zero to infinity), maximum plasma concentration (C_{max}), time to C_{max} (T_{max}) (in a subset of patients in designated PK centers)

Further exploratory assessments

Induction phase

- Changes from Baseline in biomarker and PD parameters (blood cytokines) during induction up to Week 10
- Correlation of efficacy variables at Week 10 with quartiles of IMU-838 trough levels at Week 2
- Correlation of efficacy variables at Week 10 with biomarker and PD parameters up to Week 6
- If feasible, estimate the relationship between IMU-838 PK and selected safety and efficacy parameters

8 Study design and design rationale

8.1 Overall study design

8.1.1 Design overview

This is a phase 2, multicenter, randomized, double-blind, and placebo-controlled trial in patients with moderate-to-severe UC with an option for open-label treatment extension. The study comprises a blinded **induction phase** to establish the optimal dose of IMU-838 to induce response and remission, a blinded **maintenance phase** to evaluate the potential of IMU-838 to maintain remission until Week 50, and an **open-label treatment extension** arm for all patients who discontinue the blinded phase as scheduled or prematurely, subject to certain restrictions. A subset of patients will undergo a **PK period** at the start of the open-label period to establish a full single-dose PK profile. Patients in the open-label treatment extension may also be potentially transferred to another long-term follow-up study or commercially available vidofludimus calcium. Once all patients have been transferred the open-label period will be closed.

Blinding to individual treatment assignments during the blinded treatment phase will be maintained during the induction and maintenance phase, the interim analysis as well as the open-label treatment extension arm for patients, investigators, and other personnel involved in the conduct of this trial. An overview of the design is shown in Figure 1.

Only during exceptional circumstances (e.g. COVID-19) some study assessments may be collected remotely, in case, the patients cannot attend the study visit in person. Refer to Section 12.11 for study conduct contingency measures.

8.1.2 Screening

Patients with a confirmed diagnosis of moderate-to-severe UC will be included and randomized to treatment. Diagnosis of UC must have been established at least 3 months before the first randomization by clinical and endoscopic evidence, and endoscopic confirmation of disease activity (colonoscopy or flexible sigmoidoscopy at Screening with independent central reading). Randomization at the start of the induction phase will be stratified by prior use of any biologics and concurrent use of corticosteroids. In addition, the proportion of patients who had received previous biologics will be limited to approximately 75% of all included patients.

8.1.3 Induction phase

The induction phase will have a 2-stage design:

- In **Enrollment Period 1** approximately 60 patients were to be randomized 1:1:1:1 to oral 10 mg/day, 30 mg/day, or 45 mg/day IMU-838, or placebo (about 15 patients each). An interim analysis was conducted after approximately 60 patients had been randomized into Enrollment Period 1 and had received at least 1 dose of IMU-838. Initially it was planned that Enrollment Period 2 will include up to 2 doses of IMU-838 and placebo, excluding likely ineffective and/or intolerable doses based on an interim analysis of safety, PK, biomarker, PD and efficacy data after Enrollment Period 1. Because the interim analysis did not reveal a likely ineffective and/or intolerable dose according to the findings of the unblinded DRC, the Steering Committee recommended to continue all 3 IMU-838 doses in Enrollment Period 2. These recommendations were accepted and implemented by the sponsor. Thus, Enrollment Period 2 will include approximately a further 180 patients randomized 1:1:1:1 to oral 10 mg/day, 30 mg/day, 45 mg/day IMU-838, or placebo (about 45 patients each).
- **Enrollment Period 2** will include approximately further 180 patients randomized 1:1:1:1 to oral 10 mg/day, 30 mg/day, 45 mg/day IMU-838, or placebo (about 45 patients each).

In total, approximately 240 patients will be randomized in both Enrollment Periods 1 and 2. During the first 7 days of treatment during the induction period in both Enrollment Period 1 and 2, patients will receive only half of their assigned dose i.e. 1 tablet of 5 mg/day, 15 mg/day, 22.5 mg/day IMU-838, or placebo, respectively. Patients will be dosed with their full assigned dose starting Day 7 of the induction phase and thereafter.

During the induction phase, safety, biomarker and PD, disease activity biomarkers (fCP and CRP), genotyping, symptomatic and endoscopic assessments (full and partial Mayo score, and respective subscores), and IMU-838 plasma trough levels will be regularly evaluated (see Table 1).

After Week 10, patients will be treated as follows:

- Patients who have achieved symptomatic remission at Week 10 will enter the maintenance phase.
- Patients who have achieved symptomatic response but not yet symptomatic remission, will continue into an extended induction phase until Week 22. If these patients have achieved symptomatic remission at Week 22 they will enter the maintenance phase.
- Patients who do not show symptomatic response at Week 10 or symptomatic remission at Week 22 (if the patient had continued into the extended induction phase) will be discontinued from the blinded treatment but will have the option to enroll in the open-label treatment extension arm.

The final analysis of the induction period will be performed when all patients enrolled in Enrollment Periods 1 and 2 have completed their induction or, if applicable, extended induction phase, including all scheduled EoI/EoEI assessments.

8.1.4 Maintenance phase

All patients with symptomatic remission at Week 10 or Week 22, will be treated as follows:

- Patients who had received IMU-838 during induction will be re-randomized to receive either 10 mg/day or 30 mg/day IMU-838.
- Patients who had received placebo will be "re-randomized" to continue to receive placebo. However, patients, investigator and other study personnel will remain blinded and unaware to this continued placebo treatment as these patients will undergo the same randomization procedures and study drug assignments as patients receiving IMU-838.
- Patients will be treated until they have received IMU-838 or placebo treatment for a total of 50 weeks (adding up induction phase, potential extended induction phase and maintenance treatment) or until UC relapse, whichever occurs first.

Randomization at the start of the maintenance phase will be stratified by the IMU-838 dose received in the induction phase.

Safety and partial Mayo score (including respective patient-reported subscores, e.g. PRO-2) will be regularly assessed during the maintenance phase (see Table 2). Patient visits in the maintenance phase will be scheduled every 4 weeks. All patients who remain in the maintenance phase until Week 50 will undergo a scheduled flexible sigmoidoscopy with biopsy and will have the full Mayo score (including all subscores) assessed. Patients that experience a symptomatic UC relapse before Week 50 will undergo a scheduled flexible sigmoidoscopy with biopsy and will have the full Mayo score (including all subscores) assessed at the time of relapse (see Table 2, End of Maintenance [EoM]). Patients with symptomatic UC relapse will be discontinued from the maintenance phase with the option to enter the open-label treatment extension arm, subject to certain conditions (see Section 9).

The final analysis for the maintenance phase will be performed when all patients enrolled in the maintenance phase have terminated maintenance treatment prematurely or as scheduled. An explorative data analysis for the maintenance phase will be done at the time point of final analysis for the induction phase.

8.1.5 Open-label treatment extension

The following patients will have the option to enroll in the open-label treatment extension arm and will be treated with 30 mg IMU-838, once daily (however, the sponsor reserves the right to change

the dose at any time additional information regarding safety and efficacy of IMU-838 becomes available):

- Patients in the induction phase who had received at least 6 weeks of blinded study treatment and completed the EoI sigmoidoscopy (including biopsy) regularly scheduled at Week 10, and have neither reached symptomatic remission nor symptomatic response
- Patients in the extended induction phase who had completed all Week 10 assessments (including EoI sigmoidoscopy), and have not reached symptomatic remission during or at the end of the extended induction phase
- Patients in the maintenance phase who had discontinued from the maintenance treatment due to symptomatic UC relapse or other reasons with the EoM sigmoidoscopy performed at discontinuation (unless the previous sigmoidoscopy had been performed less than 4 weeks before the discontinuation)
- Patients having completed the maintenance phase as scheduled (including all EoM/Week 50 assessments)

Although patients may be eligible for open-label treatment extension, those patients with significant protocol deviations or significant non-compliance at any time during the blinded treatment are not allowed to enter the open-label treatment extension arm. When patients eligible to enter the open-label treatment extension arm have ongoing relevant significant treatment-emergent AEs, those patients are allowed a waiting period (including treatment suspension) of up to 30 days following blinded treatment and will only be allowed to enter the open-label treatment extension arm when such treatment-emergent AEs have subsided to levels observed at Baseline or have fully recovered from such AEs.

Open-label treatment has to start within 30 days of the last dose of the blinded treatment arms, otherwise patients will be discontinued from this trial.

Visits will be scheduled every 4 weeks for the initial 50 weeks of overall study treatment (i.e. combining treatment periods in induction, extended induction and maintenance, if applicable, and open-label treatment extension phases), and every 10 weeks thereafter. Following the implementation of Protocol Version 6.0, the 10-week schedule, for patients in the open-label extension and with more than 50 weeks of overall treatment, will be changed to a 24-week schedule at the next scheduled visit. Safety, concomitant medication, Mayo PRO-2 score, and CRP, will be regularly assessed during clinic visits (see Table 3). No endoscopic assessment will be performed but results from such procedures will be collected if done in the course of routine clinical care.

The IMU-838 formulation (IMU-838 vs IMU-838-RC) may be changed during the open-label extension treatment. For more details see Section 11.1.3.

Treatment for a patient in the open-label extension arm will continue as long as no clinically significant safety issue (as assessed by the investigator) occurs, that is related to study procedures or study treatment, until the patient no longer receives a benefit from study treatment (as assessed by the investigator), until the patient withdraws consent, or until the sponsor terminates the study. In addition, patients in the open-label extension arm may be transferred by the sponsor to a separate and comparable follow-up study in which they can continue treatment with IMU-838 or, if patients have access, transfer to commercially available vidofludimus calcium. Once all remaining participating patients have been transferred respectively, the CALDOSE-1 study will be closed. Patients will be allowed to receive a maximum of 10 years *(not applicable for UK, see below)* total combined treatment with study medication in this trial.

For the UK the following applies: With a maximum allowed treatment of 3 years in the open-label extension arm, patients will receive a maximum of 4 years total combined treatment with study medication in this trial. However, if no safety concerns arise during future regular safety assessments and sufficient safety data are available, the steering committee may recommend extending the overall treatment period including all phases to a maximum of 10 years as per a substantial amendment.

The blinding of the individual randomized treatment assignments during the blinded treatment phase will be maintained as described in Section 10 for investigators and other study personnel, as well as for patients entering the open-label extension arm. When all patients have completed the induction phase, the individual treatment assignments for patients during induction treatment will be unblinded and a final data analysis for the induction phase performed, even so some patients may still undergo treatment in the blinded maintenance phase following the second randomization.

During open-label treatment extension in addition to data review (as outlined in the Steering Committee Charter), safety interim analyses may be performed at the request of the sponsor or the Steering Committee.

8.1.6 Pharmacokinetics period

The procedures described in this section are done in addition to population PK and IMU-838 trough levels done in the induction phase (see Section 8.1.3), both of which are done in all patients. This section only applies to the additional single-dose PK assessment in a subset of patients to be performed in designated PK centers only.

Across designated study centers (“PK centers”), the first 8 patients who completed the maintenance phase as scheduled inclusive the EoI/Week 10 or EoM/Week 50 Visit (both, including the required sigmoidoscopy examinations) and who have opted to continue into the open-label treatment extension arm will be included in a PK subpopulation for which a full single-dose PK profile (up to 72 hours post-dose) will be established. These patients will receive their first open-label dose of

30 mg IMU-838 at the Start$_{OLE}$ visit. Blood samples will be collected pre-dose and up to 72 hours post dose. No doses will be taken on Day 1$_{OLE}$ and Day 2$_{OLE}$ of the open-label period. On Day 3$_{OLE}$ and after the last PK blood sample has been taken, patients will continue daily dosing as all other patients (see also Sections 12.6 and 14).

8.2 Study design rationale

This is a placebo-controlled, double-blind study including a double randomization (initial randomization for induction and second randomization for maintenance). A placebo arm is included due to regulatory recommendations to evaluate dose-related benefits and adverse effects in randomized, double-blind, placebo-controlled studies. [2,3]

The distribution of male and female patients will be according to the natural distribution within the study population for this trial. No corrective measures will be taken. Because this is a phase 2 study, it is not planned to enrol a sufficient number of patients necessary to detect sex-related differences.

To evaluate the time course of the clinical effects, an induction period of 10 weeks and an extended induction period of 22 weeks were chosen.

To obtain a full single-dose PK profile in UC patients, a subset of patients will undergo a PK period at the beginning of the open-label treatment arm.

As required by respective guidelines, [2,3] the in- and exclusion criteria ensure that only patients for whom a diagnosis of UC has been established by clinical and endoscopic evidence at least 3 months before study start and for whom disease activity was confirmed at Screening by a flexible sigmoidoscopy with central reading will be included.

The interim analysis after completion of Enrollment Period 1 of the induction phase was planned to allow to reduce the dose groups to the most appropriate dose(s) of IMU-838 and to ensure that patients were not unnecessarily exposed to ineffective or intolerable IMU-838 doses. However, because the interim analysis did not reveal a likely ineffective and/or intolerable dose (Section 8.1.3) all 3 IMU-838 doses will be continued in Enrollment Period 2.

To evaluate the potential of IMU-838 to maintain remission, only patients with symptomatic remission are included in the maintenance phase and patients are re-randomized as recommended. [2] Patients with symptomatic response at the end of the initial induction phase but have not yet achieved symptomatic remission will continue induction treatment to Week 22 to evaluate if continued treatment in responders eventually leads to delayed symptomatic remission. This will also allow achieving sufficient patient numbers in the maintenance phase.

The primary endpoint at Week 10 includes a composite of both patient-reported symptomatic remission (i.e. stool frequency [stool frequency Mayo subscore of 0 or 1][4], rectal bleeding Mayo score [=0]), and endoscopic healing (modified Mayo endoscopy subscore of 0 or 1) as recommended. [2,3]

The treatment period of the maintenance phase is 40 or 28 weeks (depending on the length of the preceding induction period) and the overall blinded treatment period is 50 weeks which is both considered appropriate for a phase 2 trial.

An explorative data analysis of the maintenance phase at the time of the final analysis for the induction phase helps to plan for further IMU-838 development, including Phase 3 studies, and to evaluate if the remaining maintenance phase must be adjusted to accommodate for observed relapse rates.

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, which have been identified in animals or during early clinical studies. 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. Additionally, no increased rate of infections and infestations were seen in the treatment arm as compared to placebo in the same study.

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 red blood cells 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.

Based on results of Phase 1 studies with IMU-838, 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.

[4] Because patients must present with a stool frequency of ≥2 at Screening the stool frequency must decrease by ≥1 as requested by respective guidelines or clinical remission.

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 for patients in whom IMU-838 metabolism is decreased potentially leading to increased drug blood concentrations.

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

- 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 >1.2 x upper limit of normal (ULN), and/or history of gout or symptoms suggestive of gout will be excluded from the study.

During clinical trials using the previous formulation 4SC-101, 1 serious adverse event (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 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 study.

A thorough analysis of the clinical data did not confirm a potential adverse effect of vidofludimus on liver function in patients other than those with Gilbert syndrome. However, patients with liver impairment 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

Based on the PD of vidofludimus and the pathology of UC, patients with UC may benefit from IMU-838 treatment. A small uncontrolled study in patients with steroid-dependent patients with CD and UC confirmed the beneficial effects vidofludimus. The response rate with 4SC-101 was substantially higher compared with historical placebo rates and the use of steroids could be reduced (see also Section 5.2.5).

Risk management

As mentioned above, risk minimization procedures are implemented for this study 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, and
- an interim analysis by an independent DRC.

Risk-benefit assessment

Considering the known safety data, the implemented risk minimization measures, the expected benefits in the target population, and the medical need for further treatment in UC, the benefit-risk evaluation is considered favorable.

9 Patient selection

9.1 Sample size

Overall approximately 240 patients will be enrolled: Approximately 60 patients during **Enrollment Period 1** and approximately 180 patients in Enrollment Period 2 each randomized 1:1:1:1 to oral 10 mg/day, 30 mg/day, or 45 mg/day IMU-838, or placebo (about 15 patients or 45 patients each).

The 30 mg/day and 45 mg/day IMU-838 dose groups pooled for the primary efficacy analysis will include about 120 patients.

For sample size calculation see Section 16.1.

The maximum numbers of patients enrolled will be 30 per center and 80 per country.

9.2 Inclusion criteria

Induction phase

1. Male and female patients, aged 18 - 80 years
2. UC diagnosed more than 3 months before Screening (Day -30) as documented in the medical chart
3. Previous treatment failure defined as:
    a. Patient had an inadequate response with, lost response to, or was intolerant to approved or experimental immunomodulators (azathioprine, 6-mercaptopurine, 6-thioguanine,

methotrexate, or tofacitinib) or biologics (no more than 2 treatment failures with biologic drugs i.e. anti-tumor necrosis factor α antibodies [infliximab, adalimumab, golimumab and their biosimilars], vedolizumab, or certain experimental antibodies [ustekinumab]); or

b. Patient had an inadequate response to, was intolerant to, or is corticosteroid dependent (corticosteroid-dependent patients are defined as i) unable to reduce steroids below the equivalent of prednisolone 10 mg/day within 3 months of starting steroids, without recurrent active disease, or ii) who have a relapse within 3 months of stopping steroids. [4])

4. Active disease defined as
   a. Mayo stool frequency score of ≥2 at Screening Visit 1
   b. Mayo rectal bleeding score of ≥1 at Screening Visit 1
   c. modified Mayo endoscopy subscore of ≥2 at the screening flexible sigmoidoscopy (endoscopy assessed by an independent central reader blinded to screening center and patient information)
5. Endoscopic appearance typical for UC and extending >15 cm from the anal verge as confirmed by an independent central reader (blinded to screening center and patient information)
6. Laboratory values: Neutrophil count >1500 cells/μL (> 1.5 x 10^9/L), platelet count ≥100 000/mm^3 (≥ 100 10^9/L), serum creatinine <1.5 x upper limit of normal (ULN), total bilirubin, alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT) <1.5 x ULN
7. Female patients must
   a. Be of non-child-bearing potential i.e. surgically sterilized (hysterectomy, bilateral salpingectomy, bilateral oophorectomy at least 6 weeks before Screening) or post-menopausal (where postmenopausal is defined as no menses for 12 months without an alternative medical cause), or
   b. If of child-bearing potential, must have a negative pregnancy test at Screening (blood test) and before the first study drug administration (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 2 months before Screening, during treatment with IMU-838, and at least 3 months after the last dose of study therapy

      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 has undergone effective surgical sterilization before the female patient entered the clinical trial and he 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)

8. Male patients must agree not to father a child or to donate sperm starting at Screening and throughout the clinical trial and for 3 months after the last dose of study medication. Male patients must also either
   - 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 IMU-838 and for at least 3 months after the last dose of study medication

   For Poland and the UK the following additional requirement apply:
   - if male patients have a female partner of childbearing potential, the partner should use a highly effective contraceptive method as outlined in inclusion criterion 7

   And additionally, for Poland only:
   - if male patients have a pregnant partner, they must use condoms while taking study medication to avoid exposure of the fetus to study medication
9. Ability to understand and comply with study procedures and restrictions
10. The patient is legally competent, has been informed of the nature, the scope and the relevance of the study, voluntarily agrees to participation and the study's provisions and has duly signed the informed consent form

Maintenance phase

1. Symptomatic remission achieved at Week 10 or Week 22 of the induction phase

Open-label treatment extension arm

1. Patient is in the induction phase, had received at least 6 weeks of blinded study treatment and completed the sigmoidoscopy (incl. biopsy) regularly scheduled at Week 10/EoI, and has neither reached symptomatic remission nor symptomatic response

   Or

Patient is in the extended induction phase, had completed all Week 10 assessments, and has not reached symptomatic remission during or at the end of the extended induction phase,

Or

Patient is in the maintenance phase and discontinues from the maintenance phase due to symptomatic UC relapse or other reasons with a flexible sigmoidoscopy performed at discontinuation (if the previous sigmoidoscopy had been performed more than 4 weeks before discontinuation)

Or

Patient has completed the maintenance phase as scheduled (including all Week 50 assessments)

9.3 Exclusion criteria

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

Gastrointestinal exclusion criteria

1. Diagnosis of Crohn's disease, inflammatory bowel disease type unclassified, ischemic colitis, microscopic colitis, radiation colitis or diverticular disease-associated colitis
2. Ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine
3. History of colectomy with ileorectal anastomosis or ileal-pouch anal anastomosis or imminent need for colectomy (i.e. colectomy is being planned)
4. Active therapeutically uncontrollable abscess or toxic megacolon
5. Malabsorption or short bowel syndrome
6. History of colorectal cancer or colorectal dysplasia (with the exception of dysplasia in polyps which have been removed)

Infectious disease exclusion criteria

7. *Clostridium difficile* (*C. difficile*) infection
   - Evidence of, or treatment for *C. difficile* infection within 30 days before first randomization
   - Positive *C. difficile* toxin B stool assay during the screening period
8. Treatment for intestinal pathogens other than *C. difficile* within 30 days prior to first randomization
9. Other chronic systemic infections
   - History of chronic systemic infections including but not limited to tuberculosis, human immunodeficiency virus (HIV), hepatitis B or C, within 6 months before Screening

- Positive interferon-gamma release assay (IGRAs) for *Mycobacterium tuberculosis* at Screening
- Positive HBsAg (hepatitis B virus surface antigen), HBcAb (hepatitis B core antibody), positive hepatitis C virus and/or HIV-antigen-antibody (HIV-Ag/Ab) test[5] at Screening

10. Any live vaccinations within 30 days prior to study drug administration except for the influenza vaccine

Other medical history and concomitant disease exclusion criteria

11. Known history of nephrolithiasis or underlying condition with a strong association of nephrolithiasis, including hereditary hyperoxaluria or hereditary hyperuricemia
12. Diagnosis or suspected liver function impairment which may cause, as assessed by the investigator, a potential for fluctuating liver function tests during this trial
13. Renal impairment i.e. estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73m²[6]
14. Serum uric acid levels at Screening >1.2 x ULN (for women >6.8 mg/dL, for men >8.4 mg/dL)
15. History or clinical diagnosis of gout
16. Known or suspected Gilbert syndrome
17. Indirect (unconjugated) bilirubin ≥1.2 x ULN at Screening (i.e. ≥ 1.1 mg/dL)
18. 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

Therapy exclusion criteria

19. Use of any investigational product within 8 weeks or 5 x the respective half-life before first randomization, whatever is longer
20. Use of the following medications within 2 weeks before first randomization:
    a. Tofacitinib
    b. Methotrexate
    c. Mycophenolate mofetil
    d. Any calcineurin inhibitors (e.g. tacrolimus, cyclosporine, or pimecrolimus)

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[5] If any HIV, HBV, or HCV antigen or antibody screening test shows reactive or borderline results, a confirmatory Nucleic Acid Amplification Test (NAAT) will automatically be performed for the detection of the virus by using the same blood draw sample. If no virus specific nucleic acid is detected, and the clinical history of the patient, other laboratory examinations, and current clinical pictures also exclude a concurrent infection, the patient will not be excluded from the study.

[6] Calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

e. Oral systemic corticosteroids >20 mg/day prednisolone equivalent including beclomethasone dipropionate (at >5 mg/day) and budesonide (multi-matrix [MMX] at >9 mg/day)

f. Oral aminosalicylates (e.g. mesalazines) >4 g/day

21. Use of the following medications within 4 weeks before first randomization:
    a. Use of intravenous corticosteroids
    b. Use of thiopurines including azathioprine, mercaptopurine and 6-thioguanine
    c. Use of any rectal and topical aminosalicylates and/or budesonide
22. Use of oral systemic corticosteroids ≤20 mg/day prednisolone equivalent including beclomethasone dipropionate (at ≤5 mg/day) and budesonide (MMX at ≤9 mg/day) unless they have been used for at least 4 weeks before first randomization and at a stable dose for at least 2 weeks before first randomization
23. Oral aminosalicylates (e.g. mesalazines) ≤4 g/day unless they have been used for at least 6 weeks and with a stable dose for at least 3 weeks before first randomization
24. Use of biologics as follows:
    a. anti-tumor necrosis factor α antibodies (infliximab, adalimumab, golimumab, including their biosimilars) within 4 weeks before first randomization
    b. vedolizumab and ustekinumab within 8 weeks before first randomization
25. Use of the DHODH inhibitors leflunomide or teriflunomide within 6 months before first randomization
26. Any use of natalizumab (Tysabri™) within 12 months before first randomization
27. Use of the following concomitant medications is prohibited at Screening 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
    - Rosuvastatin at doses >10 mg/day

General exclusion criteria

28. History of, or current serious, severe, or unstable (acute or progressive) physical or mental illness, or any medical condition, including laboratory anomalies or renal or hepatic

impairment, that may require treatment or would put the patient in jeopardy if he/she was to participate in the study

29. Known hypersensitivity to DHODH inhibitors (teriflunomide, leflunomide) or any ingredient of the investigational product
30. Pregnancy or breastfeeding
31. History of drug or alcohol abuse during the past year
32. Concurrent participation in any other clinical trial using an investigational medicinal product or medical device
33. An employee of an investigator or sponsor or an immediate relative of an investigator

Exclusion criteria for open-label treatment extension arm

1. Any ongoing, clinically significant treatment-emergent (started during the IMU-838 treatment in the blinded treatment arms) adverse event (AE) or laboratory abnormality (including blood chemistry and urinalysis) as assessed by the investigator *
2. Significant treatment or study non-compliance during induction and/or maintenance phase (as assessed by the investigator), and/or inability or unwillingness to follow instructions by study personnel as assessed by the investigator
3. Significant protocol deviations during induction and/or maintenance phase that are assessed by the investigator to negatively affect further patient cooperation in this study

* If treatment-emergent AEs are the reason for exclusion from the open-label extension arm, the eligibility can be re-assessed up to 30 days following the last treatment in the blinded treatment arms.

10 Randomization, blinding and unblinding procedures

10.1 Blinding

Study participants, investigators, and all other personnel directly involved in the conduct of the study will be blinded to treatment assignments during the blinded treatment phase. If patients switch to the open-label treatment arm, the blind of their previous treatment assignment during induction and maintenance will be kept until after database hard lock for the final analysis of the induction and maintenance phase, respectively. The blinding for study participants, investigators, and all other persons directly involved in the conduct of the study will also be kept during interim and explorative data analyses.

To maintain the blind, the IMU-838 as well as the 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 study center personnel, or the sponsor's designee(s) until after database hard lock for the final analysis of the induction and maintenance phase, respectively.

10.2 Emergency unblinding

The premature breaking of the code should be restricted to emergency cases in which knowledge of the administered drug is necessary for treatment of clinically significant AEs. Whenever possible, the sponsor should be contacted before breaking the blind. Should any blind be broken, the respective patient will be withdrawn from further blinded treatment in the study (however, the patient may continue open-label treatment, if applicable) and a written explanation must be given by the investigator to the sponsor immediately. Emergency unblinding, if necessary, will be conducted via IWRS or via an emergency phone service, in cases the web-based system cannot be accessed for any reason.

10.3 Maintenance of blinding during interim or exploratory analyses

An interim analysis was performed for the induction phase of Enrollment Period 1 and an exploratory analysis will be performed for the maintenance phase at the final analysis of the induction phase. Care will be taken to maintain the blind of patients, investigators and sponsor during these analyses, and to avoid introducing any biases into the study.

After approximately 60 patients had been randomized into Enrollment Period 1 and had received at least 1 dose of IMU-838 an interim analysis was performed for the induction phase data.

After all patients have completed their induction phase and, if applicable, their extended induction phase, the respective data base part will be hard locked, and data of the induction phase will be unblinded and analyzed. An exploratory analysis of the maintenance phase will be performed at this time. However, the blind for the maintenance phase will be kept until completion of the maintenance phase and hard lock of the respective data base part.

Access to interim comparative and individual patient data will be restricted to members of the DRC and the independent data manager and independent biostatistician performing the interim and explorative data analyses. The statistical analysis will be done by the independent statistician not otherwise involved in the clinical trial.

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

To minimize bias, the statistical analysis plan (SAP) for the induction period (which includes the primary endpoint of the study) was finalized before any data was analyzed in the interim analysis.

10.4 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.

10.5 Randomization

The study includes a double randomization, i.e. initial randomization for induction, second randomization for maintenance.

Eligible patients will be randomized by means of IWRS. The IWRS will assign the appropriate initial and all subsequent study medication kits for each patient. The sites will be supplied with user guides for the IWRS in English or the national language.

The investigators will be provided with technical options and password information to selectively break the code for an individual patient by telephone or through electronic message transfers. For further information, please see Section 10.2.

11 Treatments

11.1 Study medication

All medications 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, crospovidone and magnesium stearate; tablets manufactured by wet granulation additionally contain povidone and talc.
Formulation:	Tablets containing a specific polymorph of vidofludimus calcium manufactured by wet granulation or roller compactor (IMU-838 or IMU-838-RC); the 2 formulations are considered bioequivalent (see investigator's brochure and Section 5.2.3)
Matrix:	White uncoated tablets, biconvex shape, diameter of 8 mm
Dose strengths:	Before implementation of Protocol Version 6.0: 5 mg, 15 mg, and 22.5 mg (IMU-838) Following implementation of Protocol Version 6.0: 5 mg, 15 mg, and 22.5 mg (IMU-838), and 30 mg (IMU-838-RC, will only be used in the open-label treatment extension)

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 study medication will be packed and labeled according to applicable regulatory requirements.

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

IMU-838 and placebo tablets will be packaged in 30 mL polyethylene bottles containing 85 tablets; IMU-838-RC will be packed in 30 mL polyethylene bottles containing 100 tablets.

Study medication (one bottle with 85 tablets) during the blinded treatment phase will be dispensed at D0, Week (W)6, W10, W14, W18, W22, W26, W30, W34, W38, W42, and W46, if applicable.

Study medication during the open-label treatment will be dispensed every 4 weeks (during first 50 weeks of treatment, one bottle will be dispensed at each visit) or every 10 weeks (after first 50 weeks of treatment, 2 bottles will be dispensed at each visit) until Protocol Version 6.0 comes into force. After the Protocol Version 6.0 approval, the patient can receive at each visit 1 bottle of IMU-838-RC instead of 2 bottles of IMU-838.

After implementation of Protocol Version 6.0 either up to 5 bottles of IMP (when the previous IMU-838 formulation is used) or up to 2 bottles of IMP (when the simplified IMU-838-RC formulation is used) will be dispensed every 24 weeks (until EoT). The number of bottles dispensed depends on the specific circumstances of the visit schedule of the patient and the amount of remaining IMP estimated from the currently used bottles available to the patient. During the extended treatment period, dispensed bottles must be used until empty and then be returned. Patients will be advised to bring all IMP (including full, in-use and empty bottles) to all visits; the empty bottles will be kept, the in-use and full ones will be returned to the patient (together with newly issued ones). Patients will also be advised to completely use up the tablets in one bottle before starting a new bottle. In-use non-empty bottles (without counting of remaining tablets) will be returned to the patients for continued use, unless a safety interim analysis is being performed as communicated by the sponsor.

The switch from the IMU-838 to the simplified IMU-838-RC formulation will depend on the remaining availability of the previous formulation. The sponsor will communicate to sites when formulations must be switched at the next regular study visit for all patients still on treatment. After switching to the simplified IMU-RC formulation, patients must take only one instead of 2 tablets per day. The investigator and other study personnel must make patients aware of this change when first dispensing the IMU-838-RC formulation.

As an exception only during any extraordinary circumstances (e.g. COVID -19 pandemic), the sponsor acknowledges that some organizational and/or logistical adjustments might be necessary at the investigational sites. Only during these exceptional circumstances sites are allowed to ship IMP directly to the patients.

11.1.4 Storage and stability

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

In stability studies, the medicinal product was stable at ambient (25°C/60% relative humidity) and at accelerated storage conditions (40°C/75% relative humidity). Thus, IMU-838 does not require any special storage conditions. However, the tablets in general should be protected from direct sun light, moisture, freezing, and excessive heat (excessive heat is customarily defined as any temperature above 40°C [104 F]). It should also be advised to keep the bottle tightly closed in order to protect from moisture.

11.1.5 Treatment dose, dose selection, and administration

Doses administered are summarized in Table 6. Tablets (1 tablet per administration and day for the initial week of treatment, 2 tablets per administration and day thereafter; if the IMU-838-RC formulation is used during the open-label extension treatment only 1 tablet per day) will be taken once daily in the morning in the fasted state (no food after midnight, intake of water allowed) and taken with one glass of water approximately 15 minutes to 1 hour before breakfast.

For treatment administration, the following must be considered:

- At study visit days in the induction phase, medication must be taken at the study center to allow for pre-dose assessments (i.e. plasma IMU-838 trough levels).
- During the entire study, patients will not be allowed to have breakfast before they arrive at the study center (to allow for blood chemistry). Intake of water is always allowed.
- Patients selected for the full PK assessment for the single dose given during the open-label treatment must fast for a minimum of 10 hours (no food, only intake of water allowed) before dosing and blood drawings and 2 hours after dosing.

Table 6: Doses administered

Phase		Daily dose [mg]		No of tablets, tablet strength	
		Week 1 D0 - D6	Weeks 2-10 or Weeks 2-22	Week 1	Weeks 2-10 or Weeks 2-22
Induction and extended induction phase	Enrollment Periods 1 and 2	0	0	1 x placebo	2 x placebo
		5	10	1 x 5 mg	2 x 5 mg
		15	30	1 x 15 mg	2 x 15 mg
		22.5	45	1 x 22.5 mg	2 x 22.5 mg
		Daily dose [mg]		**No of tablets, tablet strength**	
Maintenance phase		0		2 x placebo	
		10		2 x 5 mg	
		30		2 x 15 mg	
		Daily dose [mg]		**No of tablets, tablet strength**	
Open-label treatment		30[a]		2 x 15 mg IMU-838 Or 1 x 30 mg IMU-838-RC	

[a] The sponsor may change the dose whenever additional information regarding safety and efficacy of IMU-838 becomes available.
D = Day, No = number.

Doses of 10 to 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 plasma exposure of the free acid and calcium salt formulation of vidofludimus. The highest dose used in this trial will be 45 mg/day IMU-838. The area under the drug concentration-time curve (AUC) 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 of their assigned full 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 hours allows a once daily administration.

The doses used for Enrollment Period 2 are based on the interim data of Enrollment Period 1. All available data (PD, efficacy and safety data) were reviewed by the DRC during the interim analysis (see Section 6). Subsequently a maximum of 2 effective and safe IMU-838 doses were to be selected for Enrollment Period 2. Ineffective doses and doses with dose-limiting toxicities were to be discontinued. The dose selection process was based on many parameters and thus no direct and easy algorithm to identify the best doses existed. However, the decision was to be justified on the

observed results. Details about the interim analysis were defined in a DRC charter finalized prior to data base lock for the interim analysis. However, from the interim results the DRC concluded that none of the IMU-838 doses used in Enrollment Period 1 were likely ineffective and/or intolerable and the Steering Committee recommend continuing all 3 IMU-838 doses in Enrollment Period 2. These recommendations were accepted and implemented by the sponsor and thus Enrollment Period 2 will include all 3 IMU-838 doses.

11.1.6 Drug accountability and patient compliance

Study medication must not be used outside the context of this study protocol. The investigator must ask the patient to return excess study medication as well as all packaging materials (including empty containers) at all applicable visits (see Table 1, Table 2, Table 3, Table 4) for drug accountability. Unused study medication cannot be used outside this study. Dispensed and returned medication cannot be re-used for other patients in this study.

The investigator or authorized staff must document the receipt, dispensation, and return of all study medication received during this study. These records will include but are not limited to dates, quantities, batch numbers, and patient identifiers and unique IRT codes, as applicable. The investigators must maintain records documenting that the patients were provided with study medication as outlined in the protocol. Furthermore, they should reconcile all study medication received from the sponsor and returned from the patient. It is the responsibility of the investigator to give reasons for any discrepancies in study medication accountability. Forms will be provided to enhance drug accountability.

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

During the open-label extension treatment, compliance will be assessed by the number of bottles dispensed and empty bottles returned (dispensed bottles must be used until empty and then returned; remaining tablets in in-use bottles will not be counted at every trial visit). This differs for the EoT visit and in case of an interim safety analysis (see Section 16.5) at which remaining tablets of in-use bottles will be counted.

11.2 Prior and concomitant medications

11.2.1 UC-related treatments

All previous medications administered within 1 month before randomization must be documented in the corresponding section of the eCRF. In addition, all **UC-related** therapies since UC diagnosis will be documented in the eCRF.

All medications taken by the patients at entry into the study and all treatments given in addition to the study medication during the study are regarded as concomitant treatments and must be documented in the eCRF.

An overview on allowed and prohibited prior and concomitant therapies is also provided in Appendix 1.

Table 7: Allowed concomitant UC-related treatments

	Induction phase	Maintenance phase	Open-label extension
Oral corticosteroids	Stable dose of ≤20 mg/day prednisolone equivalent allowed, if a stable dose was given for at least 2 weeks before randomization	No initiation allowed, doses of ≤20 mg/day prednisolone equivalent allowed[a]	Initiation allowed, doses of ≤20 mg/day prednisolone equivalent allowed
Oral budesonide MMX	Stable dose of ≤9 mg/day allowed, if a stable dose was given for at least 2 weeks before randomization	No initiation allowed, stable doses of ≤9 mg/day allowed[a]	Initiation allowed, doses of ≤9 mg/day
Oral beclomethasone dipropionate	Stable dose of ≤5 mg/day allowed, if same stable dose was given for at least 2 weeks before randomization	No initiation allowed, stable doses of ≤5 mg/day allowed[a]	Initiation allowed, doses of ≤5 mg/day
Oral aminosalicylates (e.g. mesalazines)	Stable dose ≤4 g/day allowed, if same stable dose was given for at least 3 weeks before randomization	No initiation, stable doses of ≤4 g/day allowed	Initiation allowed, doses of ≤4 g/day
Rectal and topical aminosalicylates and/or budesonide	Not allowed	Not allowed	Allowed
Biologics	Not allowed	Not allowed	Allowed
Antiobiotics (oral or systemic)	Not allowed	Not allowed	Allowed

[a] Tapering must be initiated (see Section 11.3).
MMX = multi-matrix

11.2.1.1 Allowed UC treatments

Allowed treatments during Screening and Induction

- Oral systemic corticosteroids (at or below 20 mg/day prednisolone equivalent), including budesonide (multi-matrix [MMX] formulation, at or below 9 mg/day) and beclomethasone dipropionate (at or below 5 mg/day), will be allowed if they had been used for at least 4 weeks and with a stable dose for at least 2 weeks before first randomization, however:

Cannot be initiated during induction, allowed only if already taken at stable doses of ≤20 mg/day (budesonide at ≤9 mg/day, beclomethasone dipropionate ≤5 mg/day) for at least 2 weeks before first randomization

Doses should be stable throughout the induction phase

- Oral aminosalicylates (e.g. mesalazine) ≤4 g/day will be allowed if they had been used for at least 6 weeks and at a stable dose for at least 3 weeks before first randomization

Cannot be initiated during induction phase, allowed only if already taken at stable doses for at least 3 weeks before first randomization

Doses should be stable throughout induction phase

Allowed treatments during Maintenance

- Oral systemic corticosteroids, including budesonide (MMX formulation, at or below 9 mg/day) and beclomethasone dipropionate (at or below 5 mg/day), can be used during the maintenance phase:
  - Dose can be changed during maintenance phase but must be maintained at ≤20 mg/day (≤9 mg/day for budesonide, ≤5 mg/day for beclomethasone dipropionate)
  - Weaning should be initiated (see Section 11.3)
- Oral aminosalicylates (e.g. mesalazine) can be used during the maintenance phase

Doses can be changed during maintenance phase but must be maintained ≤4 g/day

Allowed treatments during open-label extension

- Oral systemic corticosteroids including budesonide (MMX formulation) and beclomethasone dipropionate treatment can be continued or newly initiated during open-label extension, however must be maintained at ≤20 mg/day (budesonide at ≤9 mg/day, beclomethasone dipropionate ≤5 mg/day)
- Oral aminosalicylates (e.g. mesalazine) treatment can be newly initiated, however must be maintained at ≤4 g/day
- Biologics such as anti-TNFα antibodies (infliximab, adalimumab, golimumab including their biosimilars), vedolizumab and ustekinumab (if licensed in your country for the treatment of UC) can be newly initiated during the open-label extension
- Topical treatments (enemas or suppositories) containing aminosalicylates and/or budesonide
- Oral and/or systemic antibiotic treatments used for treatment of a *Clostridium difficile* infection or other bacterial infections

11.2.1.2 Prohibited UC-related treatments during the trial

Any UC-related medication not listed under allowed treatments or any doses of allowed medications not listed under UC-related medications are not allowed during the trial (oral systemic corticosteroids >20 mg/day prednisolone equivalent, budesonide >9 mg/day, and beclomethasone dipropionate >5 mg/day are allowed to treat UC flares only during the open-label treatment extension). The following medications or treatments are prohibited during the entire trial:

- Thiopurines including azathioprine, 6-mercaptopurine and 6-thioguanine
- Janus kinase inhibitors approved for the treatment of IBD (e.g. tofacitinib)
- Intravenous corticosteroids
- Use of the DHODH inhibitors leflunomide or teriflunomide
- Any use of natalizumab (Tysabri™)
- Use of methotrexate
- Use of mycophenolate mofetil
- Use of any calcineurin inhibitors (e.g. tacrolimus, pimecrolimus cyclosporine)

11.2.2 Other prohibited and restricted medications

Prohibited medications

- Any investigational product within 8 weeks or 5 x the respective half-life before the first randomization
- 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
- Rosuvastatin at >10 mg/day
- Life vaccines
- Sphingosine-1-receptor (S1P) modulators (including, but not limited to fingolimod, siponimod, and ozanimod), monomethyl fumarate, and diroximel fumarate

Restricted medications

Restricted concomitant medications are not generally prohibited (Appendix 1), but use should be restricted in terms of dose and treatment duration, if possible. In accordance with the prescribing information, the lowest effective dosage for the shortest duration should be applied based on the

individual patient treatment goals whenever possible. Alternatives to these drugs should be considered and patients should be carefully monitored for any indication of overdose and/or toxicity.

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

11.3 Oral corticosteroid tapering regimen

At the start of the maintenance phase (at Weeks 10 or 22) a corticosteroid tapering regimen should be initiated for patients receiving oral steroids. For prednisone, the dose should be reduced at a rate of 5 mg (or equivalent) every 2 weeks. For beclomethasone dipropionate and budesonide other suitable tapering regimen should be used according to the investigator's discretion.

11.4 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) 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 (blood test) and before the first study drug administration (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 2 months before Screening, during treatment with IMU-838, and at least 3 months after the last dose of study therapy

  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 has undergone effective surgical sterilization before the female patient entered the clinical trial and he 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)

Male patients must agree not to father a child or to donate sperm starting at Screening and throughout the clinical trial and for 3 months after the last dose of study medication. Male patients must also either

- 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 IMU-838 and for at least 3 months after the last dose of study medication

If male patients do have a female partner of childbearing potential, it is recommended that the female partner should also use an effective contraceptive method.

For Poland and the UK the following applies additionally:

If male patients have a female partner of childbearing potential, the female partner must use an effective contraceptive or other effective birth control method (see above) throughout the study and for 3 months after the last dose of study medication.

And additionally, for Poland only:

If male patients have a pregnant partner, they must use condoms while taking the study medication to avoid exposure of the fetus to the study medication.

For restrictions concerning the administration of study medication see Section 11.1.5.

11.5 Management of clinical events

11.5.1 Adverse events of anticipated clinical events of UC

UC-related intestinal symptoms such as diarrhea and rectal bleeding that were present at Screening and fluctuate based on the individual patient's disease history during the course of the study are considered anticipated clinical events of the underlying condition and will not be collected as AEs. These disease characteristics will be regularly captured in the Mayo score (and respective subscores).

Any worsening of intestinal UC disease symptoms should only be recorded as an AE if their course is abnormally severe or significant or unexpected. New UC typical extra-intestinal manifestations which have never been seen before in this particular patient should also be recorded as AEs.

The terms "UC exacerbations" or "UC relapse" will not be considered as AEs. Symptomatic UC relapses (for definition see Section 4) will be separately documented in the eCRF.

11.5.2 Monitoring of hepatotoxicity

Patients will be monitored throughout the study for evidence of hepatotoxicity with regular assessments (every 4 weeks) of liver enzymes e.g. aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), gamma-glutamyl transferase (GGT) and total and indirect bilirubin. In addition, the exploratory biomarker miR-122 of drug-induced liver injury will be assessed pre-dose and at 24 hours after the first dose of study drug in the induction phase.

In case of an increase in ALT, GGT or AST to >3 × ULN, or indirect or total bilirubin >2 × ULN during dosing with study medication, testing of all liver parameters (ALT, AST, GGT, total and indirect bilirubin) will be repeated within 48 to 72 hours. Patients will also be asked about symptoms. Concomitant medication will be checked for hepatotoxic medications.

If repeat testing still shows ALT or AST to be >3 × ULN, or bilirubin >2 ×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 other cause of liver enzyme increases, further liver function tests as considered appropriate by the investigator).

Study medication will be discontinued if at least one of the following applies

- 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 international normalized ratio (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

11.5.3 Monitoring of red blood cells in urine

Plasma uric acid levels and urinalysis (microscopic examination of urinary sediment) will be regularly assessed throughout the initial 10 weeks of study treatment. Urinary screening during continued treatment beyond 10 weeks 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.[5] For further information please see Section 15.1.3.

12 Study schedule

12.1 Study conduct

An overview on the study conduct is provided in the schedules of assessments (Table 1, Table 2, Table 3, Table 4, and Table 5). Patients will be given a patient's identification card at Screening 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 along with them throughout the entire trial.

Visits in the induction and maintenance phase should be scheduled at the same time in the morning so that visits are all within ±2 hours of the Day 0 visit.

Patients should be advised to bring to the specified visits their diary cards. Patients will also be advised to completely use up the tablets in one bottle before starting a new bottle. Patients will also be advised to bring all IMP (including full, in-use, and empty bottles) to every trial visit; the empty bottles will be returned to the site, the started in-use and full ones will be returned to the patient (together with newly issued ones). In case of a safety interim analysis during the extended treatment period (see Section 16.5), a full compliance will be performed at the respective last visit before the scheduled interim analysis i.e., at this visit tablets of started in-use bottles will be counted, and the patient will receive a complete new set of bottles. In addition, patients must be advised at each visit to drink a generous amount of fluid per day to ensure adequate urine flow.

During the induction phase patients will be asked to withhold study medication on days of clinic visits. Patients will take study drug at the clinic. Patients will also be asked to fast overnight before all clinic visits as specified in Section 11.1.5.

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

At all visits (except the end-of-study visit), patients will be asked to return to the trial site according to the schedule listed in Table 1, Table 2, Table 3, and Table 4 for the following visit. However, patients should 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.

For study conduct contingency measure during exceptional circumstances (e.g. COVID-19 pandemic) see Section 12.11.

12.2 Screening

Patients for whom written informed consent (for consent procedures see Section 18.3) has been obtained will undergo the assessments listed in Table 1. Patients will be screened for eligibility based on the study's inclusion and exclusion criteria. Only patients who have passed all eligibility criteria on Screening Visit 1 should be advanced to Screening Visit 2 (endoscopy). If there is a delay in assessments from Screening Visit 1 or assessments need to be repeated due to technical difficulties, assessments from Screening Visit 1 are valid for up to 60 days between Screening Visit 1 and randomization. If 60 days are exceeded, Screening Visit 1-assessments must be repeated. Note that tests can solely be repeated if tests are inconclusive or had technical problems. A re-screening of patients is not allowed (if not requested or approved by the sponsor).

If a full colonoscopy was not performed in the previous year, a colonoscopy must be performed during Screening. If results of a full colonoscopy from the previous year are available, a flexible sigmoidoscopy with biopsy will be performed.

A sigmoidoscopy or full colonoscopy will only be scheduled if all other eligibility criteria assessed at Screening Visit 1 (see Table 1) are met and randomization should be performed within 14 to 3 days of Screening Visit 2. An independent central reading of the completed screening sigmoidoscopy or colonoscopy will be performed to confirm eligibility of the patient. The patient can only be randomized following confirmation of eligibility by the central reader. A central endoscopy manual which was finalized before study initiation at the first study center describes more details. In case of technical problems, assessments at Screening Visit 2 may also be repeated within the times indicated for repetition of Screening Visit 1 assessments.

Diary cards will be completed for the 5 days before initial randomization.

12.3 Induction phase

Visit Day 0

Patients will undergo the assessments and procedures listed in Table 1 and will be randomized to treatment. Before a patient will be randomized, endoscopic eligibility must have been confirmed by an independent central reader. Following randomization, the patient will take the first dose of study medication at the site.

Visits Days 1, and 7 of Week 1, Weeks 2 and 6

Patients will undergo the assessments and procedures listed in Table 1.

At Week 2, IMU-838 plasma levels will be assessed pre-dose (trough level) and 3 to 10 hours post dose (the actual time of the second blood collection can be chosen based on the patient's preference, but must be between 3 and 10 hours after dosing).

Visit Week 10/EoI

Patients will undergo the assessments and procedures listed in Table 1.

Patients will be assessed for symptomatic response and symptomatic remission. Based on these results patients will be further treated as follows:

- Patients who have achieved symptomatic remission will enter the maintenance phase.
- Patients who have achieved symptomatic response, but not yet symptomatic remission will continue into an extended induction phase until Week 22.
- Patients who do not show symptomatic response at Week 10 will be discontinued from the blinded treatment but will have the option to enroll in the open-label treatment extension arm.

In case of an early termination from the induction phase at or after Week 6 but before Week 10, the assessments and procedures outlined for the Week 10/EoI visit should be performed. Patients discontinuing from the study before Week 6 should perform the EoS visit 30 days after their last intake of study medication.

Extended induction phase: Visits Weeks 14, 18, and 22/EoEI

Patients who have achieved symptomatic response but not yet symptomatic remission at Week 10 will continue into an extended induction phase until Week 22 with assessments at Weeks 14, 18, and 22. All assessments and procedures as listed in Table 1 will be performed.

Patients will be assessed for symptomatic remission at Week 22. Based on these results patients will be further treated as follows:

- Patients who have achieved symptomatic remission will enter the maintenance phase.

- Patients who do not show symptomatic remission at Week 22 will be discontinued from the blinded treatment but will have the option to enroll in the open-label treatment extension arm.

For eligibility criteria to enter the open-label treatment arm see Section 9.

In case of an early termination from the extended induction phase the assessments as outlined for the Week 22/EoEI visit should be performed.

12.4 Maintenance phase

Start of maintenance phase (Week 10 or Week 22)

This visit corresponds to the last visit of the induction phase or extended induction phase at which the patient reaches symptomatic remission. Patients entering the maintenance phase will be re-randomized and treated as follows:

- Patients who had received IMU-838 during induction will be re-randomized to 10 mg/day or 30 mg/day IMU-838.
- Patients who had received placebo will be "re-randomized" but will continue placebo treatment.

Visits Week 14, 18, and 22

Patients who entered the maintenance phase at Week 10 will have the assessments and procedures listed in Table 2 performed. Patients who are in the extended induction phase will have the assessments performed as described in Table 1. In addition, for those achieving symptomatic remission at Week 22, the assessments and procedures described under start of maintenance phase (see above and Table 2) will be performed.

Visits Weeks 26, 30, 34, 38, 42, and 46

All patients in the maintenance phase will have the assessments and procedures performed as listed in Table 2.

Visit Week 50/EoM

The maintenance phase and blinded treatment period will stop when the patient has received study treatment for a total of 50 weeks during induction and maintenance, or the patient experiences a UC relapse. In both cases, the assessments and procedures as listed in Table 2 for Week 50/EoM will be performed.

In case of an early termination from the maintenance phase the assessment as outlined for the Week 50/EoM visit should be performed.

Patients who discontinue the maintenance phase either as scheduled or prematurely and have a sigmoidoscopy performed at their last visit of blinded treatment (if the previous sigmoidoscopy

had been performed more than 4 weeks before discontinuation) will have the option to continue into the open-label treatment arm.

For eligibility criteria to enter the open-label treatment arm see Section 9.

12.5 Open-label treatment arm

Visit Start$_{OLE}$

The Start$_{OLE}$ visit must be performed within 30 days of the last dose of the blinded treatment during the induction or maintenance phase.

If ongoing TEAEs are the reason for exclusion from the open-label extension arm, the eligibility can be re-assessed up to 4 weeks following the last treatment in the blinded treatment arms.

The assessments and procedures as listed in Table 3 will be performed. If the visit occurs within 3 weeks of the last visit of the induction or maintenance phase only inclusion and exclusion criteria will be checked and study medication dispensed. The first open-label study drug intake will be performed while the patient is on site.

Visit Week X$_{OLE}$

Clinic visits will be scheduled every 4 weeks until 50 weeks of total study participation (i.e. induction + maintenance + open-label part) and every 10 weeks thereafter. Following the implementation of Protocol Version 6.0 the 10-week schedule, for patients in the open-label extension and with more than 50 weeks of overall treatment, will be changed to a 24-week schedule at the next scheduled visit. During these visits the assessments and procedures as listed in Table 3 will be performed.

Patients can continue treatment as long as there are no clinically significant safety issues (as assessed by the investigator), that are related to study procedures or study treatment, as long as the patient benefits from study treatment (as assessed by the investigator), until the patient withdraws consent, or until the sponsor terminates the study. In addition, patients in the open-label extension arm may be transferred by the sponsor to a separate and comparable follow-up study in which they can continue treatment with IMU-838 or, if patients have access, transfer to commercially available vidofludimus calcium. Once all remaining participating patients have been transferred respectively, the CALDOSE-1 study will be closed. Patients will be allowed to be treated with study medication for a maximum of 10 years *(not applicable for UK, see below)* including all periods of the trial.

For UK the following applies: Patients will be allowed to be treated with open-label treatment for a maximum of 3 years (may be extended, see Section 8.1.5).

EoOLE

At the last visit of a patient's participation in the open-label phase, the assessments and procedures as listed in Table 3 for the EoOLE visit will be performed.

12.6 Pharmacokinetics period

The PK period is part of the open-label treatment arm and will include 8 patients at designated PK centers (see Section 8.1.6).

Visit Start$_{OLE}$, Day 1$_{OLE}$, Day 2$_{OLE}$, and Day 3$_{OLE}$

Patients will undergo the assessments and procedures listed in Table 4. Before a patient will be dosed, eligibility for the open-label treatment period must have been confirmed. Patients will take the first open-label single dose and a full PK profile up to 72 hours post-dose will be obtained (during this period the patient will take no additional dose). At Start$_{OLE}$ patients will stay at the site for at least 6 hours for blood sample collections for PK assessments. After Day 3$_{OLE}$ the patients in the PK subpopulation will follow the schedule of assessments of the open-label phase (Table 3) as all other patients participating in the open-label phase.

12.7 Unscheduled visit due to disease exacerbations or due to safety issues and AEs

Patients who visit the study center at any time outside the protocol-specified visit schedule (i.e. an unscheduled visit) due to disease exacerbation or safety issues will undergo the assessments as listed in Table 5.

If a serious disease exacerbation is identified at an unscheduled visit during the induction phase, the investigator will assess if the patient should be withdrawn from further blinded drug treatment. If the patient is withdrawn at Week 6 or thereafter see Section 12.8 for further details.

If a symptomatic UC relapse is identified at an unscheduled visit during the maintenance phase the patient must be withdrawn from the maintenance phase. For further details see Section 12.8.

If a symptomatic UC relapse is identified at an unscheduled visit during the open-label phase, the investigator will assess if the patient should be withdrawn. If the patient is withdrawn see Section 12.8 for further details.

12.8 Premature termination

If a patient prematurely discontinues the trial (for reasons, see Section 17) or blinded treatment the following should be performed depending on when the patient discontinues:

- If the patient discontinues during the induction phase before Week 6, the patient should perform an EoS visit 30 days after the last intake of study medication.
- If the patient discontinues during the induction phase at or after Week 6 up to Week 10, the current visit (as scheduled or unscheduled) should be performed and documented as Week10/EoI visit (at the earliest opportunity), including the EoI sigmoidoscopy. If the patient does not switch to the open-label extension arm, an EoS visit at 30 days after the last intake of study medication should be performed. If the patient is eligible and switches

to the open-label extension the visit schedule as outlined in Table 3 should be followed, after the Week10/EoI assessments have been performed.

- If the patient discontinues during the extended induction phase, the current visit (as scheduled or unscheduled) should be performed and documented as Week22/EoEI visit (at the earliest opportunity) and, if the patient does not switch to the open-label extension arm, an EoS visit, 30 days after the last intake of study medication. If the patient is eligible and switches to the open-label extension the visit schedule as outlined in Table 3 should be followed, after the Week22/EoEI assessments have been performed.
- If the patient discontinues during the maintenance phase, the current visit (as scheduled or unscheduled) should be performed and documented as Week50/EoM visit (at the earliest opportunity), including EoM sigmoidoscopy (if discontinuation occurs less than 4 weeks after the EoI endoscopic examination, the Week 50/EoM sigmoidoscopy does not need to be performed). If the patient does not switch to the open-label extension arm, an EoS visit at 30 days after the last intake of study medication will be performed. If the patient is eligible and switches to the open-label extension the visit schedule as outlined in Table 3 should be followed, after the Week50/EoM assessments have been performed.
- If the patient discontinues during the open-label phase, the current visit (as scheduled or unscheduled) should be performed and documented as an EoOLE visit at the last day of study medication, followed by an EoS visit at 30 days after the last intake of study medication. No EoS visit is required for patients transferring to the long-term follow-up study or commercially available vidofludimus calcium.

All patients withdrawing consent for further study participation should be encouraged to complete the EoS examination documenting patient status at 30 days following last study treatment.

In case of premature withdrawal either from blinded treatment or the trial, reasons, circumstances and findings should be fully described on the "Early Termination" page in the eCRF respecting the patient’s rights.

12.9 Transfer into a long-term follow-up trial or to commercially available vidofludimus calcium

The sponsor may set up a separate long-term follow-up study for patients who are currently on IMU-838 treatment. Once this study is initiated, all remaining patients in the open-label treatment extension of the CALDOSE-1 study will be transferred to this follow-up trial. In case patients are transferred to the follow-up trial, no EoS visit is required. The transfer to another long-term follow-up trial can occur during any regular visit, and the long-term follow-up trial should be started for the patient at the same visit the patient discontinues the CALDOSE-1 study. The reason for termination of a patient from this study will be recorded as “transfer to another IMU-838 long-term

follow-up study". Any ongoing AEs and/or clinically significant laboratory abnormalities will be marked as "unresolved" and then followed up in the follow-up trial.

At any time of the study, the sponsor may also decide to transfer patients who have access to commercially available vidofludimus calcium (defined as regulatory approval and reimbursement available) to commercially available vidofludimus. The transfer to commercially available vidofludimus calcium can occur at any regular trial visit and no EoS visit is required in this case. When such transition occurs the same rules as for transfer into the long-term follow-up trial apply and the reason for termination of the respective patient will be recorded as "transfer to commercially available vidofludimus calcium". This will be an individual decision per patient by the sponsor based on the patient's access situation. Such transition to commercially available vidofludimus calcium (patients with access) may also occur during and in parallel to the transfer of patients to the long-term follow-up trial (for patients without access). Ongoing AEs at the time of transition should be marked as "unresolved" in this trial and then be followed up during regular clinical care.

Medically important AEs, defined as new malignancies within 6 months or SAEs within 28 days after transferring patients to a follow-up trial or to commercially available IMU-838, must still be reported within this clinical study.

12.10 End of study visit

Patients who discontinue the treatment (blinded or open-label) will be asked to return to an EoS visit 30 days (-3 days/+4 weeks) after their last treatment dose with assessments as listed in Table 5. Please see also Section 15.1.6 for follow-up of adverse events. No EoS visit is required for patients transferring to the long-term follow-up study or commercially available vidofludimus calcium.

12.11 Study conduct contingency measures

As an exception and only during extraordinary circumstances (e.g. COVID-19 pandemic), the sponsor acknowledges that some organizational and/or logistical adjustments might be necessary at the investigational sites.

Deviations from this protocol that might arise in case of exceptional circumstances must be documented and discussed with the sponsor without delay. Every effort should be made to ensure the continuity of this study as per this study protocol and to avoid delays, treatment, discontinuation, missing assessments, and study dropout.

Some study assessments may be collected remotely, in case, the patients cannot attend the study visit in person due to pandemic measures. The site will obtain basic safety information by phone, such as AEs, any worsening of UC and concomitant medication.

Patients are provided with clinical study supplies (i.e. IMP) for this study. As an exception only sites are allowed to ship IMP directly to the patients. The investigator must be confident to be able to oversee patient safety appropriately and ensure high-quality data can be collected.

In addition, to ensure the quality of clinical study data and to protect the rights, safety and well-being of the patients, remote source data verification (SDV) can be used in this clinical study. Remote SDV will be considered only during extraordinary situations (e.g. the COVID-19 pandemic) related to public health crises, if the Clinical Research Associate is not allowed to visit the clinical site and as far as this is in line with EU and national law (or temporary national emergency measures).

Remote SDV will focus on the quality control of critical data such as primary efficacy data and important safety data. Important secondary efficacy data may be monitored simultaneously, provided this does not result in a need to access additional documents and therefore in an increased burden for study site staff. The sponsor will determine the extent and nature of remote SDV that they consider needed for this study under such exceptional circumstances (e.g. COVID-19 situation). Principal investigators should make their own determination as to whether or not the situation at their clinical site allows options for remote SDV according to applicable guidelines.

13 Efficacy assessments and procedures

13.1 Demographics and other baseline assessments

During Screening, demographics (including sex, age, and race), tobacco use, a complete medical history including a detailed UC history and the reference stool frequency as well as reference blood in stool will be collected.

13.2 Mayo score

The full, partial, and PRO-2 Mayo score will be regularly assessed during the study as specified in the schedules of assessments (Table 1, Table 2, Table 3, Table 4). The Mayo stool frequency and rectal bleeding scores will be assessed at the first screening visit.

The full Mayo score is composed of 4 categories (bleeding, stool frequency, physician assessment, and endoscopic appearance) each rated from 0 to 3 that are added up to give a total score that ranges from 0 to 12. Throughout the study the endoscopy subscore will be modified such that a value of 1 does not include friability.

The **partial Mayo score** includes only the non-invasive Mayo subscores, i.e. stool frequency, rectal bleeding, and physician's global assessment, the **Mayo PRO-2** score only the patient-reported outcomes i.e. stool frequency and rectal bleeding score.

Table 8: Full Mayo score

Stool frequency[a]
0 = Normal number of stools for this patient
1 = 1–2 stools more than normal
2 = 3–4 stools more than normal
3 = 5 or more stools more than normal
Rectal bleeding[b]
0 = No blood seen
1 = Streaks of blood with stool less than half the time
2 = Obvious blood with stool most of the time
3 = Blood alone passed
Findings of flexible proctosigmoidoscopy[c]
0 = Normal or inactive disease
1 = Mild disease (erythema, decreased vascular pattern, [mild friability])
2 = Moderate disease (marked erythema, absent vascular pattern, [any][c] friability, erosions)
3 = Severe disease (spontaneous bleeding, ulceration)
Physician's global assessment[d]
0 = Normal
1 = Mild disease
2 = Moderate disease
3 = Severe disease

[a] Each patient serves as his/her own control to establish the degree of abnormality of the stool frequency.
[b] The daily bleeding score represent the most severe bleeding of the day.
[c] In the study the modified Mayo endoscopic subscore will be used i.e. friability will not be included in 1; any friability is considered 2.
[d] The physician's global assessment acknowledges the 3 other criteria, the patient's daily record of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patients' performance status.
Extracted from [6].

Patients will be provided standardized instructions for recording the number of stools and their worst rectal bleeding over a 24-hour period as described below. The instructions will be incorporated into the diary.

Definition of stool frequency

Patients will be instructed that a stool is defined as a trip to the toilet when the patient has either a bowel movement, or passes blood alone, blood and mucus, or mucus only.

Reference remission stool frequency (over 24 hours)

- The patient will be asked to identify at the screening visit how many stools he or she had in a 24-hour period when in remission from UC.
- If the patient does not report that he or she has ever achieved remission, then the patient will be asked to identify the number of stools he or she had per day before initial onset of signs and symptoms of UC.

Patients will be instructed to indicate the most severe category that describes the amount of blood in their stools for a given day following the categories given in Table 8. If they do not pass stool during a given day, patients are instructed to select "no blood seen".

Patients will be instructed to capture their rectal bleeding and stool frequency assessments in their daily diaries

- for every day during the induction period and for 5 days before the first study drug administration at Day 0, and
- for 5 days before each visit during the extended induction phase and maintenance phase.

It will be recorded in the eCRF if the reference remission stool frequency is based on reported stool frequency when the patient was in remission or reported stool frequency before initial onset of signs and symptoms of UC. Both the remission and pre-UC stool frequency should be collected at Screening. This allows exploration of the natural history of pre-diagnosis stool frequency versus remission stool frequency.

Investigational sites will be provided instructions for calculations of stool frequency and rectal bleeding scores. The stool frequency and rectal bleeding scores will be based on the average (rounded up) of the most recent 3-day consecutive period within the week before the visit.

13.3 Sigmoidoscopy with biopsies

A sigmoidoscopy including biopsy will be performed at the visits as specified in the schedules of assessments (Table 1, Table 2, Table 3). The screening sigmoidoscopy will be replaced with a full colonoscopy if results of a full colonoscopy from the previous year are not available.

The flexible sigmoidoscopy or colonoscopy will be done with video-endoscopes, and all examinations will be videotaped. All sigmoidoscopy examinations (and the screening colonoscopy assessment if applicable) will be evaluated by an independent central reader blinded to the local reader's assessment. The central reader will also assess the modified Mayo endoscopy score and will confirm endoscopic eligibility, before a patient will be randomized.

The Central Endoscopy Manual will standardize procedures, video recordings/equipment, and assessment of endoscopy and will allow the local endoscopist to request more information on the

central reader's assessment, if necessary. The central reader's assessments will be used for patient eligibility and for efficacy assessments.

Biopsies

The area from which the biopsies will be taken should be between 15 to 25 cm above the anal verge. The investigator should try to consistently perform the biopsies at the same location independent of disease activity of ulcerations visible at this particular patient. Two biopsy specimens will be taken during each sigmoidoscopy and those will be fixed in formalin/ethanol for histological and, if applicable, immunohistochemical assessments. Standardized protocols for biopsy collection, fixation, and staining will be provided.

At the discretion of investigators, additional biopsies may be taken for extraction of tissue RNA and determination of tissue RNA expression profiles.

Histological activity of UC will be assessed with the Geboes score (see Appendix 2).

13.4 Diary completion and review

Patients will be given a diary card to record stool frequency and rectal bleeding (see also Section 13.2). At Screening, patients will be instructed and trained on how to complete the diary and one diary card. At the screening endoscopy visit patients will receive a diary and asked to record data for the 5 days before the Day 0 visit.

Diaries will be completed daily during the induction phase until Week 10. During the extended induction phase and maintenance phase the diary will only be completed for the 5 days preceding a clinic visit.

Diaries will be reviewed at each visit for completeness and legibility, and if needed the patient will be re-educated on how to complete the diary.

Diary entries preceding each study visit will be used to calculate the Mayo score. Because the flexible sigmoidoscopy may interfere with clinical parameters diary data from days on which the sigmoidoscopy was performed will not be used for calculation of the Mayo score.

14 Pharmacokinetics and pharmacodynamics assessments

14.1 Pharmacokinetics

IMU-838 plasma concentrations will be determined by a validated direct liquid chromatography tandem-mass spectrometry (LC-MS/MS) technique. This method determines the concentration of the active blood moiety vidofludimus contained in IMU-838. Details of the assay will be described in a separate bioanalytical report.

Plasma samples for analytical assay will be collected by venous puncture or indwelling venous catheter and will be assessed for IMU-838 plasma trough levels centrally. Samples will be collected and subsequently stored at -20°C at the site, and shipped to the central laboratory as frozen sample, 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 plasma trough values will be collected in all patients as specified in the schedule of assessments for the induction phase (Table 1).

Patients are required to withhold dosing of IMU-838 at each visit until the blood collection has been completed. If the patient had inadvertently taken the IMU-838 dose at such days, blood for trough levels should only be taken within 1.5 hours of the time of dosing. Otherwise, no blood for trough levels should be collected. In both cases, this should be recorded as protocol deviation.

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

Population PK

If feasible all PK concentrations measured in the study, possibly in combination with IMU-838 PK concentration data collected in different studies, will be evaluated using a non-linear mixed effects modeling. A correlation with safety and efficacy might be evaluated if warranted by the data.

Full single-dose PK profile

A full single-dose PK profile will be assessed in the first 8 consecutive patients completing the induction, extended induction or maintenance phase as scheduled and opted to continue into the open-label treatment arm at the centers selected for full PK assessment (designated as PK centers). Patients in the PK subpopulation will receive one single dose of the open-label 30 mg IMU-838 dose at the Start$_{OLE}$ visit. Blood samples for full PK will be collected on

- Day 0$_{OLE}$: pre-dose, and 1, 2, 3, 4, 5, and 6 hours (±15 min) post PK dose
- Day 1$_{OLE}$: 24 hours (±1 hour) post PK dose
- Day 2$_{OLE}$: 48 hours (±1 hour) post PK dose
- Day 3$_{OLE}$: 72 hours (±1 hour) post PK dose

On Day 3$_{OLE}$, after the last PK blood sample has been collected, patients will continue with daily dosing like other patients in the open-label treatment arm.

The following non-compartmental PK parameters will be calculated from the individual blood concentration-time data of IMU-838:

AUC_{0-t}	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to time t_{last}, where t_{last} is the time of the last measurable concentration (C_t).
AUC_{0-24h}	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to 24 hours.
AUC_{0-inf}	Area under the drug concentration-time curve from time zero to infinity, $AUC_{0-inf} = AUC_{0-t} + C_t/\lambda_z$, where λ_z is the apparent terminal elimination rate constant.
C_{max}	Maximum observed drug concentration.
λ_z	Apparent terminal rate constant, calculated by linear regression of the terminal linear portion of the log concentration vs time curve, where λ_z =-slope.
$t_{1/2}$	Apparent terminal elimination half-life, calculated as $\ln(2)/\lambda_z$.
t_{max}	Time of the maximum drug concentration (obtained without interpolation). If the maximum value occurs at more than one time point, t_{max} is defined as the first time point with this value.
CL/f	Apparent total clearance, calculated as dose/AUC_{0-inf}
V_z/f	Apparent volume of distribution at the terminal phase, calculated as $(CL/f)/\lambda_z$.

Samples will be collected and stored at -20°C at the site, and shipped to the central laboratory, as appropriate.

14.2 Pharmacokinetic sampling

Pharmacokinetic sampling for all patients is done only during the induction phase as specified in Table 1. An additional single dose PK is performed in a subset of patients in designated PK centers as described in Section 8.1.6.

Throughout the induction phase, all patients will have blood samples taken for determination of blood plasma concentrations of IMU-838.

There are two types of blood samples taken for PK measurements:

- Plasma trough levels: taken pre-dose at D0, D1, D7, W2, W6 and W10 (patients should arrive at the center at those days before taking their dose, have their blood drawn and only then are allowed to have their dose taken), and
- 1 additional blood plasma level: taken post-dose at W2 (the blood sample should be taken at 3-10 hours following oral dosing by the patient).

For plasma trough levels, if patients have inadvertently taken their study drug within 1.5 hours of arriving at the study center, the blood samples for IMU-838 trough levels can still be drawn. If longer than 1.5 hours, the blood levels should not be determined.

Plasma PK samples will be stored at -20°C at the site before being shipped to the central laboratory following Week 10 assessments.

14.3 Biomarkers and blood genotyping

Blood cytokines will be collected as specified in Table 1. The cytokines assessed will include IL-17 and IFNγ.

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

Samples for cytokines and genotyping will be collected and stored at -20°C at the site, and shipped to the central laboratory, as appropriate. Investigators will be provided with detailed written instructions how to collect, handle, store, and ship the respective samples. Samples will be evaluated centrally.

14.4 Disease activity biomarkers: fecal calprotectin and C-reactive protein

A stool sample to measure fCP, a biomarker of intestinal inflammatory activity, will be collected at specific time points as listed in the schedules of assessments (Table 1, Table 2, Table 3, Table 4, Table 5). Investigators will be provided with detailed written instructions how to collect, handle, store, and ship the respective samples. Samples will be evaluated centrally.

CRP will be analyzed from the blood samples taken for clinical chemistry analysis.

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 a

medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

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 Section 15.1.1.2).

Untoward medical experiences occurring during drug-free 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. Should they already be present at the screening visit, they will be documented as medical history.

A surgery or procedure scheduled to occur during the study 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 pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (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 endoscopy 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 study medication (Day 0) are defined as pre-treatment AEs.

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

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 AEs of special interest (AESI) see Section 15.1.3.

15.1.1.2 Adverse drug reactions and unexpected adverse drug reactions

An adverse drug reaction (ADR) is defined as any untoward and unintended response to an IMP related to any dose administered, i.e. there are facts or arguments to suggest a causal relationship between the administration of the IMP and the occurrence of the event.

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 which 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 first report of a fulminant 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 subject 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 should 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 subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should 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 pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (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 also not be recorded as SAE.

15.1.1.4 Suspected unexpected serious adverse reaction (SUSAR)

A **suspected unexpected serious adverse reaction (SUSAR)** is a serious adverse reaction (SAR) that is unexpected or for which the development is uncommon (unexpected issue) observed during a clinical trial and for which there is a relationship with the experimental drug.

15.1.2 Classification of adverse events

Classification of AEs will be performed by the investigator.

Causality

The causal relationship of the AE and the administration of the study medication will be assessed as follows:

- Related: Implies a reasonable possibility of a causal relationship between the event and the study medication. 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 study medication. 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 hematurias please 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 outcome is not known or not reported

15.1.3 Adverse events of special interest

The following AEs are defined as AESI 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 in connection with suspected or confirmed nephrolithiasis

Evaluation and assessments of RBC in urine

Evaluation of RBC in urine should be based solely on findings from microscopic examination of urinary sediment and not from dipstick reading only.[5] Therefore all conspicuous dipstick readings should 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 when assessed by the investigator of not being clinically significant. The investigator should also assess any increased RBC in urine as not clinically significant when there are more probable alternatives to explain this finding. The following alternate explanations of RBC in urine high should be considered:

- The urine sample was not properly collected (random midstream clean-catch collection) or there is evidence of contamination (e.g. by finding of bacteria or an unusual number of epithelial cells in urine sediment not explained by other conditions).
- There is evidence of infection not considered secondary to a drug-induced damage.
- There are 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 an AE of RBC urine positive.

Evaluation and assessment of hematuria

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

- five or more RBCs per HPF were found in at least 2 consecutive, properly collected urinalysis specimens,[7] **and/or**
- the finding of RBC urine positive had diagnostic or therapeutic consequences.

Severity assessment of hematurias

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

The severity of hematurias 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 in connection 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).

* Defined as treatment for less than 24 hours.

15.1.4 Documentation of adverse events

All AEs that occur after the patient has signed the informed consent form until 30 days after the patient's last study medication 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 feeling 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 which occur during the observation period of the study as described above will be recorded in the patient's AE section of the eCRF and will include the following information: a description, date of onset and resolution, severity, relationship to study medication, relationship to study procedure, action taken, and outcome. For SAEs, the SAE form must also 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 patients or the conduct of the study and any SAE, which occurs during the course of this study, will be reported (via the "Adverse Event of Special Interest Form" or the "Serious Adverse Event Form") to the sponsor immediately (i.e. no later than within 24 hours). The information will comprise at least the following data:

- Name, address, and telephone number of the reporting investigator
- Investigational product(s)
- Study code
- Patient identification number, sex, and date of birth
- Description of the AE, measures taken and outcome (at the time of reporting)
- Likelihood of drug causation of the AE assessed by the investigator

Reports will be addressed to:

SCRATCH Pharmacovigilance GmbH & Co. KG	
Schlossstrasse 25, D-35510 Butzbach	
E-mail:	safety-immunic@scratch-pv.com
Telephone:	+49 6033 7453 550
Fax:	+49 6033 7453 559

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) or institutional review boards (IRBs), 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 or IRBs about any event which necessitates reconsideration of the benefit-risk-ratio of the investigational drug. These events are in particular:

- single cases of expected SARs with an unexpected outcome,
- an increased incidence of expected SARs which is considered clinically significant,
- SUSARs occurring after a concerned person has completed the study,
- events related to the conduct of the study or the development of the drugs 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 or IRBs, if applicable.

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

In the event of a fatality, the "Study participant's insurer" will be informed by the sponsor's designee within 24 hours after the fatality has come to the sponsor's designee knowledge. In case of other SAEs, the "Study participant's insurer" has to be informed promptly.

15.1.6 Follow-up of adverse events

All SAEs judged to be related to the study medication 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 (S)AEs must be followed by the investigator until the conditions mentioned above are met or until the end of the safety follow-up period (30 days after last study medication) 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 has to ensure that adequate medical care is provided to a patient for any AEs, including clinically significant laboratory values, related to the trial.

15.1.7 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 immediately, i.e. no later than within 24 hours of the first awareness of the event and be recorded on the appropriate pregnancy form. Patients who become pregnant during the study after signing the informed consent should discontinue the study immediately.

A pregnancy in itself is not regarded an AE unless there is a suspicion that the study medication 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 study. All reports of congenital abnormalities or birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

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

15.2 Laboratory investigations

Clinical laboratory tests will be performed at the times indicated in the schedules of assessments (Table 1, Table 2, Table 3, Table 4, Table 5).

All laboratory samples have to 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 AEs, unless already clinically significantly abnormal at Baseline (pre-dose on Day 0) or Screening Visit 1, or unless there are known circumstances unrelated to a disease or the medication (such as patient activities or sample handling) that are a likely explanation 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 return to normal or to pre-dose value.

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 study medication. A blood pregnancy test is required at Screening. A local blood pregnancy test must be performed at any time in case of a positive urine pregnancy test.

Additional urine pregnancy tests will be performed at the centers throughout the trial at the times indicated in the schedules of assessments (Table 1, Table 2, Table 3, Table 4, Table 5) for all female patients of childbearing potential.

For instructions in case of pregnancy, see Section 15.1.7.

15.2.2 Blood chemistry, hematology, and coagulation

Blood chemistry, hematology and coagulation assessments will be performed using Lab Kits A, B and C as indicated in the schedules of assessments (Table 1, Table 2, Table 3, Table 4, Table 5) including the following parameters:

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, AP, 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 (Mg), chloride (Cl), inorganic phosphate (P), calcium (Ca), creatine phosphokinase, lactate dehydrogenase, amylase, lipase, C-reactive protein (CRP), total protein, albumin, glucose, HbA1c, triglycerides, cholesterol

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 will be calculated according to CKD-EPI equation. ***Other parameters****:* Na, K, Cl, P, Ca, CRP, total protein, amylase, lipase, albumin, glucose, triglycerides, cholesterol

Coagulation (inlcuded in Lab Kit A)

Coagulation parameters will be assessed at the time points indicated in the schedules of assessments (Table 1) including the following parameters: prothrombin time, activated partial thromboplastin time, and INR.

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, and shipped to the central laboratory, as appropriate.

15.2.3 Urine assessments

Urinalysis assessments will be performed using Lab Kits A, B, and C as indicated in the schedules of assessments (Table 1, Table 2, Table 3, Table 4, Table 5) including the following parameters:

Lab Kits A and B

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

Lab Kits C

- pH, nitrites, hemoglobin, protein, albumin, glucose, ketones, creatinine
- a dipstick analysis, including the assessment of RBC in urine, performed and read centrally[7]
- 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.

Details on urine sampling and handling of urine samples will be given in the Laboratory Manual.

15.2.4 miR-122 expression

MicroRNA-122 is an early indicator of drug induced liver injury. Blood samples to assess miR-122 will be collected at time points given in Table 1. Samples for miR-122 will be collected and stored at -20°C at the site, and shipped frozen to the central laboratory, as appropriate.

15.2.5 Serology and stool sample for *C. difficile* test

Tests for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), HCV, and human immunodeficiency virus (HIV) antigen-antibody (Ag/Ab) combined test, and a *Mycobacterium tuberculosis* IFNγ-release assay (Tbc-IGRA) will be performed during Screening. The HBcAb assay will be a combined immunoglobulin G (IgG) and IgM test. In case of a positive result, IgM will be evaluated separately.

If any HIV, HBV, or HCV antigen or antibody screening test shows reactive or borderline results, a confirmatory Nucleic Acid Amplification Test (NAAT) will automatically be performed for the detection of the virus by using the same blood draw sample. If no virus specific nucleic acid is detected, and the clinical history of the patient, other laboratory examinations, and current clinical pictures also exclude a concurrent infection, the patient will not be excluded from the study.

A stool sample will be collected at Screening to test for *Clostridium difficile (C. difficile)* toxin B.

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

The Tbc-IGRA and *C. difficile* toxin B will be done at the local laboratory, all other screening tests will be performed centrally.

15.2.6 Screening laboratory

The Screening Panel includes:

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

The screening tests for Tbc-IGRA and *C. difficile* toxin B will be done locally at the study site. All other tests will be done centrally and are included in the central Screening Lab Kit S.

15.3 Vital signs, physical examination, and ECG

Vital signs, routine physical examinations, and ECG will be performed at the times indicated in the schedules of assessments (Table 1, Table 2).

Vital signs

Vital signs will include blood pressure and heart rate, and should be obtained seated, 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 include height (only at Screening) and weight, and 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 must be documented as AE in the eCRF.

Any clinically significant finding at Screening 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 min rest using the site's own standard ECG machine. The ECG will be analyzed qualitatively by the investigator (normal or abnormal). 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. The detailed procedure used will be according to local practice. Any findings from ECGs collected after study drug administration will be captured as AEs if, in the opinion of the investigator, there has been a clinically significant change from Screening.

16 Biostatistical methods

16.1 Sample size calculation

Sample size calculation is based on the final analysis of the induction phase as follows:

With 3 dose groups (2 IMU-838 doses and placebo) about 49 patients per group are required to show a difference of 16% between the verum group and placebo assuming a placebo remission rate of about 10%, a significance level of 0.097, and a power of 80%. Assuming a drop-out rate of 20%, approximately 60 patients will be required per group.

Underlying assumptions:

Primary endpoint: composite of symptomatic remission and endoscopic healing

Underlying test: Chi square test

Randomization: Enrollment Periods 1 and 2: 1:1:1:1
The sample size is based on a comparison of the 30 mg/day and 45 mg/day IMU-838 doses combined vs placebo.

Power: 80%

Significance level: 0.097, 1-sided

In this early stage development study a higher α, i.e. 0.1, than the standard 0.025 level is considered appropriate. Due to the interim analysis and to keep the overall α-level to 0.1, this level must be adjusted. A group sequential design with O'Brien-Fleming boundaries will be applied. Accordingly, the sample size calculation is based on a significance level of 0.097, 1-sided.

No formal sample size calculation was performed for the sample size of the interim analysis of this small phase 2 study. However, and based on preliminary experiences, 15 patients per group were deemed sufficient to show numerical differences between placebo and verum, and between 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 have received at least one dose of study medication, i.e. any dose of IMU-838 or placebo. If it is uncertain if the patient has received any study medication, 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 have actually received.

Full analysis set

The full analysis set (FAS) will consist of all randomized patients who have received at least one dose of study medication, i.e. any dose of IMU-838 or placebo. The analyses based on the full analysis set 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 ("intention-to-treat").

Per-protocol set

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

Pharmacokinetic set

All patients of the FAS will also be included in the PK set, if they have completed at least two of the scheduled PK samples.

Assignment of analysis sets to analyses and allocation of patients

All efficacy analyses will be based on the FAS. The primary efficacy endpoint only will be additionally analyzed for the PP set. The analysis of the primary efficacy endpoint using the FAS will be considered confirmatory. 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 induction and maintenance phase will be done separately during a blind data review meeting for the induction and maintenance phase, respectively. The allocation of patients to the PP set needs only to be done for the induction phase since the primary endpoint belongs to the induction phase. The analysis sets to be used for the interim analysis between the 2 enrollment periods, for the explorative analysis of the maintenance phase, and for the analysis of the open-label treatment extension will be defined in the corresponding SAPs.

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. interim analysis, explorative analysis of maintenance phase, final analysis induction phase, final analysis maintenance phase, and analyses for the open-label phase) will be provided in respective SAPs. To minimize bias, the SAP for the induction period (which includes the primary endpoint of the study) was finalized before any data was analyzed in the interim analysis.

16.4 Primary efficacy analysis

The primary endpoint for this study is the composite endpoint of proportion of patients with both, symptomatic remission and endoscopic healing at Week 10.

All patients (both, Enrollment Period 1 and Enrollment Period 2 patients) who were randomized to 30 mg/day or 45 mg/day IMU-will be pooled and compared with placebo.

A stratified Cochran-Mantel-Haenszel test will be used for the analysis of the primary endpoint to adjust for the stratification factors prior use of any biologics and current use of corticosteroids.

In this early stage development study a higher α, i.e. 0.1, than the standard 0.025 level is considered appropriate. Due to the interim analysis (conducted after approximately 60 patients had been randomized into Enrollment Period 1 and had received at least 1 dose of IMU-838) and to keep the overall α-level to 0.1, this level must be adjusted. A group sequential design with O'Brien-Fleming boundaries will be applied. Accordingly, a significance level of 0.097, 1-sided, will be used for the primary efficacy analysis.

Patients discontinuing from the study during the induction phase due to the underlying disease will be counted as "treatment failures" (i.e. not achieving the primary endpoint), if these patients had at least 2 valid assessments of the Mayo PRO-2 score post-baseline, and had received at least 6 weeks of treatment without any major protocol deviations of the dosing schedule (as defined in the SAP), and had the Week 10/EoI sigmoidoscopy performed at the time of discontinuation (when discontinuation occurred before Week 10). Any discontinuation for other reasons or patients not fulfilling these criteria will be considered "dropouts" for the primary efficacy analysis. For dropouts between Week 6 and Week 10, the EoI value will be carried forward. In case that the corresponding information is missing or that the patient drops out before Week 6, the patient will constitute a missing value for the primary efficacy analysis.

16.5 Interim analysis

An interim analysis was conducted after approximately 60 patients had been randomized into Enrollment Period 1 and had received at least 1 dose of IMU-838. The aim of this interim analysis was to identify ineffective and/or intolerable IMU-838 dose(s).

An independent DRC assessed unblinded safety and efficacy data and gave recommendation on the dose(s) selection for Enrollment Period 2. A charter, which includes a detailed description of responsibilities and the procedures on dose selection, was implemented prior to data base lock for this interim analysis.

Safety interim analyses may be performed during the open-label treatment extension at the request of the sponsor or the Steering Committee to support regulatory filings or as part of intended program-wide safety evaluations of IMU-838. This safety analysis will summarize any safety and

tolerability data (including laboratory data) specifically for the extension period only. These safety assessments may be supplemented by complementary data regarding the clinical and disease status of patients. No unblinding is required as the interim analyses will be performed during the open-label part of the extended treatment period.

16.6 Final analysis of induction phase

The final analysis of the induction phase will be conducted when all patients in both enrollment periods have either completed or discontinued the induction phase (including extended induction phase, if applicable). A data base closure will be performed prior to this analysis. All parameters belonging to the induction phase will be checked, as specified in the data validation plan, and all queries resolved before data base closure and analysis. A blind data review will be conducted prior to unblinding for the induction phase based on all data to check for protocol deviations and to allocate the patients to the analysis sets.

16.7 Explorative analysis of maintenance phase

An exploratory analysis of the maintenance phase will be conducted at the time of the final analysis of the induction phase. It will be based on the parameters belonging to the maintenance phase that are available at that time point. A detailed description of the analyses will be provided in the corresponding SAP.

16.8 Final analysis of maintenance phase

The final analysis of the maintenance phase will be conducted when all corresponding patients have either completed or discontinued the maintenance phase. A data base closure will be performed prior to this analysis. All parameters belonging to the maintenance phase will be checked, as specified in the data validation plan, and all queries will be resolved before data base closure and analysis. A blind data review will be conducted prior to unblinding for the maintenance phase based on all data to check for protocol deviations and to allocate the patients to the analysis sets.

17 Patient withdrawal from study participation

Participation in the study is voluntary and patients may withdraw from the study at any time and for any reason. However, all patients should be encouraged to complete the study. If a patient withdraws or is withdrawn from study, the patient should return to the clinic as outlined in Section 12.8. All patients withdrawing from the study should also be encouraged to complete the EoS assessment 30 days after the last intake of study drug.

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

- Patient withdraws consent due to
  - AE(s)
  - UC relapse, disease exacerbation, and/or ongoing disease activity
  - 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 study objectives
  - relevant non-compliance with the protocol, which in the opinion of the investigator may jeopardize the study integrity or scientific goals of the study
  - reasons other than AE or non-compliance (to be specified)
- Pregnancy
- Stopping criteria regarding liver enzymes (Section 11.5.2)
- Treatment with prohibited concomitant medication
- Transfer to another long-term follow-up study
- Transfer to commercial vidofludimus calcium
- The patient has fully completed this study

The primary reason for discontinuation from the study is to be recorded in the source documents and on the eCRF.

Patients who prematurely discontinue the study will be treated according to the investigator's discretion and standard treatment guidelines, irrespective of the reason for withdrawal.

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

Patients who prematurely discontinue the study will not be replaced.

18 Ethical and legal requirements

18.1 Ethical conduct of the study

The study will be conducted in a manner consistent with all applicable regulatory authority and IRB/IEC regulations (e.g. ICH Guideline for Good Clinical Practice [GCP, CPMP/ICH/135/95], the Declaration of Helsinki [in its currently acknowledged version], IRBs [21 CFR 56], and

Obligations of Clinical Investigators [21 CFR 312]) as well as in keeping with applicable local law(s) and regulation(s). The investigator must also comply with all applicable privacy regulations (e.g. Health Insurance Portability and Accountability Act of 1996 [HIPAA], European Union Data Protection Directive 95/46/EC).

Financial disclosure by the investigator(s) pursuant to 21 CFR Part 54 will be obtained.

18.2 Independent ethics committee or institutional review board

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 or IRB will be submitted to the competent IEC or IRB for review. A favorable opinion for the clinical trial must be obtained from the IEC or IRB before any patient is enrolled at a center.

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

18.3 Patient information and consent procedure

Before any clinical study-related activities are performed, the investigator (or authorized designee) must review the informed consent form and explain the study to potential study 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 study 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 study 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.

For sites in the United States of America: The investigator will comply with all applicable state and federal requirements, including the requirement of the HIPPA Privacy Rule. The authorization

to use and disclose protected health information for research is part of the informed consent form, and a signed copy of the informed consent form must be placed in the study record.

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 study application will be submitted to the responsible competent authority (CA). The study will not start until this authority has authorized the study. Amendments to the study 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 study 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 European Data Protection Directive [8] (or General Data Protection Regulation [9] whichever applies), the HIPPA Privacy Rule, and other applicable international and national requirements.

The investigator must ensure that the pseudonymity of study 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 study-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 study center

19.1 Criteria for halting or terminating the study

The sponsor reserves the right to halt or terminate the study 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 study no longer feasible/valid
- Insufficient enrollment of patients
- All patients have been transferred to a long-term follow-up trial or to commercial supply of vidofludimus calcium
- All patients have completed the full duration of this study

19.2 Criteria for closing a study center

A study 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 study management requests
- Repeated protocol deviations or non-compliance
- The approval of the IEC or IRB in charge of the clinical trial is irrevocably revoked
- Additional local criteria might be established by written agreements between the sponsor and the study center
- All patients of this trial center have completed the full duration of this trial, have been transferred or have otherwise withdrawn from this trial, and investigators have stated in writing that they will provide answers to queries after trial site closure

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

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 early termination. In terminating the study, 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, IEC(s), or IRBs in writing if required, submit a copy of this notification to the sponsor and return the entire study medication and all related study 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 Study protocol, documentation and archiving of data

20.1 Amendments to the protocol

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

Substantial amendments, i.e. amendments which are likely to affect to a significant degree

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

will be submitted to the CA and IEC or IRB for an approval and favorable opinion as required by applicable regulations. If such amendments affect the patient's participation in the clinical study (e.g. a change in any procedure), the patient information and informed consent form must be updated to incorporate this modification, and currently enrolled patients must re-consent to participate 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/IRB 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 study or the development of the study medication, which 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 or IRB 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 or IRB.

Under emergency circumstances deviations from the protocol may proceed without prior approval by the sponsor and favorable opinion of the IEC or IRB 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 or IRB as soon as possible in accordance with national regulations.

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

20.3 Data retention

The study center, the sponsor or sponsor's designee(s) should maintain all study 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 study medication, 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 drug was taken off the market according to the legal stipulations. The documents should however, 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 are no longer needed to be retained.

The medical files of study 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 and provided for each patient. eCRFs will be provided as a regulatory compliant, electronically secure and protected web-based database, and should be handled in accordance with the instructions provided. An audit trail will record all entries and corresponding changes.

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

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

Only investigators and authorized designees will enter and edit the 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 Monitoring

The extent of monitoring and source data verification will be specified in a monitoring plan.

The study center must not enroll any patient before the initiation visit. During the study further monitoring visits will be performed according to ICH GCP, the sponsor's designee's standard operating procedures, and local regulations. eCRFs will be reviewed against source data for adherence to the study 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 study drug is being stored, dispensed and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

The investigators must permit the monitors access to the patient's medical records and all applicable source documents. Throughout the study, 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 study enrolment, visit dates, results of examinations, administrations of medication, and AEs.

21.3 Audits and inspections

During the study, 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.

21.4 Data management procedures

All data management activities will be conducted by FGK Clinical Research 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 final analyses of the induction and maintenance phase as well as after termination of the open-label phase, 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. For other analyses (interim analysis, explorative analysis of maintenance phase, and regular analyses for open-label phase), a soft lock will be performed to preserve the status of the database used for the corresponding analyses.

22 Study report and publications

The results of the final analyses of the induction phase will be summarized in a clinical study report according to the ICH E3 Note for guidance on structure and content of clinical study reports. Results of the exploratory data reviews, and final analysis of the maintenance phase will be reported in respective abbreviated reports. Short summaries will be provided for the regular analyses of the open-label treatment.

The 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 of manuscripts including the study results must be in line with the process specified in the investigator's clinical trial agreement. The publication or presentation of any study results shall comply with all applicable privacy laws, for example, the HIPAA.

23 Study periods

Actual start:	25-Jun-2018 (first patient in)
Estimated end main maintenance phase:	Oct 2022 (main part: last patient out)
Open-label treatment:	Not defined, but maximum treatment duration in this trial limited to a maximum of 10 years (including all phases of the trial; *in UK: maximum of 4 years*). Patients may also be transferred to a follow-up trial or to commercially available vidofludimus calcium, if applicable for patients with access

Actual recruitment period: ~41 months (24-Apr-2018 to 30-Sep-2021)

The end of the study is defined as last patient visit in any participating center.

24 References

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25 Approval and signatures

Protocol agreed to by sponsor:

Dr. Andreas Muehler

Sponsor's signatory name (print)

DocuSigned by:
Dr. Andreas Muehler
A41EC7FA4C974F3...

15.12.2021

Sponsor's signatory signature | Date

Protocol agreed to by coordinating investigator:

Dr. Geert D'Haens

Coordinating investigator name (print)

DocuSigned by:
Dr. Geert D'Haens
434ECBD7EB9C4B5...

15.12.2021

Coordinating investigator signature | Date

Principal investigator agreement page for the protocol

I agree:

- To assume responsibility for the proper conduct of the clinical study at this site, and to conduct the study in compliance with national law, the valid version of the Declaration of Helsinki, the GCP-guidelines, the present study protocol including its amendments, and with any other study 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 or institutional review board 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 study (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 study are adequately informed about the investigational medicinal product and of their study-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 study 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

26 Appendices

Appendix 1 Prior and concomitant treatments

	Withdrawal before Random.	Induction phase	Maintenance phase	Open-label extension
UC treatments				
Oral systemic corticosteroids >20 mg/day prednisolone equivalent including beclomethasone dipropionate (at >5 mg/day) and budesonide (MMX at >9 mg/day)	2 weeks	Not allowed	Not allowed	Not allowed (short course of no more than 6 weeks allowed to treat UC flares)
Oral systemic corticosteroids ≤20 mg/day prednisolone equivalent including beclomethasone dipropionate (at ≤5 mg/day) and budesonide (MMX at ≤9 mg/day)	-	Allowed if already used for at least 4 weeks and at a stable dose of ≤20 mg/day (≤9 mg/day for budesonide and and ≤5 mg/day for beclomethasone dipropionate) for at least 2 weeks before first randomization; dose must be stable throughout induction phase	Allowed if already used for at least 4 weeks and at a stable dose of ≤20 mg/day (≤9 mg/day for budesonide or ≤5 mg/day for beclomethasone diproprioniate) for at least 2 weeks before first randomization; dose can be changed but must be ≤20mg/day (≤9 mg/day for budesonide, and (≤5 mg/day for beclomethasone diproprioniate). **Tapering must be initiated (see Section 11.3)**	Allowed, can be initiated
Oral aminosalicylates (e.g. mesalazines) >4 g/day	2 weeks	Not allowed	Not allowed	Not allowed

Prior and concomitant treatments (continued)

	Withdrawal before Random.	**Induction phase**	**Maintenance phase**	**Open-label extension**
Oral aminosalicylates (e.g. mesalazines) ≤4 g/day		Allowed if they had been used for at least 6 weeks and with a stable dose for at least 3 weeks before first randomization, dose must be stable throughout induction phase at ≤4 g/day	Allowed if they had been used for at least 6 weeks and with a stable dose for at least 3 weeks before first randomization and during induction; dose can be changed but must be maintained ≤4 g/day	Can be initiated at stable doses
Biologics to treat UC:				
Anti-TNFα antibodies (infliximab, adalimumab, golimumab, including their biosimilars)	4 weeks	Not allowed	Not allowed	Allowed
Vedolizumab and ustekinumab	8 weeks	Not allowed	Not allowed	Allowed (if licensed for UC)
Rectal or topical treatments (enemas or suppositories) containing aminosalicylates and/or budesonide	4 weeks	Not allowed	Not allowed	Allowed
Oral and/or systemic antibiotic treatments used for a *Clostridium difficile* infection or other bacterial infections	30 days	Not allowed	Not allowed	Allowed
Intravenous corticosteroids	4 weeks	Not allowed	Not allowed	Not allowed
Janus kinase inhibitors approved for the treatment of IBD (e.g. tofacitinib)	2 weeks	Not allowed	Not allowed	Not allowed
Thiopurines (e.g. azathioprine, 6-mercaptopurine, 6-thioguanine)	4 weeks	Not allowed	Not allowed	Not allowed

Prior and concomitant treatments (continued)

	Withdrawal before Random.	Induction phase	Maintenance phase	Open-label extension
Use of other DHODH inhibitor (i.e. leflunomide or teriflunomide)	6 months	Not allowed	Not allowed	Not allowed
Natalizumab (Tysabri™)	12 months	Not allowed	Not allowed	Not allowed
Methotrexate, mycophenolate mofetil, or any calcineurin inhibitors (e.g. tacrolimus, cyclosporine or pimecrolimus)	2 weeks	Not allowed	Not allowed	Not allowed
Other treatments				
Any investigational product	8 weeks or 5 x the respective half-life	Not allowed	Not allowed	Not allowed
Any drug significantly restricting water diuresis, in particular vasopressin and vasopressin analogs	-	Not allowed	Not allowed	Not allowed
Any medication known to significantly increase urinary elimination of uric acid, in particular lesinurad (Zurampic™) as well as uricosuric drugs such as probenecid	-	Not allowed	Not allowed	Not allowed
Rosuvastatin >10 mg/day	Not allowed during Screening	Not allowed	Not allowed	Not allowed

Prior and concomitant treatments (continued)

	Withdrawal before Random.	Induction phase	Maintenance phase	Open-label extension
Any active treatments for malignant disease (in particular irinotecan, paclitaxel, tretinoin, bosutinib, sorafinib, enasidenib, erlotinib, regorafenib, pazopanib and nilotinib)	-	Not allowed	Not allowed	Not allowed
Life vaccine	30	Not allowed	Not allowed	Not allowed
Sphingosine-1-receptor (S1P) modulators (including, but not limited to fingolimod, siponimod, and ozanimod), monomethyl fumarate, and diroximel fumarate	-	Not allowed	Not allowed	Not allowed
Restricted medications	Restricted concomitant medications are not generally prohibited, but use should be restricted in terms of dose and treatment duration, if possible. In accordance with the prescribing information, the lowest effective dosage for the shortest duration should be applied based on the individual patient treatment goals whenever possible. Alternatives to these drugs should be considered and patients should be carefully monitored for any indication of overdose and/or toxicity.			
CYP2C8 strong inducers: rifampicin, barbiturates (e.g. phenobarbital), carbamazepine, ritonavir	-	Potentially decrease exposure to IMU-838 and may thus decrease efficacy.		
CYP2C8 strong inhibitors: gemfibrozil, clopidogrel	-	Potentially increase exposure to IMU-838 and may thus increase the risk for AEs; however uncertain due to alternative metabolic pathways of IMU-838.		
BCRP substrates with a narrow therapeutic window: rosuvastatin (maximum dose: 10 mg/day), mitoxantrone, sulfasalazine, topotecan, daunorubicin, doxorubicin, warfarin	-	IMU-838 may inhibit transport of BCRP substrates and lead to increased exposure in plasma and/or hepatocytes and thus increased risk for substrate's side effects. Patients should be closely monitored for signs and symptoms of excessive exposure to these medications and dosing of these medications should be carefully considered. Statins		

Prior and concomitant treatments (continued)

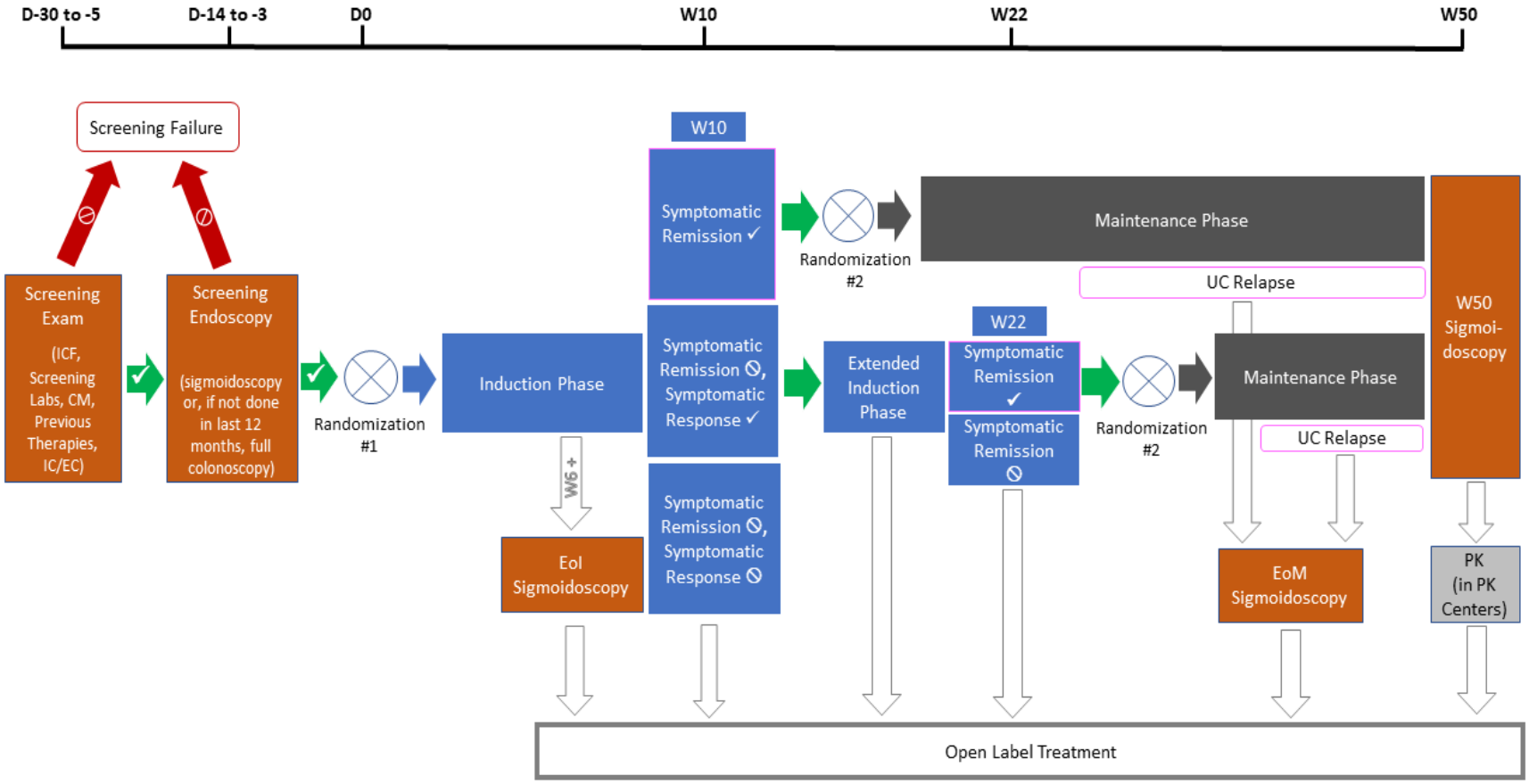
	Withdrawal before Random.	Induction phase	Maintenance phase	Open-label extension
(Note: methotrexate is not allowed, see above)		should be lowered to the lowest possible dose. See also rosuvastatin which is not allowed at doses >10 mg daily.		
BCRP strong inducers: DMARDs such as sulfasalazine (Note: methotrexate is not allowed, see above)	-	Potentially decrease exposure to IMU-838 and may thus decrease efficacy.		
BCRP strong inhibitors: immunosuppressants (cyclosporine A, tacrolimus, sirolimus), azole anti-fungals (ketoconazole, itraconazole, fluconazole), proton pump inhibitors (omeprazole, pantoprazole), NSAIDs (ibuprofen, naproxen, salicylates)	-	Potentially increase exposure to IMU-838 and may thus increase the risk for AEs.		
UGT1A1 inhibitors: atazanavir, canagliflozin, pazopanib, regorafenib, sorafenib, tocilizumab, tranilast	-	Combination therapy of IMU-838 and other UGT1A1 inhibitors may lead to disturbance of the bilirubin metabolism and subsequently to hyperbilirubinemia.		

BCRP = breast cancer resistance protein, CYP = cytochrome P450, DHODH = dihydroorotate dehydrogenase, DMARD = disease-modifying anti-rheumatic drug, MMX = MMX = multi-matrix, NSAID = non-steroidal anti-inflammatory drug, rando. = randomization, TNFα = tumor necrosis factor α, UC = ulcerative colitis.

Appendix 2 Geboes score for assessment of ulcerative colitis histologic disease activity

Grade 0		**Structural (architectural changes)**
Subgrades	0.0	No abnormality
	0.1	Mild abnormality
	0.2	Mild or moderate diffuse or multifocal abnormalities
	0.3	Severe diffuse or multifocal abnormalities
Grade 1		**Chronic inflammatory infiltrate**
Subgrades	1.0	No increase
	1.1	Mild but unequivocal increase
	1.2	Moderate increase
	1.3	Marked increase
Grade 2		**Lamina propria neutrophils and eosinophils**
2A Eosinophils	2A.0	No increase
	2A.1	Mild but unequivocal increase
	2A.2	Moderate increase
	2A.3	Marked increase
2B Neutrophils	2B.0	No increase
	2B.1	Mild but unequivocal increase
	2B.2	Moderate increase
	2B.3	Marked increase
Grade 3		**Neutrophils in epithelium**
Subgrades	3.0	None
	3.1	<5% Crypts involved
	3.2	<50% Crypts involved
	3.3	>50% Crypts involved
Grade 4		**Crypt destruction**
Subgrades	4.0	None
	4.1	Probable-local excess of neutrophils in part of crypt
	4.2	Probable-marked attenuation
	4.3	Unequivocal crypt destruction
Grade 5		**Erosion or ulceration**
Subgrades	5.0	No erosion, ulceration, or granulation tissue
	5.1	Recovering epithelium+ adjacent inflammation
	5.2	Probable erosion focally stripped
	5.3	Unequivocal erosion
	5.4	Ulcer or granulation tissue

Appendix 3 Patient flow chart P2-IMU-838-UC



CM concomitant medication, D = day, EC = exclusion criteria, EoI = end-of-induction (phase), EoM = end-of-maintenance (phase), IC = inclusion criteria, ICF = informed consent form, PK = pharmacokinetics, W = week, UC = ulcerative colitis.