**COVER PAGE**

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|---|---|
| **Official Title:** | A Double Blind, Randomized, Placebo-Controlled, Multicenter Phase IIa, Clinical Trial to Assess Efficacy and Safety of the Human Anti-CD38 Antibody felzartamab in IgA Nephropathy - IGNAZ |
| **NCT Number:** | NCT05065970 |
| **Document Date:** | 10 October 2022 |

# CLINICAL TRIAL PROTOCOL

## A Double Blind, Randomized, Placebo-Controlled, Multicenter Phase IIa, Clinical Trial to Assess Efficacy and Safety of the Human Anti-CD38 Antibody felzartamab in IgA Nephropathy - IGNAZ

| | |
|---|---|
| **Brief Description of Clinical Trial** | Randomized, placebo-controlled, multi-center, double-blind, proof of concept phase IIa trial and dose evaluation trial of felzartamab in IgAN |
| **Clinical Trial Protocol Name:** | IGNAZ |
| **Clinical Trial Phase:** | IIa |
| **Product Name:** | Felzartamab (MOR202) |
| **Sponsor:** | Human Immunology Biosciences, Inc. |
| **Sponsor's Address:** | SmartLabs<br>2 Tower Place<br>HIBio - 16th Floor<br>South San Francisco, CA 94080<br><br>USA |
| **Clinical Trial Protocol No.:** | MOR202C206 |
| **EudraCT No.:** | 2020-005054-19 |
| **IND No.:** | 142840 |
| **Protocol version:** | 4.1, 10 October 2022 |

**Sponsor Signatory:**

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I have reviewed this document
Signing Time: 10/25/2022 | 11:39:14 AM PDT
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10/25/2022

[redacted], MD
[redacted]

Date

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I have reviewed this document
Signing Time: 10/25/2022 | 9:39:18 AM PDT
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10/25/2022

[redacted], PhD
[redacted]

Date

**Medical Monitor Name and Contact Information:**

Provided separately in the Investigator Site File (ISF).

**Principle Investigator's Signature**

I agree to conduct the clinical trial in accordance with this clinical trial protocol, the ICH E6 Guideline for Good Clinical Practice (GCP), the principles which have their origin in the Declaration of Helsinki, and applicable local regulations, including the following:

- Personally conduct or supervise the investigation
- Ensure that an IRB/IEC, that complies with the requirements of GCP and local regulations, will be responsible for the initial and continuing review and approval of the clinical trial.
- Promptly report to the IRB/IEC (directly or through the sponsor) changes in the research activity, and new information that may adversely affect the safety of the patients or the conduct of the trial.
- Not implement any deviation from, or changes to the protocol without agreement by the sponsor and prior review and documented approval/ favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to patients
- Inform patients, that the investigational medicinal product is being used for investigational purposes, and ensure that the requirements relating to obtaining informed consent, including IRB/IEC review and approval thereof, are met.
- Report adverse events to the sponsor.
- Read and understand the information in the investigator's brochure.
- Ensure that sub-investigator(s) and other staff assisting in the conduct of the clinical trial are informed about their obligations in meeting this commitment.
- Maintain adequate and accurate records, provide direct access to those records for monitoring, audits and inspection, and allow any regulatory agency to inspect the trial site.

Signature: ---------- **Date:** ----------

*(DD, Mmm,YYYY)*

Printed Name: ----------

< Insert name and qualifications of the Investigator>

Address: ----------

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| DOCUMENT HISTORY | |
|---|---|
| **Document Version** | **Date** |
| *Original Protocol CTP v1.0* | *23-Nov-2020* |
| *Amended Protocol CTP v1.0 – SK 1.0* | *07-May-2021, South Korea only* |
| *Amended Protocol CTP v1.0 – JP 1.0* | *14-May-2021, Japan only* |
| *Amended Protocol CTP v1.0 - JP 2.0* | *17-Jun-2021, Japan only* |
| *Amended Protocol CTP v1.0 – CZ 1.0* | *28-Jun-2021, Czech Republic only* |
| *Amended Protocol CTP v1.0 – DE 1.0* | *13-Jul-2021, Germany, only* |
| *Amended Protocol CTP v2.0* | *01-Sep-2021* |
| *Amended Protocol CTP v3.0* | *01-Dec-2021* |
| *Amended Protocol CTP v4.0* | *17-Feb-2022* |

## Amended Protocol v4.1 (10 October 2022)

### Rationale for the Global Amendment

The Sponsor for the study was changed to Human Immunology Biosciences, Inc.

## Amended Protocol v4.0 (17-Feb-2022)

### Rationale for the Global Amendment

The study design was revised to allow competitive recruitment in all participating countries including Japan in global Part I whilst, at the same time provide flexibility in recruitment of Japanese patients in Part II, thus allowing assessment of PK and safety data in 8 Japanese patients. There is no change in the overall benefit-risk assessment.

A summary of changes included in this global protocol amendment is presented in the table below.

### Summary of changes due to flexible enrollment in Japan and other changes

| **Changes related to enrollment in Japan:** | | |
|---|---|---|
| **Section** | **Change(s)** | **Rationale** |
| Section 1.1 Trial design and Section 5 Trial design | Changes implemented to enable flexible enrollment in Japan across Part I and Part II | To ensure completion of competitive recruitment in global Part I for a timely Proof of Concept readout and to provide flexibility in recruitment of Japanese patients in global Part I or II |
| Section 1.1 Trial design Figure 1-1 | Update on Trial design figure | Visualization of flexible enrollment in Japan |
| Section 1.3 Dosing and Section 1.4 Trial population | Changes on dosing and trial population implemented to enable flexible enrollment in Japan | Update on number of patients in Japan in trial Part II |

| | | |
|---|---|---|
| Section 7.5.2 Method of treatment assignment | Clarify stratification in Part I based on country (Japan vs ex-Japan) | Update stratification procedure in Part I to ensure balanced assignment of patients in four treatment arms in Japan and countries outside Japan due to flexible enrollment in Japan |
| Section 10.1 Sample size determination and Section 10.2 Integrative analysis of dose and dosing regimens | Update on number of patients in Japan | Update on number of patients to be enrolled in Japan due to flexible enrollment |
| **Other changes to protocol** | | |
| [redacted] | [redacted] | [redacted] |
| Section 7.1 Treatments administered | Provide recommendation to the Investigator to consult Medical Monitor and Sponsor for an alternative premedication(s) in case of unavailability of any of the prespecified premedication | No availability of any protocol specified premedication [redacted] |

**Amended Protocol v3.0 (01-Dec-2021)**

**Rationale for the Amendment:**

An interim analysis (IA) at 3 months will be implemented to perform a Pharmacokinetic/[redacted](PK/[redacted]) analysis by evaluating the relationship between drug exposure and [redacted] The results of this IA will support the use of a further optimized dosing regimen for the future clinical development of felzartamab. No primary or secondary endpoints, except PK, will be analyzed at this 3-month IA.

An unblinded Sponsor team (Data Review Committee), which is independent of clinical trial team will be established to maintain the double-blind of clinical study team during and following the IA.

In addition, minor changes triggered by protocol template update are incorporated.

A summary of changes included in this global protocol amendment are presented in the table below.

**Summary of Changes**

| **Changes related to 3-month IA:** | | |
|---|---|---|
| **Section** | **Change(s)** | **Rationale** |
| Section 7.6 | An overview of procedures related to IA including unblinding procedures was included. | To include IA related procedures in the blinding section for ensuring blinded study team (internal/external) is not unblinded due the IA. |
| Section 10.3 | Timing of the 3-months PK/[redacted]IA was included. | To provide timing of the 3-months IA for completeness of the section. |
| Section 10.6.5 | IA section was added to describe timing, scope, and procedures related to 3-months PK [redacted]IA with no changes to the planned study design or conduct. | To describe timing, scope, and procedures related to 3-months PK/[redacted] IA. |
| **Other changes** | | |
| **Section** | **Change(s)** | **Rationale** |
| Section 1 | A summary of statistical analysis was included.<br>In addition, protocol title was added. | For completeness and in compliance with the new protocol template, protocol title and a summary of planned statistical analysis was added to the Protocol Synopsis section that may be used in clinical trial applications (CTAs) and submission to Ethics committees [ECs]). |
| Section 9.5.5 and Section 12.4 (Appendix 4) | Reporting of treatment error, misuse or abuse section was added. | As treatment errors and uses outside of the protocol is a safety concern and has the potential to harm to the patient, this section was included providing guidance on reporting of such events. |

[redacted]

| | | |
|---|---|---|
| Section 12.3 (Appendix 3) | Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines was added under Regulatory and ethical consideration.<br><br>For completeness or clarification minor updates were added to Appendix 3 | Addition of text on CIOMS in accordance with the new protocol template to reflect that the trial will be conducted in compliance with CIOMS International Ethical Guidelines.<br><br>Minor updates to the list of documents to be submitted to Ethics Committee; Clarification text on data protection i.e. patient data is pseudonymized limiting the risk of personal data security breaches. |
| Section 12.3 (Appendix 3) | Text on Quality tolerance limits (QTLs) was added. | In accordance with ICH GCP E6 (R2) guidelines, a description of regular review of QTL was added, which is important to identify systematic issues that can impact patient safety and/or reliability of study results. |

**Global Protocol Amendment - CTP v2.0 (01-Sep-2021)**

**Overall Rationale for the Amendment:**

The amendment is implemented primarily to incorporate changes requested by HA and to optimize management of IRRs. Detailed rationale are as follows:

- To implement selected changes requested by the German Competent Authority (PEI), the Czech Competent Authority (SUKL), the South Korean Health Authority (MFDS) and the Japanese Competent Authority (PMDA) on a global basis for all participating patients.

Note: changes for individual countries are denoted as “For Czech”, For “Germany”, For “South Korea” and “For Japan”, which apply to patients enrolled in the specific country only

- To optimize the prevention and management of infusion-related reactions through the implementation of additional pre-medication requirements, post-infusion monitoring requirements, and post-infusion medication recommendations for patients with a history of asthma or chronic obstructive pulmonary disease.
- Administrative changes, minor updates or correction of typos or clarifications etc. were added.

A summary of changes included in this global protocol amendment are presented in the table below.

| Section# and Name | Description of Changes |
|---|---|
| Section 1.1<br>Trial Design, Sections 1.3, 1.4, 10.1 and 10.2 updated | Added country specific (Japanese) open-label cohort to enroll 4 additional patients in M3 dosing arm (Part II)<br>Rationale: Based on PMDA consultation to allow enrollment for sufficient number of patients to evaluate safety and PK assessment in Japanese vs. non-Japanese patients treated with felzartamab |
| Section 1.2<br>Objectives and endpoints, Table 1.1 | Corrected Section numbers under Analysis column to reflect revised section numbering<br>3 month time point was added for ACR per schedule of activities<br>Rationale: Minor update/clarification |
| Section 1<br>Exclusion criteria | Revised Exclusion criterion no. 9 (i.e. minimum hemoglobin limit at screening changed from 80 to 90 g/L)<br>Rationale: Based on request by MFDS to exclude patients with severe anemia |
| Section 4, 5, and 6<br>Trial Objectives and Endpoints, Trial Design, Trial population | Added the specified sections from Synopsis to the protocol<br>Rationale: Following request from SUKL these sections were added to the protocol. |
| Section 7.1<br>Treatment administered | Implemented post infusion monitoring requirements, added additional pre-medication for prevention of IRRs, and recommendation of post infusion medication for patients with a history of asthma and chronic obstructive pulmonary disease<br>Rationale: To introduce additional measures to prevent IRRs. Incorporation of additional monitoring of patients after administration of IMP also requested by SUKL. |
| Section 7.1,<br>Table 7.1 | Revised the total volume to [redacted] in the table providing an example of infusion speeds; added reference to Drug Handling Manual for additional information related to infusion speed/administration; and provided additional clarification on flushing the infusion line after IMP dosing<br>Rationale: Clarification/minor update |
| Section 7.5.2<br>Method of Treatment Assignment | Added stratification information for the 4 Japanese patients enrolling in Global Study (Part I)<br>Rationale: Based on PMDA consultation to ascertain sufficient patients are dosed with felzartamab for comparing PK and safety in Japanese vs non-Japanese patients |
| Section 7.8<br>Management of other toxicity | Included guidance on monitoring patients with Elevated Liver Function Tests<br>Rationale: To provide additional guidance on management of liver toxicities requested by SUKL. [redacted] and is implemented to ensure prompt identification and evaluation of liver safety events. |
| Section 8.1<br>Discontinuation of treatment with IMP | Revised treatment discontinuation criterion to ensure that patient with [redacted] cannot continue receiving felzartamab.<br>Rationale: Change requested by PEI |

| | |
|---|---|
| Section 8.1 Discontinuation of treatment with IMP and Appendix 9 | Added criteria of [redacted] related to IMP and clinically significant [redacted] to the list of reasons for discontinuation from treatment. Added Appendix 9 to provide guidance on Monitoring Patients with Elevated Liver Function Tests<br>Rationale: To incorporate the two additional discontinuation criteria requested by SUKL. [redacted] and is implemented to ensure patient safety in the unexpected presence of [redacted] |
| Section 8.1 Discontinuation of treatment with IMP | Removed criteria of "use of prohibited treatment" to clarify that patients using prohibited treatment will be discontinued from the trial<br>Rationale: To clarify that patients using prohibited treatment should withdraw from the trial |
| Section 8.2 Withdrawal from Study | Clarified that a patient can be withdrawn from the study due to lack of efficacy<br>Rationale: Based on request by SUKL to clarify that a patient can be withdrawn from the study due to lack of efficacy |
| Section 10.1 sample size determination | Probability of success was re-calculated based on simulation.<br>Rationale: To make estimate of calculation more accurate |
| Section 10.3<br>Timing of statistical analysis | Clarified timing of analysis; Primary analysis will be conducted after all patients in Global Study (Part I) complete their 9-month visit or discontinued early. Final analysis will be conducted after all randomized patients in Global Study (Part I) and Japanese Cohort (Part II) have completed their last visit, or discontinued the trial earlier.<br>Rationale: Based on PMDA consultation to revise and clarify timing of analysis after inclusion of Japan Cohort |
| Section 10.4<br>Analysis population | Adding Japan population to facilitate further analysis on Japanese patients' safety and PK profile<br>Rationale: Based on PMDA consultation to define patient population for analysis on Japanese patient's safety and PK profile |
| Section 10.6.1.1 Primary endpoint | Updated analysis method for primary endpoint<br>Rationale: To utilize a more appropriate method of analysis considering potential differences in progression of disease in patients |
| Section 10.6.2.7<br>eGFR | Added description of eGFR under the statistical consideration section<br>Rationale: To clarify analysis method for secondary endpoint of eGFR |

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## List of tables



## List of figures

# 1 Synopsis

**Protocol Title**

A double blind, randomized, placebo-controlled, multicenter phase IIa, clinical trial to assess efficacy and safety of the human anti-CD38 antibody felzartamab in IgA Nephropathy – IGNAZ

## 1.1 Trial design

This randomized, placebo-controlled, multi-center, double-blind parallel-group phase IIa trial assesses the efficacy, safety and pharmacokinetic (PK)/[redacted] relationship of the human anti-CD38 antibody felzartamab in patients with IgA Nephropathy (IgAN) (Figure 1-1). It serves as a proof of concept and dose evaluation trial for felzartamab in patients with IgAN. The trial has 2 parts i.e. Part I (applicable to all countries including Japan) and Part II (Japanese Cohort – applicable to Japan). A total of 8 Japanese patients will be enrolled in Part I and/or Part II of the study.

**Global Study Part I:**

All patients will receive angiotensin-converting enzyme inhibitors (ACEi) and/or angiotensin receptor blockers (ARB) – the supportive standard of care therapy - throughout the trial. Patients will be randomized to receive one of 3 different dosing schedules of felzartamab (dosing arms M1, M2 or M3) or placebo. Overall, approximately 44 patients will be randomized in this trial with 11 patients per dosing arm (including placebo). Up to four patients from Japan can be enrolled during the double-blind part of the trial (Part I) and receive felzartamab (dosing arms M1, M2 or M3) or placebo.

**Japanese Cohort Part II (applicable to Japan only):**

Once 44 patients are randomized in Part I, the remaining Japanese patients will be enrolled in an open-label part II of the trial to achieve the target number of 8 Japanese patients in the trial in total. Patients in this open label part II will receive 9 doses of felzartamab according to M3 dosing schedule.

All patients will follow the clinical trial schedule (Section 2) consisting of a:

- Screening Phase (up to 6 weeks)
- Treatment Phase (6 months)
- Follow-up Phase (18 months)

Patients will attend 17 trial visits. A patient is considered to have completed the trial if s/he has completed all applicable phases of the trial.

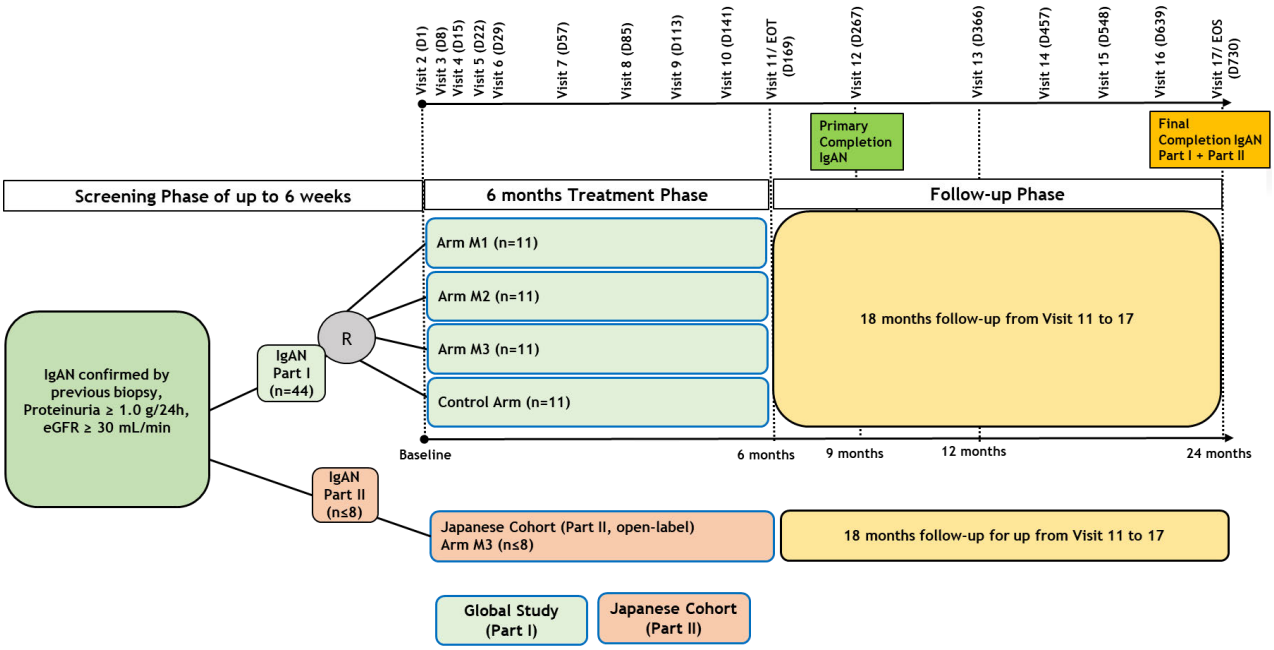


**Figure 1-1 Trial design MOR202C206 IGNAZ**

## 1.2 Objectives and endpoints

The study objectives and endpoints are presented below in Table 1-1, and efficacy parameters are defined in Section 9.2.

**Table 1-1 Objectives and endpoints**

| Objectives | Endpoints | Analysis |
|---|---|---|
| **Primary** | | 10.6.1 |
| • To assess the efficacy of felzartamab compared to placebo in patients with IgAN based on the change in urine protein to creatinine ratio (UPCR) at 9 months. | • Relative change in UPCR in 24h urine at 9 months compared to the reference proteinuria value in the felzartamab dose groups vs. placebo. | |
| **Secondary** | | 10.6.2, 10.6.4 |
| • To assess the relationship between exposure, safety, and efficacy in each of the three dose groups vs. placebo to support a decision for a dose in further trials | • Integrative analysis of several endpoints, please refer to Section 10.2 | |
| • To assess the efficacy of felzartamab compared to placebo in patients with IgAN based on the following: | | |
| ○ Change in UPCR at 3, 6, 12, 18 and 24 months. | • Relative change in UPCR in 24h urine at 3, 6, 12, 18 and 24 months compared to the reference proteinuria value in each felzartamab dose group vs. placebo. | |
| ○ Complete response (CR) at 3, 6, 9, 12, 18 and 24 months. | • CR at 3, 6, 9, 12, 18 and 24 months in each felzartamab dose group vs. placebo. | |
| ○ Proportion of patients with response at 3, 6, 9, 12, 18 and 24 months. | • Proportion of patients with response at 3, 6, 9, 12, 18 and 24 months in each felzartamab dose group vs. placebo. | |
| ○ Albumin-creatinine ratio (ACR) at 6, 9, 12, 18 and 24 months. | • ACR from 24 h urine at 3, 6, 9, 12, 18 and 24 months in each felzartamab dose group vs. placebo. | |
| ○ Duration of response. | • Duration of response in each felzartamab dose group vs. placebo. | |
| ○ Time to response. | • Time to response in each felzartamab dose group vs. placebo. | |

| Objectives | Endpoints | Analysis |
|---|---|---|
| • To assess the renal function of felzartamab compared to placebo in patients with IgAN. | • Renal function (determined by estimated glomerular filtration rate [eGFR] over time) in each felzartamab dose group vs. placebo. | |
| • To assess the safety of felzartamab in patients with IgAN. | • Frequency, incidence, seriousness, relatedness, and severity of treatment-emergent adverse events (TEAEs) across all treatment groups. | |
| • To assess the pharmacokinetic (PK) profile of felzartamab in patients with IgAN. | • Serum concentrations of felzartamab over time in each felzartamab dose group. | |
| • To investigate the potential immunogenicity of felzartamab in patients with IgAN. | • Formation of anti-drug antibodies (ADAs) over time in all groups | |
| [redacted] | | |

## 1.3 Dosing

Patients in the Part I will receive 9 infusions of either felzartamab or Placebo on Day 1, 8, 15, 22, 29, 57, 85, 113 and 141 according to Table 1-2.

All patients enrolling in the Japanese Cohort (Part II) will receive felzartamab treatment as per the dosing arm M3 and will receive 9 infusions of felzartamab on Day 1, 8, 15, 22, 29, 57, 85, 113 and 141.

**Table 1-2 Dosing Arms**

| Dosing arm | Felzartamab | Placebo |
|---|---|---|
| M1 | **2 Doses:** Day 1 and 15 | Day 8, 22, 29, 57, 85, 113 and141 |
| M2 | **5 Doses:** Day 1, 8, 15, 29 and 57 | Day 22, 85, 113 and141 |
| M3 | **9 Doses:** Day1, 8, 15, 22, 29, 57, 85, 113 and 141 | none |
| Control arm | none | Day 1, 8, 15, 22, 29, 57, 85, 113 and 141 |

[redacted]

## 1.4 Trial population

All patients will be screened for conformance with the following inclusion and exclusion criteria. The study will enroll approximately 44 patients with biopsy confirmed diagnosis of IgAN in the Part I and up to eight Japanese patients in the Japanese Cohort (Part II). The sponsor will not approve deviations (provide waivers) from eligibility criteria as this can have a negative impact on patient safety or the scientific integrity and regulatory acceptability of the clinical trial. *Parameters in italics will be tested at screening in the central laboratory*. Parameters not in italics will be determined locally.

### 1.4.1 Inclusion criteria

1. Patients ≥ 18 to ≤ 80 years (at date of signing the informed consent form [ICF]), but at least of legal age in the given country (For Czech Republic: ≥ 18 to ≤ 70 years).
2. Biopsy confirmed diagnosis of IgAN within the past 8 years prior to signature of the ICF
3. *Proteinuria at screening visit ≥ 1.0 g/d.*
4. Treatment with an angiotensin-converting enzyme inhibitor (ACEi) and/or angiotensin receptor blocker (ARB) at maximum doses or maximally tolerated doses for ≥ 3 months prior to date of informed consent and adequate blood pressure (BP) control (recommended BP is < 125 mm Hg systolic and < 75 mm Hg diastolic).
   In case a patient is intolerant to even a very low dose of either ACEi or ARB therapy, approval for participation in the trial has to be obtained from the Medical Monitor prior to randomization.
5. A female of childbearing potential (FCBP), defined in Appendix 5) is only eligible to participate if she is not pregnant, not breast feeding, and agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 3 months after the last dose of felzartamab.
   For Czech Republic and Germany: Sexually active male patients should at least use one method of contraception (as a minimum in form of a condom) during treatment and until 3 months after the last dose of felzartamab).
6. For South Korea: Patient vaccinated against Pneumococcus within the last 5 years prior to date of signing ICF (patients may be vaccinated to meet this criterion during screening; interval to first dose of felzartamab must be at least 14 days).

### 1.4.2 Exclusion criteria

Patients are excluded from the trial if any of the following criteria apply:

1. Secondary forms of IgAN, indicated by the presence of any other systemic disease potentially leading to IgA deposits (e.g. Lupus nephritis, Schönlein-Henoch purpura, ankylosing spondylitis, dermatitis herpetiformis, chronic liver disease, inflammatory bowel disease, celiac disease).
2. Severe renal impairment as defined by estimated GFR < 30 mL/min (using chronic kidney disease-epidemiology collaboration [CKD-EPI] formula, see Section 9.2) or the need for dialysis or renal transplant.
3. Rapidly progressive variant of IgAN, defined as eGFR loss by more than 30% per 3 months and not explained by changes in renin angiotensin system (RAS) blockade.
4. Minimal change variant of IgAN.
5. Concomitant other progressive glomerulonephritis or non-immunologic glomerular disease such as diabetic nephropathy.
6. Systemic immunosuppression (e.g. mycophenolate mofetil [MMF], cyclophosphamide, biologics like rituximab [RTX]), in particular corticosteroid therapy exceeding 20 mg/day prednisone-equivalent (see Appendix 8) for more than 7 consecutive days within 180 days prior to signing ICF.
7. Any previous treatment with an anti-CD38 antibody.
8. Body mass index (BMI) > 35 kg/m$^2$.
9. Hemoglobin < 90 g/L

10. Thrombocytopenia: Platelets < 100.0 x $10^9$/L.
11. Neutropenia: Neutrophils < 1.5 x $10^9$/L.
12. Leukopenia: Leukocytes < 3.0 x $10^9$/L.
13. Diabetes mellitus type 1.
14. Diabetes mellitus type 2: Patients with type 2 diabetes mellitus may only enter the clinical trial if a kidney biopsy performed within 6 months prior to signing ICF shows IgAN without evidence of diabetic nephropathy and their disease is controlled, such as:
    a. *Glycated hemoglobin (HbA1c) < 8.0% or < 64 mmoL/mol.*
    b. No diabetic retinopathy known.
    c. No peripheral neuropathy known.
15. Significant uncontrolled cardiovascular disease (including arterial or venous thrombotic or embolic events) or cardiac insufficiency (New York Heart Association [NYHA] class IV) as judged by the investigator.
16. Clinically significant findings on a 12-lead electrocardiogram (ECG) as determined by the investigator at screening.
17. History of significant cerebrovascular disease or sensory or motor neuropathy of toxicity ≥ grade 3.
18. *Aspartate aminotransferase or alanine aminotransferase >1.5 x ULN, alkaline phosphatase >3.0 x ULN.*
19. Known or suspected hypersensitivity to felzartamab and its excipients (L-histidine, sucrose, polysorbate 20).
20. *Serologic markers positive for HIV or history of HIV, hepatitis C (patients with positive anti-hepatitis C virus [anti-HCV] antibody but negative HCV RNA polymerase chain reaction [PCR] can enroll) or active or latent hepatitis B (patients with positive hepatitis B surface antigen [HBsAg] are excluded). For patients with positive hepatitis B core antibody [anti-HBc], hepatitis B virus (HBV) DNA test by PCR must be non-detectable to enroll).*
21. Any malignancy within 5 years prior to screening start, with the exception of adequately treated *in situ* carcinoma of the cervix uteri, basal or squamous cell carcinoma or other non-melanomatous skin cancer.
22. Treatment within 5 terminal half-lives (if known) or within the last 30 days prior to Visit 2, whatever is longer) with investigational drugs.
23. Any active infection (viral, fungal, bacterial) requiring systemic therapy.
24. For Japan: Tonsillectomy within 6 months prior to the Screening Visit.
25. For South Korea: Patients with ≤ 4.0 g/L of serum immunoglobulin (Hypogammaglobulinemia; Patients may receive immunoglobulin substitution to meet the criterion).

### 1.4.3 Lifestyle restrictions

No restrictions pertaining to meals and dietary restrictions are mandated by this trial protocol. In general, patients with kidney diseases are advised to follow a low sodium diet and abstain from nicotine.

### 1.4.4 Statistical Analysis

The primary endpoint of relative decrease in UPCR will be estimated based on an MMRM (mixed effects model for repeated measure) model. The secondary and [redacted] endpoints will be evaluated using descriptive statistics.

The primary analysis will be performed after all randomized patients in the Global Study (Part I) have completed their 9 month-visit or discontinued the trial earlier.

The final analysis of all endpoints will be performed after all randomized patients (both Part I and Part II) have completed their last visit, or discontinued the trial earlier.

An interim analysis of only key [redacted] and PK data is planned when at least 80% of patients have completed 3-months visit (Day 85 visit).

# 2 Schedule of activities

**Table 2-1 Schedule of activities**

| Study Visit | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11/ EOT | 12 | 13 | 14 | 15 | 16 | 17/ EOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **-42 to 0** | **1** | **8** | **15** | **22** | **29** | **57** | **85** | **113** | **141** | **169** | **267** | **366** | **457** | **548** | **639** | **730** |
| **Window (days)** | | | **±2** | **±3** | **±3** | **±7** | **±7** | **±7** | **±14** | **±14** | **±14** | **±14** | **±14** | **±14** | **±14** | **±14** | **±14** |
| **EVENT** | **SCR** | **BL** | | | | | | **3m visit** | | | **6m visit** | **9m visit** | **12m visit** | **15m visit** | **18m visit** | **21m visit** | **24m visit** |
| Informed consent | X | | | | | | | | | | | | | | | | |
| Medical history (IgAN history)/demography/ disease therapy history/ allergies | X | | | | | | | | | | | | | | | | |
| Prior medication | X | | | | | | | | | | | | | | | | |
| Concomitant medication | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Height | X | | | | | | | | | | | | | | | | |
| Body weight | X | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X | | X | | | | X |
| Kidney biopsy[1] | X[1] | | | | | | | | | | | | | | | | |
| Randomization | | X | | | | | | | | | | | | | | | |
| Blood typing and screening for irregular antibodies | | X | | | | | | | | | | | | | | | |
| *Serum pregnancy (in FCBP)* | X | | | | | | | | | | X | X | | | | | |
| Urine pregnancy stick test (in FCBP) | | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | | | | | | | |
| *Serum tests for hepatitis, HIV* | X | X[6,7] | | | | X[6] | X[6] | X[6] | X[6] | X[6] | X[6,7] | X[6] | X[6] | | | | X[6] |

| **Study Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11/ EOT** | **12** | **13** | **14** | **15** | **16** | **17/ EOS** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **-42 to 0** | **1** | **8** | **15** | **22** | **29** | **57** | **85** | **113** | **141** | **169** | **267** | **366** | **457** | **548** | **639** | **730** |
| **Window (days)** | | | **±2** | **±3** | **±3** | **±7** | **±7** | **±7** | **±14** | **±14** | **±14** | **±14** | **±14** | **±14** | **±14** | **±14** | **±14** |
| **EVENT** | **SCR** | **BL** | | | | | | **3m visit** | | | **6m visit** | **9m visit** | **12m visit** | **15m visit** | **18m visit** | **21m visit** | **24m visit** |
| *HbA1c in patients with diabetes mellitus II* | X | | | | | | | | | | | | | | | | |
| Dosing felzartamab /Placebo | | X | X | X | X | X | X | X | X | X | | | | | | | |
| Adverse event recording | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| 12-lead ECG (in triplicate) | X | X[3] | X[3] | | | | | X[3] | | | X | | X | | | | X |
| Physical examination | X | X | | | | | | X | | | X | | X | | | | X |
| Vital signs | X | X[3] | X[3] | X[3] | X[3] | X[3] | X[3] | X[3] | X[3] | X[3] | X | X | X | X | X | X | X |
| Urine analysis | X | X[2] | | | | X[2] | | X[2] | | X[2] | X | | X | | X | | X |
| Blood count | X | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X | X | X | X | X | X | X |
| *Serum biochemistry* [redacted] | X | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X[2] | X | X | X | X | X | X | X |
| *Lipid panel* | | X | | | | | | | | | X | | X | | | | X |
| *Anti-drug antibodies (ADA) sampling* | | X[2] | | | | X[2] | X[2] | X[2] | | | X | X | X | X | X | | X |
| *24 h urine collection for proteinuria, UPCR and ACR ratio, $Na^+$* | X | X[4] | | | | | | X[2] | | | X | X | X | X | X | X | X |
| *PK sampling felzartamab (serum)* | | X[3] | X[2] | X[3] | | X[3] | X[2] | X[2] | X[2] | X[2] | X | X | | | | | X[5] |
| [redacted] | | | | | | | | | | | | | | | | | |

| Study Visit | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11/ EOT | 12 | 13 | 14 | 15 | 16 | 17/ EOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | -42 to 0 | 1 | 8 | 15 | 22 | 29 | 57 | 85 | 113 | 141 | 169 | 267 | 366 | 457 | 548 | 639 | 730 |
| **Window (days)** | | | ±2 | ±3 | ±3 | ±7 | ±7 | ±7 | ±14 | ±14 | ±14 | ±14 | ±14 | ±14 | ±14 | ±14 | ±14 |
| **EVENT** | SCR | BL | | | | | | 3m visit | | | 6m visit | 9m visit | 12m visit | 15m visit | 18m visit | 21m visit | 24m visit |
| [redacted] | | | | | | | | | | | | | | | | | |

ACR: albumin to creatinine ratio; BL: baseline; ECG: electrocardiogram; EOS: end of study; EOT: end of treatment; FCBP = female of childbearing potential; HIV: human immunodeficiency virus; PK: pharmacokinetics; SCR: screening; UPCR: urine protein to creatinine ratio.

1: Mandatory for all patients if not done within the last 8 years prior to signing ICF, mandatory for patients with diabetes mellitus type II if not done within the last 6 months before start of screening. The results of all kidney biopsies performed (taken as routine clinical care or stipulated by this trial protocol) will be recorded in the eCRF.

2: Predose if felzartamab/Placebo dosing occurs on the same day.

3: Predose and 30 min after end of infusion. ECG should be performed in triplicate.

4: 24 h urine collection at baseline to be completed before felzartamab/Placebo infusion.

5: For end of study visit only

6: Only hepatitis B virus (HBV) DNA test by PCR for patients with positive hepatitis B core antibody [anti-HBc] at screening.

7: Only HCV RNA PCR for patients with positive anti hepatitis C virus [anti-HCV] antibody at screening.

The minimum interval between Visit 10 and Visit 11 is 28 days.

Patients missing a treatment visit within the specified visit window for reasons other than toxicity will get the next dose at the next scheduled visit and thus receive less than the planned 9 IMP applications.

*Parameters in italics are measured in a central laboratory.*

# 3 Introduction

## 3.1 Background

Felzartamab is a recombinant purified human immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that binds to human CD38. It is in clinical development for multiple myeloma (MM) and is now being further developed for autoimmune kidney diseases such as IgA nephropathy (IgAN) and antibody-positive membranous nephropathy (MN) as well as other autoimmune diseases. Additional background information is provided in the felzartamab Investigator's Brochure.

### 3.1.1 Preclinical background information

### 3.1.2 Nonclinical pharmacology

CD38, the target molecule of felzartamab, is a type II glycoprotein and exhibits ecto-enzymatic activity as NAD+-glycohydrolase/adenosine di-phosphate (ADP)-ribosyl cyclase (Deaglio 2008). CD38 is known to be expressed on plasma cells/plasmablasts as well as on myeloid progenitor cells, lymphocytes (especially natural killer cells), neutrophil granulocytes, erythrocytes and platelets (Fernandez 1998, Torti 1998, Kramer 1995).

Plasma cells/plasmablasts show the highest expression of CD38 as compared to other CD38+ cell types. For these cells, a dose dependent and highly potent antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) mediated cell lysis or respective phagocytosis were observed in *ex vivo* assays using primary cells (MOR202L004, MOR202L060, MOR202L081).

Regarding myeloid progenitor cells, *in vitro* secondary pharmacodynamic studies did not indicate a felzartamab-mediated decrease of colony formation (MOR202L003). Furthermore, no lytic potential of felzartamab on either human erythrocytes, lymphocytes or neutrophil granulocytes (MOR202L038, MOR202L037) and no stimulatory or inhibitory effects on aggregation of human platelets were observed in human whole blood *ex vivo* assays (MOR202L039).

In *in vitro* ADCC assays using purified human natural killer (NK) cells, high concentrations of felzartamab slightly reduced the number of NK cells (MOR202L046). On human peripheral blood mononuclear cells (PBMCs) no agonistic effects were observed following antigen binding or antigen crosslinking. felzartamab caused a weak dose-related release of interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα) similar to the immunoglobulin G1 (IgG1) isotype control suggesting an antigen-independent effect. No induction of interleukin-2 (IL-2) or interferon-gamma (IFN-γ) was observed. PBMC proliferation was not affected (MOR202L006).

### 3.1.3 Non-clinical pharmacokinetics

Nonclinical pharmacokinetic (PK) studies in male NMRI mice and Han Wistar rats showed a dose proportional increase in exposure (i.e. AUC) between 1 and 10 mg/kg following a single i.v. dose. The observed volume of distribution was slightly higher than the extracellular fluid and the mean terminal half-life ranged between 9.5 and 12 days. In both species felzartamab demonstrated a typical PK profile of a human IgG1 antibody without any target-mediated drug disposition effects (MOR202P014, MOR202P013).

In marmoset monkeys, plasma concentrations of felzartamab declined in a biphasic manner within the dose range studied (i.e. 3 to 50 mg/kg administered i.v. once weekly for 12 weeks). Accumulation of felzartamab following repeated administration was only observed at the lower dose level of 3 mg/kg/dose studied with an increase in exposure of up to 1.9- and 1.7-fold in males and females, respectively. Systemic exposure based upon mean $AUC_{0\text{-}168h}$ and $C_{max}$ increased in an approximately dose-proportional manner. The mean elimination half-life ($t_{1/2}$) was similar across the dose range investigated ranging from 2.3 to 3.2 days at Week 12 (MOR202P007).

### 3.1.4 Toxicology

Based on the high sequence identity between marmoset monkey and human CD38 protein, the comparable binding affinity and expression levels of CD38 on blood cells as well as the similar activity to induce ADCC by PBMCs, the marmoset monkey was selected as the relevant species for the non-clinical safety assessment of felzartamab.

A 12-week repeat-dose toxicity study was conducted in the marmoset monkey with weekly i.v. administration of felzartamab at 0, 3, 12, or 50 mg/kg. Systemic exposure to felzartamab increased in an approximately dose proportional manner in both males and females. Mild platelet reduction and slight changes in the hematopoietic system at all tested dose levels (from 3 mg/kg onwards) were observed. A reversibility of these findings was noted at the end of the recovery period. At 12 and 50 mg/kg, the unscheduled death of one male animal each was observed. The subacute intestinal inflammation observed in one male at 12 mg/kg and the intussusception in one male at 50 mg/kg were regarded as spontaneous events, which were probably not related to the test item administration (MOR202P007).

A chronic toxicity study in the marmoset monkey is currently ongoing. The objective of this study is to evaluate the toxicity profile of felzartamab in male and female marmoset monkeys following twice weekly i.v. administration of 0, 3, 15, or 75 mg/kg for 26 weeks and to assess the reversibility of findings, if any, during a 13-week recovery period, in order to support further chronic use of felzartamab in non-oncology indications. The final report for this study is expected to be available by March 2021. Preliminary data from the 26-week treatment phase do not show any new, unforeseen findings (as compared to the completed 12-week toxicity study). Drug-related effects are restricted to reduced platelet counts in animals of all felzartamab-treated groups (3, 15, and 75 mg/kg/occasion). Importantly, the reduced platelet counts did not correlate with clinical findings such as hemorrhage or with prolonged blood clotting times. Thus, no new safety signals were detected that could constitute causes of safety concern for this planned clinical trial MOR202C206.

## 3.2 Clinical background information

Felzartamab has been administered in the first-in-human (FiH) trial MOR202C101 in 91 patients with MM. This trial was a combined dose escalation and dose confirmation study with a maximum dose of 16 mg/kg administered i.v. once weekly (including a loading dose on Cycle 1, Day 4). Felzartamab was applied either as a single agent or in combination with dexamethasone (DEX), lenalidomide/DEX or pomalidomide/DEX. Responding patients were treated up to 3 years. The maximum tolerated dose (MTD) was not reached in this trial and the recommended dose was defined at 16 mg/kg once weekly (i.e. the highest dose tested). As of 30-Nov-2019, 21 patients were treated at this dose level for more than 6 months (13 patients for more than 12 months and 9

patients for more than 24 months). In addition, a partner company of the sponsor has treated 29 MM patients in China in 2 ongoing Phase II/III clinical trials (as of 20-Apr-2020).

Two early trials in PLA2R antibody positive MN assessing the safety and efficacy of felzartamab have been started recently (M-PLACE: MOR202C103 and New-PLACE: MOR202C205).

### 3.2.1 Clinical pharmacokinetics and immunogenicity

The PK of felzartamab administered i.v. to MM patients has been well characterized by a 2-compartment population PK model. The volume of distribution was found to be increased at lower felzartamab doses most likely reflecting the impact of target-mediated drug disposition (TMDD) effects.

So far, anti-drug antibody (ADA) samples from 85 MM patients with a treatment duration up to a maximum of 3 years have been analyzed. No ADA has been detected to date.

### 3.2.2 Clinical safety

The most commonly reported treatment-emergent adverse events (TEAEs) in the FiH trial in MM (MOR202C101, 91 patients, data cut off: 27-Mar-2020) were hematological AEs, including leukocytopenia (53 patients, 58%), neutropenia (44 patients, 48%), lymphopenia (43 patients, 47%), anemia (37 patients, 41%), and thrombocytopenia (35 patients, 38%). The combination drugs for MM used in the FiH study are intrinsically myelosuppressive when administered as single agents. Anti-CD38 mAbs may further deteriorate cytopenias induced by such background therapy. Cytopenic effects are well known and manageable via treatment with colony stimulating factors and blood transfusions.

Binding of felzartamab to cells expressing high levels of CD38 is expected to induce effector mediated cell lysis. For patients treated with felzartamab or felzartamab/DEX in the FiH study, a median reduction from baseline in anti-tetanus toxoid antibodies of 17% (-61% to +26%) (N = 44) after 2 weeks and 31% (-82% to +66%) (N = 31) after 6 weeks was observed. Consequently, an impairment of the adaptive immune response may be expected. Patients may have an increased susceptibility to intracellular and extracellular pathogens and infections.

Non-hematological TEAEs related to felzartamab reported in more than 5% of patients overall in the FiH trial (MOR202C101, 91 patients, data cut off: 27-Mar-2020) were fatigue (20 patients, 22%), infusion-related reactions (IRRs, 18 patients, 20%), respiratory tract infections (12 patients, 13%), diarrhea (11 patients, 12%), upper respiratory tract infection (10 patients, 11%), nausea (9 patients, 10%), hypokalemia (9 patients, 10%), pneumonia (6 patients, 7%), C-reactive protein increased (6 patients, 7%), cough (6 patients, 7%), urinary tract infections (5 patients, 5%), constipation (5 patients, 5%), hypophosphatemia (5 patients, 5%), pyrexia (5 patients, 5%), nasopharyngitis (5 patients, 5%), and oral herpes (5 patients, 5%).

Further details are provided in the felzartamab Investigator`s Brochure.

### 3.2.3 Clinical efficacy

In the MM studies, felzartamab has demonstrated clinical activity comparable to other CD38 targeting agents in MM in terms of overall response rates (Raab 2020). Anti-tetanus titer data indicate that felzartamab has the potential to deplete normal antibody secreting plasma cells.

Felzartamab therefore represents a potential treatment option for antibody or auto-antibody driven immune diseases such as IgAN.

## 3.3 Other anti-CD38 antibodies

Daratumumab and isatuximab have been approved for treating subgroups of MM patients. TAK-079 is currently in mid-stage clinical development for the treatment of MM, systemic lupus erythematosus, myasthenia gravis and immune thrombocytopenic purpura.

## 3.4 Scientific rationale for trial

IgA nephropathy (IgAN) is the most prevalent chronic glomerular disease worldwide. IgA nephropathy can affect all ages but is most common in the second and third decades of life. Eighty percent of patients are aged 16-35 years at the time of diagnosis. The condition is uncommon in children younger than 10 years (Salim 2020). The mean age in clinical trial ranges from 32 – 43 years (Manno 2009, Fellstroem 2017, Lv 2017, Rauen 2020). The disease derives its name from deposits of immunoglobulin A (IgA) in the mesangium. The exact explanation for the accumulation of IgA is currently unknown. Research currently focuses on abnormalities of the IgA1 molecule. IgA1 is one of the two immunoglobulin subclasses (the other is IgD) that is O-glycosylated on a number of serine and threonine residues in a special proline-rich hinge region. Aberrant glycosylation of IgA appears to lead to polymerization of the IgA molecules in certain tissues, especially the glomerular mesangium (Maverakis 2015). About 25–30% of patients progress to end-stage renal disease (ESRD) within 20–25 years of presentation (KDIGO 2020). Major risk factors for progression to ESRD are persistent proteinuria, hypertension, and reduced glomerular filtration rate (GFR) (Fellstroem 2017, Wyatt 2013, Berthoux 2012, Reich 2007, Zhang 2015).

Management of IgAN is focused on non-immunosuppressive strategies, so-called supportive care, to slow the rate of progression of the disease: rigorous blood pressure control, optimal inhibition of the renin angiotensin system (RAS), and lifestyle modification, including weight reduction, exercise, smoking cessation, and dietary sodium restriction (KDIGO 2020).

Multiple observational registry studies demonstrate that sustained proteinuria is the most powerful predictor of long-term kidney outcome (KDIGO 2020). Regardless of the nature of the intervention, reduction in proteinuria in observational studies is independently associated with improved kidney outcome. A recent trial-level analysis of data from RCTs confirms an association between treatment effects on proteinuria and effects on kidney survival (composite of the time to doubling of SCr, ESKD, or death, Thompson 2019), thereby establishing reduction in proteinuria as a valid surrogate marker of improved outcome in IgAN. Typical target for proteinuria reduction in these trials was < 1 g/d. Thus, reduction of proteinuria to this level is a reasonable target for interventions in patients with IgAN who remain at high risk of progressive CKD despite maximal supportive care. Reduction of proteinuria < 1 g/d is also considered a surrogate marker of improved kidney outcome in IgAN as described by the latest draft of the KDIGO 2020 guidelines.

For patients with persistent proteinuria of more than 1 g/day and GFR greater than 50 mL/min per 1.73 m² despite 6 months of optimized RAS blockade KDIGO guidelines suggest consideration of 6 months of treatment with high-dose systemic corticosteroids (KDIGO 2020). However, clinical benefit is not established (KDIGO 2020) and use of high-dose systemic corticosteroids is

associated with increased risks of adverse events (AEs) and sequelae such as serious infections, hypertension, weight gain, diabetes, and osteoporosis (Lv 2017, Manno 2009, Pozzi 2016). Systemic corticosteroids should be given with extreme caution or avoided entirely in patients with GFR less than 30 mL/min, diabetes mellitus, obesity, latent infections (e.g. viral hepatitis, tuberculosis), secondary disease (e.g. cirrhosis), active peptic ulceration or uncontrolled psychiatric disease.

Clinical Trials with azathioprine, calcineurin inhibitors and rituximab have not provided documented evidence of efficacy (Pozzi 2016, Rauen 2020; Lafayette 2017, KDIGO 2020). Cyclophosphamide may provide benefit in the setting of rapidly progressive IgAN (KDIGO 2020). Mycophenolate mofetil reportedly reduced proteinuria and stabilized eGFR in Chinese patients (Tang 2005), but not in Caucasian patients (Frisch 2005, Maes 2004).

In summary, standard of care for IgAN is currently rigorous blood pressure control by optimal inhibition of the renin angiotensin system (RAS), but not immunosuppressive therapy (IST). Therefore, specific treatment options with a more favorable risk-benefit profile are needed for patients with IgAN.

## 3.5 Justification for dose

Dosing in this trial is based on the results of the FiH trial in MM (MOR202C101) as well as a PK/[redacted] modeling approach (Raab 2020, Jarutat 2018). [redacted] 16 mg/kg dose (i.e. the recommended dose in the FiH study MOR202C101):

Dose and dosing schedules for the current trial were selected to enable drug evaluation within the expected therapeutic exposure range. The selection was based on a minimal physiologically-based PK model (mPBPK model) implementing drug distribution concepts as previously published (Niederalt 2018, Cao 2014). Assuming that the main target cells (i.e. CD38 high expressing plasma cells) are primarily located in compartments with limited drug distribution (e.g. the bone marrow), and considering a certain time range for CD38 turnover, the established mPBPK model predicts a

median target occupancy between 26% to 100% at the anticipated doses (MOR202L087). These target occupancy values are expected to lead to a direct reduction in plasma cells. The higher drug exposure during the initial 4 weeks (weekly or every 2 weeks dosing) was selected to efficiently reduce the number of target cells at the beginning of treatment. Thereafter, no further dosing (M1) or a significantly reduced drug exposure is proposed to maintain the reduction of plasma cells over time (M2 and M3: dosing every 4 weeks for a further 2 or 5 months, respectively).

To simulate the expected exposure in the current clinical trial, a population-based PK [redacted] model has been established based on the results of the FiH trial. The model takes into account the different CD38 expression levels between MM and antibody-positive membranous nephropathy patients.

As a result, the highest exposure values ($C_{max}$ and AUC) for the current study were predicted for patients with a [redacted] (i.e. dosing arm M3 with 9 administrations of felzartamab over a 24-week period). The expected exposure values were compared to the same parameters as observed in the chronic toxicity study of felzartamab in marmoset monkeys (MOR202P027) as well as the FiH trial MOR202C101.

Results of the chronic toxicity study were generated over a 26-week treatment period (i.e. covering the complete treatment period as planned for the current trial in IgAN patients) with an approximately 4-fold higher AUC value and 3-fold higher $C_{max}$ value at the highest dose tested than expected for the current trial in humans.

Also when comparing to the initial 24-week treatment period of the FiH trial, similar AUC and $C_{max}$ values are expected for the current trial (i.e. FiH trial MOR202C101 with 1.1-fold higher AUC and 0.7-fold lower $C_{max}$ values). It should be noted that in the FiH study no MTD was observed and the recommended dose for further studies was the highest dose and dosing frequency tested (i.e. 16 mg/kg administered once weekly). Overall, felzartamab was considered to be safe and well tolerated in this FiH study.

For assessing further potential risk factors of felzartamab exposure on patient safety, a detailed exposure vs. clinical safety analysis was performed using the FiH trial data (MOR202L080). In this analysis, results for all evaluable patients on AUC, $C_{max}$ and average $C_{trough}$ levels were divided into quartiles and compared with relevant safety parameters, such as number of TEAEs per treatment year and number of infections per treatment year. In this analysis, no increase in safety events was observed with increasing felzartamab exposure.

## 3.6 Benefit/risk assessment

### 3.6.1 Expected benefits

Current standard therapy of patients with the autoimmune kidney disease IgA Nephritis (IgAN) includes symptomatic therapy with ACE and ARBs. However, 25-30% of patients progress to end-stage renal disease within 25-30 years. Persistent proteinuria, hypertension and reduced GFR despite treatment with ACE and/or ARBs are robust prognostic factors of renal disease progression to end stage renal failure. These patients are the target population in this clinical trial (see inclusion criteria above).

No approved therapy is available for these patients. KDIGO guidelines suggest to consider immunosuppressive treatment with high dose corticosteroids (KDIGO 2020). However, clinical

benefit of high dose steroids is not proven and comes with substantial side effects (KDIGO 2020, Lv 2017)

Currently used treatments for IgAN have not significantly improved the outcomes when employed in randomized clinical trials:

Optimized supportive care is used for the management of IgAN patients. Additional treatment with corticosteroids is to be considered for IgAN patients that progress during ACEi and ARB treatment. According to the results of the TESTING clinical trial (Lv 2017), corticosteroids use was associated with an increased risk of serious adverse events, primarily infections. Although the results were consistent with potential improvement of renal function, definitive conclusions about treatment benefit could not be made, owing to early termination of the trial. Thus, the use of corticosteroids in IgAN is subject of an ongoing controversial discussion. Furthermore, COVID-19 patients receiving corticosteroids have an increased risk for of hospitalization (Gianfresco 2020). Patients participating in this IGNAZ trial would not be exposed to continuous corticosteroid therapy, therefore eliminating the risk of serious adverse events associated with continuous corticosteroid use.

Clinical trials with other treatment options such as azathioprine, calcineurin inhibitors and rituximab have not demonstrated evidence of efficacy (Pozzi 2016, Rauen 2020; Lafayette 2017, KDIGO 2020).

CD38+ plasma cells, including long-lived plasma cells, are deemed to be the main source of pathogenic Gd-IgA1 and its related auto-antibodies in IgAN. Therefore immunosuppression by targeting CD38 is expected to have a profound effect in IgAN.

### 3.6.2 Potential risks

For an overview of the most common TEAEs reported for felzartamab in the FiH trial in patients with MM, please refer to Section 3.2.2. Further details on the safety profile of felzartamab are provided in the Investigator`s Brochure.

For patients requiring blood transfusions the presence of high levels of therapeutic anti-CD38 antibodies can result in interference with blood bank serologic tests (Oostendorp 2015, MOR202L069) and thereby may cause delays in issuing red blood cell (RBC) units. To minimize these delays, patients must be typed and screened for the eventual presence of irregular antibodies before the first administration of felzartamab. In case of a blood transfusion, the responsible transfusion centers must be notified about the potential interference of anti-CD38 antibodies with indirect anti-globulin tests.

If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given per local blood bank practices. Red blood cell genotyping is not impacted by anti-CD38 antibodies and may be performed at any time.

Further technical guidance to mitigate this interference is published in the AABB bulletin #1602 (AABB) and literature (Chapuy 2016, Chapuy 2015).

Hepatitis B reactivation has been reported for other CD38 antibodies (for mitigation see Section 7.3).

Immunosuppression is an important part of the management of autoimmune diseases. As with all treatments, immunosuppressants are prescribed based on a balance of harm and benefit. This balance needs to be evaluated in the context of the coronavirus disease 2019 (COVID-19) pandemic, with a focus on severe acute respiratory syndrome coronavirus-2 (SARS- CoV-2). Currently, COVID-19 information is evolving, incomplete, and constantly changing (Robinson, 2020):

The following summarizes information about the risks for patients suffering from autoimmune diseases in terms of SARS-CoV-2 infection. Of note, autoimmune diseases are not listed as being associated with an increased risk according to CDC guidance (CDC 2020).

- In patients with rheumatoid arthritis treatment with prednisone at a dose of 10 mg increased the risk of hospitalization due to SARS-CoV-2 infection (adjusted odds ratio 2.05, 95% Confidence interval 1.06-3.96),while patients treated with a tumor necrosis factor inhibitor demonstrated a decreased the risk of hospitalization (adjusted odds ratio 0.4, 95% Confidence interval 0.19-0.81) (Gianfresco 2020).
- Another study comparing 52 patients with rheumatic disease infected with COVID-19, including 39 taking immunosuppressants, with 104 matched COVID-19 positive controls showed no significant difference between the groups in hospitalization, length of stay in hospital, oxygen therapy or death. However, patients with rheumatic disease were more likely to require intensive care or ventilation (D`Silva 2020).
- In a series of 525 patients with inflammatory bowel disease, poorer outcomes with COVID-19 were associated with increasing age, comorbidities and administration of systemic glucocorticoids. Tumor necrosis factor inhibitors were not associated with an increased risk of a poor outcome (Brenner 2020)
- Annapureddy (2020) evaluated 132.401 electronic medical records in TriNetX of patients with rheumatoid arthritis, juvenile arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and ulcerative colitis based on ICD-10 coding for the period starting 6 months before January 20, 2020 (first reported case of COVID-19 in the USA) and examined the rates of COVID-19 infection, hospitalizations, need for critical care services, intubations, and death among these patients. Patients were divided into two groups based on whether they were taking immunosuppressive medications (T cell co-stimulation blockade drugs and inhibitors of TNF, IL-6, IL-17, IL-12/23 kinase; 26.671 records) or not (105.730 records). The odds of acquiring COVID-19 were not significantly different and there is no significant age difference between the groups. Interestingly, the group on immunosuppressive medications had significantly lower odds of hospitalizations and intensive care unit (ICU) admissions than the group not on immunosuppressive medications.

Since CD38+ plasma cells, including long-lived plasma cells, are deemed to be the main source of pathogenic Gd-IgA1 and its related auto-antibodies in this disease, CD38 targeting could lead to more profound effects in a field where additional treatment options are definitely needed.

The procedures and interventions for the IGNAZ study follow clinical practice and thus do not impose additional risks to the patients.

### 3.6.3 Benefit/risk conclusion

It is expected that apart from COVID-19 related risks, other potential risks to patients of employing felzartamab in this clinical trial as described above will be adequately controlled by the design of this trial (e.g. by the inclusion and exclusion criteria) as well as by frequent monitoring for adverse events. The risk of interference with blood bank serologic tests can be mitigated by taking the measures described above.

The COVID-19 pandemic is having a significant global impact, and the unprecedented situation is rapidly evolving. Regulatory bodies such as European Medicines Agency and Food and Drug Administration have provided guidance and recommendations for conduct of clinical trials during the COVID-19 pandemic without compromising the participant's safety, rights and well-being (FDA 2020, EMA 2020). The situation will change as a consequence of public health measures and seasonal influences. Any decision making will be based on the most current information. The investigator should therefore carefully consider the risk to potential study participants of becoming infected during the period of this clinical trial or the risks of enrolling participants determined as being part of a risk-group for COVID 19, before starting therapy in this trial. Decisions depend on local epidemiological factors such as the numbers of active cases and the level of community transmission rate. The local situation at the institution needs to be carefully considered as well (Robinson 2020, Anders 2020).

In summary, current information on COVID-19 related risk is inconclusive and does not allow final conclusions. The sponsor will monitor the risks as the pandemic evolves and react appropriately to growing insights.

The potential benefit of treatment with felzartamab appears to outweigh the potential risks for the patients participating in this trial.

# 4 Objectives and endpoints

The trial objectives and endpoints are presented below.

| Objectives | Endpoints | Analysis |
|---|---|---|
| **Primary** | | 10.6.1 |
| • To assess the efficacy of felzartamab compared to placebo in patients with IgAN based on the change in urine protein to creatinine ratio (UPCR) at 9 months. | • Relative change in UPCR in 24h urine at 9 months compared to the reference proteinuria value in the felzartamab dose groups vs. placebo. | |
| **Secondary** | | 10.6.2, 10.6.4 |
| • To assess the relationship between exposure, safety, and efficacy in each of the three dose groups vs. placebo to support a decision for a dose in further trials | • Integrative analysis of several endpoints, please refer to Section 10.2 | |
| • To assess the efficacy of felzartamab compared to placebo in patients with IgAN based on the following: | | |
| ○ Change in UPCR at 3, 6, 12, 18 and 24 months. | • Relative change in UPCR in 24h urine at 3, 6, 12, 18 and 24 months compared to the reference proteinuria value in each felzartamab dose group vs. placebo. | |
| ○ Complete response (CR) at 3, 6, 9, 12, 18 and 24 months. | • CR at 3, 6, 9, 12, 18 and 24 months in each felzartamab dose group vs. placebo. | |
| ○ Proportion of patients with response at 3, 6, 9, 12, 18 and 24 months. | • Proportion of patients with response at 3, 6, 9, 12, 18 and 24 months in each felzartamab dose group vs. placebo. | |
| ○ Albumin-creatinine ratio (ACR) at 6, 9, 12, 18 and 24 months. | • ACR from 24 h urine at 3, 6, 9, 12, 18 and 24 months in each felzartamab dose group vs. placebo. | |
| ○ Duration of response. | • Duration of response in each felzartamab dose group vs. placebo. | |
| ○ Time to response. | • Time to response in each felzartamab dose group vs. placebo. | |
| • To assess the renal function of felzartamab compared to placebo in patients with IgAN. | • Renal function (determined by estimated glomerular filtration rate [eGFR] over time) in each felzartamab dose group vs. placebo. | |
| • To assess the safety of felzartamab in patients with IgAN. | • Frequency, incidence, seriousness, relatedness, and severity of treatment-emergent adverse events (TEAEs) across all treatment groups. | |
| • To assess the pharmacokinetic (PK) profile of felzartamab in patients with IgAN. | • Serum concentrations of felzartamab over time in each felzartamab dose group. | |
| • To investigate the potential immunogenicity of felzartamab in patients with IgAN | • Formation of anti-drug antibodies (ADAs) over time in all groups | |

| Objectives | Endpoints | Analysis |
|---|---|---|
| [redacted] | | |

# 5 Trial design

This randomized, placebo-controlled, multi-center, double-blind parallel-group phase IIa trial assesses the efficacy, safety and pharmacokinetic (PK)/[redacted] relationship of the human anti-CD38 antibody felzartamab in patients with IgA Nephropathy (IgAN) (Figure 1-1). It serves as a proof of concept and dose evaluation trial for felzartamab in patients with IgAN. The trial has 2 parts i.e. Part I (applicable to all countries including Japan) and Part II (Japanese Cohort – applicable to Japan). A total of 8 Japanese patients will be enrolled in Part I and/or Part II of the study.

**Part I:**

All patients will receive angiotensin-converting enzyme inhibitors (ACEi) and/or angiotensin receptor blockers (ARB) – the supportive standard of care therapy - throughout the trial. Patients will be randomized to receive one of 3 different dosing schedules of felzartamab (dosing arms M1, M2 or M3) or placebo. Overall, approximately 44 patients will be randomized in this trial with 11 patients per dosing arm (including placebo). Up to four patients from Japan can be enrolled during the double-blind part of the trial (Part I) and receive felzartamab (dosing arms M1, M2 or M3) or placebo.

**Japanese Cohort Part II (applicable to Japan):**

Once 44 patients are randomized in Part I, the remaining Japanese patients will be enrolled in an open-label part of the trial to achieve the target number of 8 Japanese patients in the trial in total. Patients in this open label part will receive 9 doses of felzartamab according to M3 dosing schedule.

All patients will follow the clinical trial schedule (Section 2) consisting of a:

- Screening Phase (up to 6 weeks)
- Treatment Phase (6 months)
- Follow-up Phase (18 months)

Patients will attend 17 trial visits. A patient is considered to have completed the trial if s/he has completed all applicable phases of the trial.

The rationale for the trial is presented in Section 3.

# 6 Trial population

The trial population is described below and in Section 1.

All patients will be screened for conformance with the following inclusion and exclusion criteria. The study will enroll approximately 44 patients with biopsy confirmed diagnosis of IgAN. The sponsor will not approve deviations (provide waivers) from eligibility criteria as this can have a negative impact on patient safety or the scientific integrity and regulatory acceptability of the clinical trial. *Parameters in italics will be tested at screening in the central laboratory*. Parameters not in italics will be determined locally.

### 6.1.1 Inclusion criteria

1. Patients ≥ 18 to ≤ 80 years (at date of signing the informed consent form [ICF]), but at least of legal age in the given country (For Czech Republic: ≥ 18 to ≤ 70 years).
2. Biopsy confirmed diagnosis of IgAN within the past 8 years prior to signature of the ICF
3. *Proteinuria at screening visit ≥ 1.0 g/d.*
4. Treatment with an angiotensin-converting enzyme inhibitor (ACEi) and/or angiotensin receptor blocker (ARB) at maximum doses or maximally tolerated doses for ≥ 3 months prior to date of informed consent and adequate blood pressure (BP) control (recommended BP is < 125 mm Hg systolic and < 75 mm Hg diastolic).
   In case a patient is intolerant to even a very low dose of either ACEi or ARB therapy, approval for participation in the trial has to be obtained from the Medical Monitor prior to randomization.
5. A female of childbearing potential (FCBP), defined in Appendix 5) is only eligible to participate if she is not pregnant, not breast feeding, and agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 3 months after the last dose of felzartamab.
   For Czech Republic and Germany: Sexually active male patients should at least use one method of contraception (as a minimum in form of a condom) during treatment and until 3 months after the last dose of felzartamab).
6. For South Korea: Patient vaccinated against Pneumococcus within the last 5 years prior to date of signing ICF (patients may be vaccinated to meet this criterion during screening; interval to first dose of felzartamab must be at least 14 days).

### 6.1.2 Exclusion criteria

Patients are excluded from the trial if any of the following criteria apply:

1. Secondary forms of IgAN, indicated by the presence of any other systemic disease potentially leading to IgA deposits (e.g. Lupus nephritis, Schönlein-Henoch purpura, ankylosing spondylitis, dermatitis herpetiformis, chronic liver disease, inflammatory bowel disease, celiac disease).
2. Severe renal impairment as defined by estimated GFR < 30 mL/min (using chronic kidney disease-epidemiology collaboration [CKD-EPI] formula, see Section 9.2) or the need for dialysis or renal transplant.
3. Rapidly progressive variant of IgAN, defined as eGFR loss by more than 30% per 3 months and not explained by changes in renin angiotensin system (RAS) blockade.
4. Minimal change variant of IgAN.
5. Concomitant other progressive glomerulonephritis or non-immunologic glomerular disease such as diabetic nephropathy.
6. Systemic immunosuppression (e.g. mycophenolate mofetil [MMF], cyclophosphamide, biologics like rituximab [RTX]), in particular corticosteroid therapy exceeding 20 mg/day prednisone-equivalent (see Appendix 8) for more than 7 consecutive days within 180 days prior to signing ICF.
7. Any previous treatment with an anti-CD38 antibody.
8. Body mass index (BMI) > 35 kg/m$^2$.
9. Hemoglobin < 90 g/L.

10. Thrombocytopenia: Platelets < 100.0 x $10^9$/L.
11. Neutropenia: Neutrophils < 1.5 x $10^9$/L.
12. Leukopenia: Leukocytes < 3.0 x $10^9$/L.
13. Diabetes mellitus type 1.
14. Diabetes mellitus type 2: Patients with type 2 diabetes mellitus may only enter the clinical trial if a kidney biopsy performed within 6 months prior to signing ICF shows IgAN without evidence of diabetic nephropathy and their disease is controlled, such as:
    a. *Glycated hemoglobin (HbA1c) < 8.0% or < 64 mmoL/mol.*
    b. No diabetic retinopathy known.
    c. No peripheral neuropathy known.
15. Significant uncontrolled cardiovascular disease (including arterial or venous thrombotic or embolic events) or cardiac insufficiency (New York Heart Association [NYHA] class IV) as judged by the investigator.
16. Clinically significant findings on a 12-lead electrocardiogram (ECG) as determined by the investigator at screening.
17. History of significant cerebrovascular disease or sensory or motor neuropathy of toxicity ≥ grade 3.
18. *Aspartate aminotransferase or alanine aminotransferase >1.5 x ULN, alkaline phosphatase >3.0 x ULN.*
19. Known or suspected hypersensitivity to felzartamab and its excipients (L-histidine, sucrose, polysorbate 20).
20. *Serologic markers positive for HIV or history of HIV, hepatitis C (patients with positive anti-hepatitis C virus [anti-HCV] antibody but negative HCV RNA polymerase chain reaction [PCR] can enroll) or active or latent hepatitis B (patients with positive hepatitis B surface antigen [HBsAg] are excluded). For patients with positive hepatitis B core antibody [anti-HBc], hepatitis B virus (HBV) DNA test by PCR must be non-detectable to enroll).*
21. Any malignancy within 5 years prior to screening start, with the exception of adequately treated *in situ* carcinoma of the cervix uteri, basal or squamous cell carcinoma or other non-melanomatous skin cancer.
22. Treatment within 5 terminal half-lives (if known) or within the last 30 days prior to Visit 2, whatever is longer) with investigational drugs.
23. Any active infection (viral, fungal, bacterial) requiring systemic therapy.
24. For Japan: Tonsillectomy within 6 months prior to the Screening Visit.
25. For South Korea: Patients with ≤ 4.0 g/L of serum immunoglobulin (Hypogammaglobulinemia; Patients may receive immunoglobulin substitution to meet the criterion).

## 6.2 Screen failures

Screen failures are defined as patients who consent to participate in a clinical trial but are not subsequently randomized. Information on demography, reason(s) for screening failure, eligibility criteria, and any serious adverse event (SAE) will be collected for such patients. Individuals who do not meet the criteria for participation in this trial may be re-screened once at the discretion of the investigator if:

- Patient previously failed to be eligible due to events e.g. planned surgery, pathological laboratory test result that has resolved or is no longer applicable.
- Patient previously failed screening but has become eligible for the trial based on a change in the inclusion and exclusion criteria as a result of a protocol amendment.
- Patient was successfully screened but could not start treatment within the screening phase.

Note: A patient should only be re-screened if there is a clear indication that the patient may be eligible according to the currently valid trial protocol.

If previous screening activities were discontinued and enrolment did not occur, these procedures should be implemented:

- The patient will receive a new patient number.
- A new electronic case report form (eCRF) will be completed.
- The patient will be documented as re-screened in the source documents.

A patient with an abnormal laboratory value in the screening phase may have one repeat test at the discretion of the investigator to confirm that the abnormality is not the result of a sampling error or laboratory error. Where a patient recalls a transient episode that may explain an abnormal laboratory value at screening (e.g. minor infection, symptoms suggestive of gall stones, heavy exercise), it is reasonable to follow up with the patient until the laboratory value returns to normal.

# 7 Study Treatments

[redacted]

[redacted]

## 7.2 Prior and concomitant therapy

### 7.2.1 Prior therapy

Prior therapy will be recorded in the eCRF as follows:

- Prior medications/non-drug procedures given for IgAN within the past 5 years prior to signing ICF.
- All prior immunosuppressive medications within the past 5 years prior to signing ICF.
- All other medications and therapies (including non-drug procedures) taken by/administered to the patient within 30 days prior to signing the ICF.

The entry must include the dose, regimen, route of administration, indication, and dates of use (start, end).

### 7.2.2 Concomitant therapy

Patients may take the following concomitant medications unless they fall under prohibited therapies listed in Section 7.4:

- medications used at baseline.
- medications that are medically indicated as standard of care for the treatment of symptoms and intercurrent illnesses.
- therapy to mitigate side effects of the trial medication as clinically indicated illnesses.
- best supportive care as per institutional guidelines including but not limited to prophylaxis and treatment of complications of IST (e.g. thrombotic and thromboembolic, viral, bacterial or opportunistic infection, hyperlipidemia, hypogammaglobulinemia).

Patients on a sodium-glucose co-transporter-2 (SGLT-2) inhibitor at the time of randomization may continue with their treatment, but no such therapy can be initiated during the trial.

The Investigator must instruct the patient not to take any additional medication (including over-the-counter products) during the trial without prior consultation.

Investigators must document all medication and other therapy (including non-drug procedures) taken by/administered to the patient during the entire course of the trial including the screening and the follow-up phase. The entry must include the dose, regimen, route of administration, indication, and dates of use (start, end).

Patients must not take part in any other interventional clinical trial during this clinical trial with non-approved medical products.

## 7.3 Prophylaxis and Management of Hepatitis B Reactivation

Patients in countries where prophylactic anti-viral medication for hepatitis B reactivation is standard of care may be treated prophylactically. Patients with occult HBV infection, defined as negative HBsAg and positive total HBcAb and negative HBV DNA, are eligible and must undergo ongoing HBV DNA testing (irrespective of prophylactic treatment) as described in the schedule of activities (see Section 2). If HBV-DNA becomes detectable during treatment with IMP, patients should be treated accordingly. A physician experienced in the treatment of hepatitis B should be consulted.

## 7.4 Prohibited therapy: Immunosuppressive therapies

The use of any ISTs other than felzartamab is **prohibited** during the entire trial. This includes but is not limited to chemotherapeutic agents (including alkylating agents), immunomodulators, and calcineurin inhibitors (e.g. cyclosporine, tacrolimus).

Patients in need of oral or parenteral high dose corticosteroid therapy (> 20 mg of prednisone per day or equivalent doses of other steroid medications – see Appendix 8) continuously for more than 7 days for non-renal indications may continue being treated with felzartamab, but will be excluded from the Per Protocol Analysis Set.

## 7.5 Further details for treatment

### 7.5.1 Dose modification

No dose modification of felzartamab is planned for this trial.

### 7.5.2 Method of treatment assignment

Once the investigator requests randomization, the Medical Monitor will confirm the eligibility of the patient as per the Medical Monitoring Plan. The patient will then be centrally assigned to randomized trial treatment (dose schedules M1, M2, M3 or placebo) using an Interactive Response Technology (IRT). Patients in Part I will be stratified based on their country of enrollment (Japan vs ex-Japan) and randomized to ensure a balanced distribution of patients in each of the four dosing arms (M1, M2, M3, and placebo).

The patients enrolling in open-label Japanese Cohort (Part II) will receive felzartamab treatment as per dosing arm M3.

### 7.5.3 Preparation and handling of trial treatment

[redacted] (rounding of values will be performed as described in Section 9.1.1). [redacted]

All IMP must be stored in a secure, environmentally controlled (2-8°C), and monitored (manual or automated) area with access limited to authorized site staff.

Site staff must confirm that appropriate temperature conditions have been maintained during transit for all IMP.

The site is responsible for IMP and record maintenance (i.e., receipt, inventory, accountability, reconciliation, and final disposition records).

The date and time of each dose administered in the clinic will be recorded in the source documents and in the eCRF.

Further guidance and information on the preparation and handling of the IMP are provided in the Drug Handling Manual.

## 7.6 Blinding

The Global Study: Part I is a randomized, double-blind clinical trial. The patient, investigator, clinical site staff, sponsor and the entire clinical study processing team will remain blinded to treatment assignment. Only site staff (pharmacist and/or other appropriate qualified staff) who manage IMP will be unblinded to enable IMP preparation according to the patient's assigned randomization number. The placebo in this study will be infusion of 0.9% sodium infusion solution.

The blind can be broken (via IRT) only if the investigator deems it necessary for the safe treatment of a patient. The investigator is encouraged to discuss considerations to break the blind with the Clinical Research Organization (CRO) Medical Monitor or the sponsor, whenever possible. However, the responsibility to break the treatment code in an emergency resides solely with the investigator.

If the investigator breaks the blind during the course of the clinical trial, the patient must discontinue the trial treatment (see Section 8.1). Time and reason for breaking the blind will be documented in the eCRF.

Unblinding of suspected unexpected serious adverse reactions (SUSARs) and distribution of unblinded information will be kept at minimum and according to applicable regulations. Details will be outlined in the Safety Management Plan (SMP) for the trial, including the description of unblinded personnel.

Any analysis and aggregate reporting of unblinded data before the database lock for the primary analysis and unblinding of the trial will be performed according to the SMP or Statistical Analysis Plan (SAP) or PK/[redacted]Data Analysis Plan by a separate team from the trial. No unblinded patient level data will be supplied to site before final data base lock.

For the IA, unblinding procedures, communication of the IA results, and timepoint at which blinded study team will be informed about the results are described in an Unblinding Charter (e.g. Data Review Committee Charter). This charter includes a list of all unblinded members (names, roles and responsibilities) who will receive, analyze and/or review the data in scope of the 3-months IA.

If required, auditors will have access to unblinded trial treatment records at the site at Quality Assurance audits.

The Japanese Cohort (Part II) is open-label.

## 7.7 Management of infusion-related reactions

IRR, CRS and allergic reaction will be defined according to the NCI-CTCAE, version 5.0 (or higher) (Table 7-2).

**Table 7-2 Definition of IRR, CRS and allergic reaction NCI-CTCAE Version 5.0**

| AE | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **Allergic reaction** | Systemic intervention not indicated | Oral intervention indicated | Bronchospasm; hospitalization indicated for clinical sequelae; i.v. intervention indicated | Life-threatening consequences; urgent intervention indicated |
| **CRS** | Fever with or without consti-tutional symptoms | Hypotension responding to fluids; hypoxia responding to <40% O2* | Hypotension managed with one pressor; hypoxia requiring ≥ 40% O2* | Life-threatening consequences; urgent intervention indicated |
| **IRR** | Mild transient reaction; infusion interruption not indicated; intervention not indicated | Therapy or infusion interrup-tion indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours | Prolonged (i.e. not rapidly responsive to symptomatic medication, brief interruption of infusion, or both); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. | Life-threatening consequences; urgent intervention indicated |

Abbreviations: CRS=cytokine release syndrome; IRR=infusion-related reaction; IV=intravenous; NSAIDs=non-steroidal anti-inflammatories. *Applied e.g. via breathing mask

If a patient presents with a [redacted]

- The infusion should be [redacted]
- The patient should receive appropriate treatment with [redacted] as clinically indicated.
- Once the [redacted] according to investigator assessment, the [redacted] at an [redacted] If, after [redacted] the patient's [redacted] and vital signs are [redacted] the infusion rate may be [redacted] to the baseline rate.

If a patient who developed a [redacted] receives further infusions of felzartamab/placebo, then [redacted] should be given [redacted] the trial.

If a patient presents with [redacted]

- The infusion should be [redacted] and [redacted] from the patient.
- The patient must receive appropriate treatment with an [redacted] and, if necessary, further medications [redacted] as clinically indicated.
- Patient must not receive any further IMP and must permanently discontinue treatment; however, the patient should enter the trial follow-up phase (see Section 8.1).

## 7.8 Management of other toxicity

Prior to administration of any dose of felzartamab, patients should exhibit [redacted]

[redacted] meeting the eligibility criteria. In addition, they should not have an active infection requiring systemic therapy.

[redacted] felzartamab administration should be interrupted until [redacted] For any other clinically significant adverse drug reaction ≥ CTC grade 3, felzartamab administration should be interrupted until the toxicity has resolved to CTC grade 2 or better. Patients will miss doses (see Section 8.3). For additional guidance on management of clinically significant elevation of [redacted] please refer to Appendix 9.

# 8 Discontinuation/withdrawal criteria

## 8.1 Discontinuation of treatment with IMP

Patients must be discontinued from treatment with the IMP due to:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Other unacceptable toxicity or TEAE, as determined by the investigator
- Pregnancy
- Withdrawal of patient consent
- Unblinding by the investigator

At the time of treatment discontinuation, data as per the EOT visit need to be collected. An EOT visit must be performed not earlier than 28 days after the last IMP administration. Afterwards patients will be followed up with visit 12 and onwards as per the schedule of activities (see Section 2).

## 8.2 Withdrawal from the trial

A patient may withdraw from the trial at any time at his/her own request.

Patients using prohibited treatment (see Section 7.4) must be discontinued from the trial.

Patients experiencing lack of efficacy as determined by the treating investigator.

Patients may be withdrawn from the trial due to COVID-19 (see Section 9.9).

At trial discontinuation, data as per the EOS visit schedule need to be collected (see Section 2). If the patient discontinues before EOT, the data for the EOT visit should be collected (preferably 28 days after last IMP administration).

If the patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the trial, s/he may request destruction of any samples taken and not tested, and the investigator must document this in the site trial records.

## 8.3 Missing treatments

Patients missing a treatment visit within the specified visit window will get the next dose at the next scheduled treatment visit. Thus, such patients would receive less than the planned IMP applications.

## 8.4 Lost to follow-up

If a patient fails to return to the clinic for a required trial visit, the site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned schedule of activities and ascertain whether or not the patient wishes to and/or should continue in the trial.

Before a patient is deemed lost to follow up, site staff must make every effort to regain contact with the patient. These attempts should be documented in the patient's source document.

If attempts are not successful, s/he will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.

# 9 Trial assessments and procedures

Trial procedures and their timing are summarized in the schedule of activities (see Section 2). Adherence to the trial design requirements, including those specified in the schedule of activities, is essential and required for trial conduct. Protocol waivers or exemptions are not allowed.

Toxicity and symptoms for AE reporting and medical history are graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (NCI-CTCAE 5.0) throughout this Clinical Trial Protocol unless otherwise stated. A copy will be provided in the Investigator Site File.

The investigator must conduct and report all screening procedures in the source data and eCRF. He/she must review the data, confirm that the patient fulfills the eligibility criteria in the eCRF and request randomization.

The investigator may pre-screen patients for trial inclusion and exclusion on the basis of pre-existing data or initial contact. Only routine and/or non-trial specific assessments are allowed.

## 9.1 General assessments

### 9.1.1 Demographic and baseline characteristics

Year of birth/age, gender, race/ethnicity (where allowed), and height (in centimeter without decimals) will be recorded. Body weight will be recorded in kg without decimals (with first decimal rounding in case of higher precision scales, e.g. 67.4 rounded to 67; 67.5 rounded to 68) wearing light indoor, daytime clothing with no shoes.

Disease history, including date of diagnosis of IgAN, prior biopsies, prior medications, allergies and hypersensitivities and other relevant medical and surgical history will be recorded.

### 9.1.2 Kidney biopsy

The results of all kidney biopsies performed (taken as routine clinical care or stipulated by this trial protocol) during the entire trial will be recorded in the eCRF including MEST-C score (see Appendix 7). Biopsies are performed as per institutional practice and assessed locally. Leftover biopsy specimen will be shipped to the central lab for central assessment.

### 9.1.3 Prior and concomitant medication

Recording requirements are described in Section 7.2.1 and Section 7.2.2.

### 9.1.4 Pregnancy testing

Pregnancy testing is described in Section 9.3.6 and Appendix 5.

## 9.2 Efficacy assessments

The planned time points for all efficacy assessments are provided in the schedule of activities (see Section 2). The efficacy objectives and endpoints for this trial are presented in Table 1-1.

Efficacy parameters, which are defined in Table 9-1, are based on analyses performed by the central laboratory (see Appendix 2 for details).

**Table 9-1 Efficacy parameters**

| Efficacy parameter | Definition |
|---|---|
| Proteinuria assessment | Proteinuria changes are reflected by the reduction of proteinuria as measured by UPCR. They will be evaluated as a continuous variable. The reference proteinuria value before start of treatment is defined as the mean of the values determined at screening and prior to baseline (visit 2) predose (UPCR from 24h urine). |
| Complete Response (CR) | Reduction of proteinuria to less than 0.3 g/g UPCR, serum albumin within the reference range of the central laboratory and stable eGFR (at least 80% of value at baseline visit) |
| Response | Reduction of proteinuria to below 0.6 g/g (UPCR) and stable eGFR (at least 80% of value at baseline visit), but not CR. |
| Duration of response | Date of 1st observation of progressive disease minus date of 1st observation of response+1 day |
| Progressive disease | Decrease of eGFR by more than 30% of baseline eGFR, or increase in urine protein: creatinine ratio (UPCR) by more than 50% from baseline value in non-responding patients or more than 25% over nadir in responding patients |
| Time to CR | Determined as date of 1st observation of CR minus date of randomization + 1 day |
| Time to Response | Determined as date of 1st observation of Response minus date of randomization +1 day |

| Efficacy parameter | Definition |
|---|---|
| Estimated glomerular filtration rate (eGFR) | eGFR is be calculated as per the chronic kidney disease epidemiology collaboration (CKD-EPI) equation (Levey 2007, Levey 2009):<br>eGFR = $141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa,1)^{-1.209} \times 0.993^{Age} \times 1.018$[if female]$\times 1.159$ [if black]<br>where:<br>– Scr is serum creatinine in µmol/L,<br>– κ is 61.9 for females and 79.6 for males,<br>– α is -0.329 for females and -0.411 for males,<br>min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1 estimating glomerular filtration rate (eGFR) as a measure of kidney function |

Proteinuria and UPCR will be determined from 24-hour urine samples. Patients will be given supplies for collection of a 24-hour urine sample at screening, and will return with the collected sample within the screening phase. For other visits, the sample will be collected 24 hours immediately prior to the visit.

Patients who forget to collect this sample **prior to** the baseline visit must not be dosed but must start a 24-hour urine sample at the same visit day and return it at the rescheduled baseline visit.

Patients who forget to collect this sample prior to a visit **after** the baseline visit should start a 24-hour urine sample at the same visit day and return it the next working day.

If the collected urine does not contain at least 5 mg creatinine/kg/day for females and 6 mg creatinine/kg/day for males, urine collection needs to be repeated immediately without undue delay.

## 9.3 Adverse events and serious adverse events

The investigator is responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remains responsible for following up AEs that are serious, considered related to the IMP or trial procedures, or that cause the patient to discontinue the IMP (see Section 8.1). The definitions of AEs and SAEs can be found in Appendix 4. Adverse Events of Special Interest (AESIs) are defined in Section 9.3.5.

### 9.3.1 Time period and frequency for collecting AE and SAE information

All SAEs and AEs will be collected from the signing of the ICF until EOS at the time points specified in the schedule of activities (see Section 2).

All SAEs and AESIs will be recorded and reported to the sponsor or designee immediately, and in no circumstance should this exceed 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of these being available. Investigators are not obligated to actively seek AEs or SAEs after conclusion of the trial participation. However, if the investigator learns of any SAE, including a death, at any time after a patient has finished trial participation, and the investigator considers the event to be reasonably related to the IMP or trial participation, the investigator must promptly notify the sponsor.

### 9.3.2 Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports is described in Appendix 4.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AEs.

### 9.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs, and AESIs (as defined in Section 9.3.5) will be followed-up until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 8.4). For further information on follow-up procedures see Appendix 4.

### 9.3.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of an IMP under clinical investigation are met.

Immediate safety concerns should be discussed with the sponsor or sponsor's designee promptly upon occurrence or awareness to determine if the patient should continue or discontinue trial treatment.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IMP under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary. An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure, and will notify the IRB/IEC if appropriate according to local requirements.

[redacted]

[redacted] Section 9.3.4).

[redacted]

### 9.3.6 Pregnancy

Details of all pregnancies in female patients and female partners of male patients will be collected after the start of IMP and until 3 months after the last dose of felzartamab.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

## 9.4 Treatment of overdose

In this clinical trial, an overdose of felzartamab is defined as a dose exceeding [redacted] of the planned dose. The sponsor does not recommend specific treatment for overdose of felzartamab.

In the event of an overdose, the investigator should:

- Discontinue the infusion immediately.
- Contact the Medical Monitor immediately (refer to the Investigator Site File).
- Closely monitor the patient for any AE/SAE/laboratory abnormalities for 24 hours and treat accordingly.
- Obtain a serum sample for PK analysis within 2 hours after end of infusion.
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF/study documentation. Overdose with clinical symptoms will be reported as AE (non-serious or serious) in accordance with Appendix 4.

The investigator will decide on dose interruptions or modifications in consultation with the Medical Monitor based on the clinical evaluation of the patient.

## 9.5 Other safety assessments

Planned time points for all safety assessments are provided in the schedule of activities (Section 2).

### 9.5.1 Physical examinations

A complete physical examination, must be performed according to the best standards of local medical practice at the time points outlined in the schedule of activities (Section 2). It includes as a minimum, assessment of the following organ systems: general appearance; head, eyes, ears, nose,

and throat; chest and lungs; heart; vascular; abdomen; musculoskeletal; skin; lymph nodes; and neurological.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

### 9.5.2 Vital signs

Pulse rate (beats per minute [bpm]), respiratory rate (respirations per minute [rpm]), systolic and diastolic blood pressure (mmHg) and body temperature will be assessed. Type of body temperature assessment will be recorded (oral, tympanic, rectal, axillary, skin, temporal artery).

Blood pressure and pulse measurements will be assessed in a semi-supine position after 5 minutes rest in a quiet setting with an automated device. Manual measurement will be used only if an automated device is not available. The same position should be used each time vital signs are measured for a given patient. Blood pressure should be measured from the arm contralateral to the site of trial drug administration.

At certain time points specified in the schedule of activities (Section 2) pre- and post-dose measurements have to be collected. The actual time of vital sign measurements should be accurately documented.

### 9.5.3 Electrocardiograms

Twelve-lead ECGs will be conducted at the time points outlined in the schedule of activities (Section 2) in successive triplicates with the patient being relaxed (ideally before other assessments, e.g. blood draws) after the patient has been supine for at least 5 minutes. The ECG machine automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. In case of any abnormality the investigator should ensure proper local cardiological evaluation which needs to be recorded in eCRF. Any ECG finding that is judged by the investigator as a potentially clinically significant change (worsening) compared with a baseline value will be considered an AE, recorded on the source documentation and transcribed onto the CRF, and monitored as described in Appendix 4.

### 9.5.4 Clinical laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the timing and frequency in the schedule of activities (Section 2). Actual dates and times of all sampling will be recorded in the eCRF.

The maximum amount of blood collected from each patient over the entire duration of the trial (25 months) including any extra assessments will not exceed 600 mL (Section 2). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Blood typing and all hematology assessments will be performed at the local laboratory at individual sites. All other protocol-specified laboratory parameters will be analyzed in central laboratories under the supervision of the sponsor (for details please see Schedule of activities [Section 2] and Appendix 2). Details of sample handling and shipment instructions are provided in the laboratory manual.

#### 9.5.4.1 Clinical safety laboratory assessments

The investigator must review the laboratory data and record any clinically significant and/or ≥ grade 3 changes from baseline occurring during the trial in the AE section of the eCRF. Clinically significant abnormal laboratory findings are those which have a genuine, noticeable effect on the daily life of a patient and are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.

All laboratory tests during participation in the trial or within 28 days after the last dose of IMP recorded as AE should be repeated in the same laboratory until the values return to normal or baseline or are no longer considered clinically significant by the investigator and Medical Monitor. The investigator must record these data as unscheduled visit. If such values do not return to normal/baseline within a reasonable time period, the etiology should be identified, and the sponsor notified.

Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations. They must be entered in the eCRF if performed in the context of AEs.

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the investigator (e.g., SAE or AE), then the results must be recorded in the eCRF in addition to documenting the respective (S)AE. The laboratory reports must be filed with the source documents.

### 9.5.5 Reporting of medication error, misuse or abuse

A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to harm the patient**.** Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information. Abuse refers to persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.

Study medication errors and uses outside as directed in the protocol, including misuse or abuse, will be recorded as protocol deviations. Any symptoms or signs associated with medication error, misuse or abuse should be reported as AEs in accordance with Section 9.3.

## 9.6 Pharmacokinetics

Blood and [redacted] samples will be collected for measurement of felzartamab concentrations as specified in the schedule of activities (Section 2) (PK samples felzartamab serum and [redacted]).

## 9.7 Immunogenicity assessments

Blood samples will be collected for measurement of anti-felzartamab antibodies in the serum (ADA samples; analyses comprises ADA screening, ADA confirmation and ADA titer determination).

[redacted]

## 9.9 Possible Changes in conduct of trial due to COVID-19

The safety and well-being of patients and site staff is of paramount importance during the COVID-19 pandemic. Measures will be implemented during the trial to reduce the chance that IMP will be administered to patients who are infected with SARS-CoV-2 and to maintain the integrity of the data.

The trial sites will maintain and follow, at a minimum, COVID-19 risk mitigation procedures as per regional and local guidelines and/or laws.

Every reasonable effort should be made to ensure that the patients which have been dosed continue on trial per protocol; however, if a patient cannot visit the site after the baseline visit due to self-quarantine, local restrictions, or illness due to COVID-19, the site personnel may conduct a virtual visit/tele visit. This will be limited to two non-sequential visits in the treatment phase (i.e. after visit 2 and before visit 11). If a patient misses or is expected to miss more than one sequential clinic visit due to COVID-19, the investigator must contact the medical monitor to discuss continuation of treatment with IMP. They must discuss the local situation before making a final decision.

The impact of COVID-19 pandemic on trial conduct will be evaluated and documented on an ongoing basis as early discontinuation of patients may require replacement of patients or increasing the sample size to preserve the underlying statistical assumptions. Other potential measures will be taken to assure the safety and welfare of patients and study staff, maintaining compliance with GCP, and minimizing risks to trial integrity during the COVID-19 pandemic, such as tele monitoring visits or risk-based centralized monitoring including remote source data verification. Any potential measures or changes will be handled according to the regional and local regulations. All measures taken in relation to COVID-19 will be reported to the regulatory authorities as appropriate.

Further details (e.g. blood sample logistics, prolongation of screening period, additional analyses) are specified in the study specific COVID-19 management plan or other plans (e.g. SAP).

# 10 Statistical considerations

## 10.1 Sample size determination

Approximately 11 patients will be enrolled in each arm of the Global Study (Part I). With an assumed drop-out rate of [redacted], approximately 10 patients per arm will be evaluable for the primary endpoint analysis. For the definition of a drop-out please refer to Appendix 1.

Due to the [redacted] nature of this clinical trial, no formal hypothesis regarding the primary endpoint is formulated. As such, no formal sample size calculation based on power considerations was performed.

The following operational characteristics are based on the effect of a treatment regimen (denoted by M) compared to placebo, using 10 evaluable patients per arm.

- If the true effect is an absolute difference of [redacted] ([redacted] relative decrease from baseline for M – [redacted] relative decrease from baseline for placebo) (please compare to results for narsoplimab) (see OMS721 Press Release), the probability to observe an absolute difference of at least [redacted]
- If the true effect is an absolute difference of only [redacted] ([redacted] for M – [redacted] for placebo), the probability to observe an absolute difference of at least [redacted]

Here, it is assumed that the ratio "UPCR at 9 months / UPCR at baseline" is log-normally distributed. The standard deviation of the log-value is assumed to be equal to [redacted] (placebo) and [redacted] (M) respectively and the effect in the placebo arm is assumed to be [redacted] (see Fellstroem 2017).

A separate open-label cohort of patients in Japan (Part II) is planned to ensure that in total approximately 8 Japanese patients are enrolled in this trial. This will enable a meaningful evaluation of PK and safety in comparison to non-Japanese patients.

## 10.2 Integrative analysis of dose and dosing regimens

Pharmacokinetic, [redacted], safety and efficacy results from this trial will be used for further analyses to identify a suitable dose and dosing regimen for future clinical trials. This

assessment will be performed as an integrated analysis including results from other clinical studies with felzartamab. The results will be reported separately.

A separate descriptive sub-analysis to evaluate the similarity between Japanese and non-Japanese patients will be performed with the PK and Safety data from clinical trial MOR202C206. For PK, the planned sample size of at least 7 Japanese patients dosed with felzartamab will enable a meaningful detection of substantial differences in comparison to non-Japanese patients. Considering a coefficient of variation of the PK parameter of interest within each subpopulation of [redacted], the power to detect a difference of [redacted] or more between the groups will be [redacted] for the planned sample size (α=[redacted] two sided). Analyses for other data will be descriptive.

## 10.3 Timing of statistical analysis

The statistical analysis plan (SAP) will be developed and finalized before data base lock and will describe the analysis of all trial data, define the participant populations to be included in the analyses, and detail procedures for accounting of missing or unused data. The primary analysis will be performed after all randomized patients in the Global Study (Part I) have completed their 9 month-visit or discontinued the trial earlier. The final analysis of all endpoints will be performed after all randomized patients (both Part I and Part II) have completed their last visit, or discontinued the trial earlier.

An interim analysis of key [redacted] and PK data is planned when at least 80% of patients have completed 3-months visit (Day 85 visit). Further details are discussed in Section 10.6.5. Additional follow-up analyses for safety or efficacy endpoints may be performed between the primary and final analysis if needed or requested.

## 10.4 Analysis populations

Table 10-1 summarizes the analysis populations for this trial.

**Table 10-1 Analysis populations**

| Analysis population | Description | Primary purpose |
|---|---|---|
| Screening analysis set (SCA) | All patients who are screened for this trial | Disposition |
| Full analysis set (FAS) | All patients who are randomized to the trial.<br>Analyses using FAS will be based on the treatment to which each patient is randomized. | Analysis of efficacy endpoints<br>Demographics, baseline, medical history |
| Per-protocol analysis set (PPS) | All patients who received at least one dose of trial treatment who do not have any relevant major protocol deviations (PDs). Major PDs that will lead to an exclusion of the PPS will be decided on prior to database lock. All PDs or conditions leading to exclusion from the PPS will be documented prior to any data base lock. | Sensitivity analysis of selected efficacy endpoints |
| Safety analysis set (SAF) | All patients who received at least one dose of trial treatment.<br>Analyses using the SAF will be based on the actual treatment received. | Analysis of safety endpoints |

| Analysis population | Description | Primary purpose |
|---|---|---|
| PK analysis set (PKAS) | All patients with any available quantifiable felzartamab serum concentration data. | Analysis of PK endpoints |
| Immunogenicity analysis set (IAS) | All patients with at least one ADA sample. | Analysis of immunogenicity endpoints |
| Japan analysis set | All 8 Japanese patients who were enrolled under Part I and Part II (Japan cohort) | Evaluate Japanese patients' safety and PK profile. |

## 10.5 General statistical considerations

The data will be analyzed by the sponsor and/or designated CRO. Data from participating centers in this protocol will be combined for the analysis.

Details of the analyses presented in this section will be provided in the SAP.

Any deviations from the statistical analysis outlined in this protocol and reasons for the deviations will be described in the clinical trial report.

Tabulations of summary statistics, graphical presentations, and statistical analyses will be performed using SAS software version 9.3 or higher.

Continuous, quantitative variable summaries will include the number of patients, mean, standard deviation, minimum, 25$^{th}$ quartile, median, 75$^{th}$ quartile and maximum. For selected variables including and PK parameters, the geometric mean and geometric coefficient of variation may be used.

Categorical, qualitative variable summaries will include the frequency and percentage of patients/entries in the particular category.

No formal statistical hypothesis testing will be performed. Selected inferential statistical analyses including e.g. confidence intervals (CIs) may be used but should not be interpreted in a confirmatory sense.

Details of missing value imputation rules will be discussed in the SAP. This also applies to potential sensitivity analyses based on different imputation rules.

To assess the impact of COVID-19, the following information will be captured and reported.

- Reasons for missed visits / assessments
- Reasons for treatment discontinuation and withdrawal from study
- Major protocol deviations related to COVID-19
- AEs related to COVID-19

Health Authority guidelines requesting specific COVID-19 related data analyses will be considered.

## 10.6 Analysis of Endpoints

All efficacy endpoints will be analyzed descriptively by treatment arm using the FAS.

### 10.6.1 Definition of endpoints

#### 10.6.1.1 Primary endpoint

The primary endpoint of relative decrease in UPCR will be estimated based on an MMRM (mixed effects model for repeated measure) model. In this model, UPCR change from baseline in log scale will be response variable, while baseline UPCR in log scale, treatment, visit, treatment by visit interaction will be fixed effect covariates. Within group treatment effect estimates and between group treatment comparisons will be based on least square means from this MMRM model.

Descriptive summary of raw UPCR values by treatment and visit will also be provided.

### 10.6.2 Secondary endpoints

#### 10.6.2.1 Response endpoints

The number and % of patients with complete response at 3, 6, 9, 12, 18 and 24 months will be reported by treatment arm.

The number and % of patients with response at 3, 6, 9, 12, 18 and 24 months will be reported by treatment arm.

For the main analysis of these endpoints, patients with missing values will be treated as non-responders. As a sensitivity analysis, missing values will be imputed using the "last observation carried forward" method.

#### 10.6.2.2 Albumin Creatinine Ratio (ACR)

ACR at 3, 6, 9, 12, 18 and 24 months will be summarized descriptively by treatment arm.

#### 10.6.2.3 Time to response and duration of response

For the definition of these endpoints, please refer to Section 9.2. Time to response and duration of response will be summarized descriptively using Kaplan-Meier methods. Duration of response will only be defined for patients who achieved a response.

#### 10.6.2.4 Incidence and severity of TEAEs

The safety endpoint analysis is described in Section 10.6.4.

#### 10.6.2.5 Pharmacokinetic profile of felzartamab

For patients in the PKAS, individual serum concentrations of felzartamab will be listed by treatment arm of felzartamab.

Descriptive statistics will be calculated by day for serum concentrations. Mean (± standard error) serum concentrations of felzartamab vs. time will be plotted by treatment arm using both linear and semi-logarithmic scales.

Felzartamab serum levels will be further analyzed performing population PK analyses, which will be reported separately.

#### 10.6.2.6 Immunogenicity of felzartamab

The immunogenicity of felzartamab (anti-felzartamab antibody formation) will be assessed by presenting ADA status (positive/negative), ADA titer (when ADA status was positive), and potential drug interference in the assay (yes/no when ADA status was negative). The results will be summarized descriptively for each treatment arm of felzartamab and visit. This analysis will be performed on the IAS.

#### 10.6.2.7 eGFR

eGFR will be summarized descriptively. The number of patients who reached 30% decrease from baseline will be summarized by treatment group and visit.

[redacted]

### 10.6.4 Safety analyses

All safety analyses will be based on the SAF. No formal statistical testing will be performed.

#### 10.6.4.1 Adverse events

**Pre-treatment adverse events**: AEs that start during the trial but before the start of trial treatment will be classified as pre-treatment AEs and will be presented in separate AE listings.

**Treatment-emergent adverse events:** TEAEs are defined as any AEs reported after the start of trial treatment until 28 days after the last trial treatment, defined as the treatment-emergent period.

**Post-treatment adverse events** PTAEs are defined as any AEs reported after the treatment-emergent period until the date of trial discontinuation.

Adverse events will be coded according to current version of the medical dictionary for regulatory activities (MedDRA) system organ class (SOC) and preferred term (PT). The incidence and frequency of all AEs will be summarized by SOC, PT, relationship to treatment, severity and seriousness.

Adverse event listings will have a flag to indicate in which period the AE occurred.

#### 10.6.4.2 Clinical laboratory evaluation

The analysis of laboratory parameters will be presented for each treatment arm by blood parameters (e.g. hematology, serum chemistry, coagulation) and urine parameters (urinalysis). All data collected in the course of the trial will be presented.

Descriptive summaries of absolute values and change from baseline values will be presented by visit.

Each abnormal value will be flagged in the listings to show whether it is below or above the reference range.

#### 10.6.4.3 Vital signs

Descriptive summaries of actual values and changes from baseline will be calculated for vital signs by visit. Each abnormal value will be flagged to show whether it is below or above the normal reference range.

#### 10.6.4.4 Electrocardiograms

Summary ECG assessments (categories: “normal”, “abnormal”, "not evaluable”) will be tabulated by time point using frequency tables. ECG findings including any available cardiological evaluations will be listed by visit and treatment arm.

Summary statistics for all time points will be displayed for QT and the corrected QTcF and QTcB.

The number and percentage of patients with QTc values above the normal limit (> 450 ms, > 480 ms, > 500 ms) and the number and percentage of patients who experienced a change ≥ 30 ms or a change ≥ 60 ms will be presented by time point.

### 10.6.5 Interim Analysis

The purpose of this interim analysis (IA) is to allow an early assessment of proof-of-mechanism of felzartamab in IgAN at 3 months and support further program development strategy.

An unblinded IA on below listed key [redacted] reflecting disease biology and PK data will be performed when a minimum of 80% (N=35) randomized trial participants have completed the Day 85 study visit (Visit 8).

[redacted]

**PK data:**

- Analysis of MOR202 serum concentrations

Analysis details will be described in a separate PK/[redacted]Data Analysis Plan.

In order to maintain the double-blind during and following the IA, an unblinded Sponsor team (Data Review Committee), which is independent of clinical trial team is established and described

in the Data Review Committee Charter. Unblinded interim data or results will be shared only with Data Review Committee members as specified in the Review Committee Charter.

Irrespective of the outcome of 3-months IA, the current study will continue as planned. It is not planned to terminate the study prematurely or adapt the design or conduct of the study based on the outcome of the IA. Patients will continue with their scheduled visits, double-blind nature will be maintained until primary completion, no changes to any endpoints will be implemented based on the results of this IA.

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# 12 Appendices

## 12.1 Appendix 1: Abbreviations and Definition of terms

| | |
|---|---|
| ACEI | Angiotensin-converting enzyme inhibitor(s) |
| ACR | Albumin Creatinine Ratio |
| ADA | Anti drug antibody |
| ADCC | antibody-dependent cell-mediated cytotoxicity |
| ADCP | antibody-dependent cell-mediated phagocytosis |
| ADP | Adenosine diphosphate |
| AE(s) | Adverse event(s) |
| AESI | Adverse Event of Special Interest |
| Anti-HBc | Hepatitis B core antibody |
| Anti-HCV | Anti-hepatitis C virus |
| Anti-PLA2R | Anti phospholipase A2 receptor antibodies |
| ARBs | Angiotensin receptor blockers |
| AUC | Area under the curve |
| BL | Baseline |
| BMI | Body mass index |
| BP | Blood pressure |
| CD | Cluster of differentiation |
| CD20 | B-lymphocyte antigen CD20 |
| CD38 | B-lymphocyte antigen CD38 |
| Cmax | Maximum concentration |
| CI | Confidence Interval |
| COVID-19 | Official name for disease caused by the SARS-CoV-2 (coronavirus) |
| CR | Complete response |
| CRO | Contract research organization |
| CRS | Cytokine Release Syndrome |
| Ctrough | Minimum concentration |
| CX | Various fractions of complement, C1q, C5a, …. |
| DEX | Dexamethasone |
| DNA | Deoxyribonucleic acid |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| eGFR | estimated glomerular filtration rate |
| ELISA | Enzyme-linked immunosorbent assay |
| EOS | End of study |
| EOT | End of treatment |

| | |
|---|---|
| ESRD | End stage renal disease |
| EudraCT | European Union Drug Regulating Authorities Clinical Trials |
| FAS | Full analysis set |
| FCBP | Female of childbearing potential |
| FiH | First in Human |
| FSH | Follicle stimulating hormone |
| GCP | Good Clinical Practice |
| [redacted] | [redacted] |
| HbA1c | Glycated hemoglobin |
| HBcAg | Hepatitis B core antigen |
| HBsAb | Hepatitis B surface antibody |
| HBsAg | Hepatitis B surface antigen |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| HDL | High Density Lipoprotein |
| HIV | Human Immunodeficiency Virus |
| IA | Interim Analysis |
| IB | Investigator`s Brochure |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation |
| IEC | Independent Ethics Committee |
| IFN-γ | Interferon-gamma |
| IFTA | Interstitial fibrosis and tubular atrophy |
| Ig | Immunoglobulin |
| IgA | Immunoglobulin A |
| IgAN | IgA Nephropathy |
| IgG1 | Immunoglobulin G1 |
| IL | Interleukin |
| IL-2 | Interleukin-2 |
| IL-6 | Interleukin-6 |
| IMP | Investigational medicinal product |
| IRB | Institutional Review Board |
| IRR | infusion related reaction |
| IRT | Interactive response technology |
| ISF | investigator site file |
| IST | Immunosuppressive therapy |
| i.v. | Intravenous(ly) |
| LDL | Low Density Lipoprotein |

| | |
|---|---|
| mAb(s) | Monoclonal antibody(ies) |
| MAC | Membrane attack complex |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MM | Multiple myeloma |
| mPBPK | minimal physiologically-based PK model |
| MTD | Maximum tolerated dose |
| NCI CTCAE 5.0 | National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 |
| PBMCs | Peripheral blood mononuclear cells |
| PCR | Polymerase Chain Reaction |
| [redacted] | [redacted] |
| PI | Prescribing Information |
| PK | Pharmacokinetics |
| PKAS | Pharmacokinetic Analysis Set |
| PK/[redacted] | pharmacokinetic/[redacted] |
| PKAS | Pharmacokinetic Analysis Set |
| PMDA | Pharmaceuticals and Medical Development Agency |
| PLA2R | Phospholipase A2 receptor |
| PT | Preferred Term |
| QTcB | QT interval corrected for heart rate according to Bazett |
| QTcF | QT interval corrected for heart rate according to Fridericia |
| QTL | Quality tolerance limit |
| RAS | Renin angiotensin system |
| RBCs | Red blood cells |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SCR | Screening |
| SmPC | Summary of product characteristics |
| SOC | system organ class |
| TEAE(s) | Treatment emergent adverse event(s) |
| TMDD | Target-mediated drug disposition |
| TNFα | Tumor necrosis factor alpha |
| UPCR | Urine protein to creatinine ratio |
| WHO | World Health Organization anti- |

## Definition of terms

| | |
|---|---|
| IMP | Felzartamab (MOR202) or placebo is the investigational medicinal product in this clinical trial. |
| Screening Phase | From signing of ICF to randomization (maximum 42 days) |
| Baseline | Baseline is defined as the last observation before administration of the first dose of any of the trial drugs. |
| Drop-out | Patient who discontinues the trial before the primary endpoint is evaluated |
| End of the trial | Date of the last visit of the last patient in the clinical trial |

## 12.2 Appendix 2: Clinical laboratory tests

Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 1 and of the protocol. The tests detailed in Table 12-1 will be performed by a central laboratory.

**Table 12-1 Protocol-required central laboratory assessments**

| | |
|---|---|
| Serum biochemistry | Alanine aminotranferase (ALT), total albumin, alkaline phosphatase, amylase, aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatinine, creatinine kinase, gamma-glutamyl transferase (GGT), glucose, lactate dehydrogenase (LDH), lipase, phosphate, potassium, protein (total), sodium, uric acid, magnesium, C-reactive protein, eGFR, HbA1c in patients with diabetes mellitus II |
| Lipids | Total cholesterol, HDL cholesterol, triglycerides, LDL-cholesterol (calculated), cholesterol/HDL ratio (calculated), non-HDL cholesterol (calculated) |
| HIV, Hepatitis serology/virology | HIV-1/2 antibodies;<br>anti-HCV antibody (if positive HCV RNA PCR)<br>HBs antigen (HBsAg), anti Hepatitis B core Antibody (anti-HBcAb),<br>anti-hepatitis B surface antibody (anti-HBs), HBs antibody,<br>HBc antibody (if isolated positive, HBV DNA PCR) |
| Polyclonal immunoglobulins | Immunoglobulin A (IgA); immunoglobulin G (IgG); immunoglobulin M (IgM) |
| 24h urine | Collection for determination of protein, albumin, creatinine and Na, calculation of ratios (UPCR, ACR) |
| PK samples (serum) | Felzartamab serum levels |
| [redacted] | [redacted] |
| ADA samples (serum) | Anti-felzartamab antibodies in serum |
| [redacted] | [redacted] |
| [redacted] | |
| [redacted] | [redacted] |
| Pregnancy tests in FCBP | In serum according to the schedule of activities |

If any sample cannot be analyzed (e.g. due to hemolysis), site should recall patient without undue delay for re-test since it may be an essential safety or endpoint assessment.

The tests detailed in Table 12-2 will be performed locally.

**Table 12-2 Protocol-required local laboratory assessments**

| | |
|---|---|
| Complete blood count (CBC) | Hemoglobin, hematocrit, platelet count, red blood cell count, red blood cells (mean corpuscular volume [MCV],mean corpuscular hemoglobin [MCH], %reticulocytes), white blood cell count with differentials (neutrophils, lymphocytes, monocytes, eosinophils, basophils, % and absolute) |
| Urinalysis | Dipstick (will be provided centrally): Specific gravity, (pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase)<br>Local lab: Microscopic examination of sediment |
| Pregnancy tests in FCBP | In urine according to the schedule of activities |
| Blood typing | Patients must be typed and screened for the eventual presence of irregular antibodies **before** the first dose, best by the local blood bank. Phenotyping may be considered prior to starting felzartamab treatment as per local practice. Red blood cell genotyping is not impacted by CD38 antibodies and may be performed at any time (further details above clinical safety). |

## 12.3 Appendix 3: Regulatory, ethical and study oversight considerations

### Regulatory and ethical considerations

This trial was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice (ICH-E6 (R2) GCP), with applicable local regulations and with the ethical principles laid down in the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.

Before starting this trial, the clinical trial protocol, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to the IEC/IRB and/or regulatory authorities (in accordance with local regulations) for evaluation. The trial will not start before the IEC/IRB and/or regulatory authority gives written approval or a favorable opinion as required. Any amendments to the protocol will require IEC/IRB and/or regulatory authority approval as required before implementation, except for changes necessary to eliminate an immediate hazard to patients.

The investigator will be responsible for:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the local regulations and requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to the protocol and other procedures specific to the study, requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

### Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial

information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

## Informed consent process

The investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH GCP, and if applicable, requirements of the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.

Rescreened patients need to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional [redacted]. The investigator or authorized designee will explain to each patient the objectives of the [redacted]. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a patient's agreement to allow any remaining specimens to be used for [redacted]. Patients who decline to participate in this optional research will not provide this separate signature.

## Data protection

Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; i.e. data is 'pseudonymized'; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used and protected by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent

The patient must be informed that his/her medical records may be examined by Monitors, Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The use of pseudonymized data and the encryption of the data during transfers limits the risk of personal data security breaches. Should a personal data security breach occur, a process exists in

the Data Protection Policy adopted by the sponsor to assess the facts and take mitigation actions as appropriate.

## Dissemination of clinical study data

Key information on the protocol will be posted in a publicly accessible database such as clinicaltrials.gov and/or the EU Clinical Trials Register. In addition, the results of this trial will be submitted for publication and/or posted in a publicly accessible database in accordance with local regulations.

## Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

## Data quality assurance

All patient data relating to the study will be recorded in eCRF and some data might be transmitted to CRO electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

Quality tolerance limits (QTLs) will be predefined to identify systematic issues that can impact patient safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

## Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. In addition to the current medical records, the investigator may need to request copies of previous medical records or transfer records.

## Study and site start and closure

The study start date is the date on which the clinical study will be open for recruitment of patients. The first site open will be the study start date.

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the investigator
- Discontinuation of further felzartamab development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

## 12.4 Appendix 4: Adverse events: Definitions and procedures for recording, evaluating, follow-up, and reporting

### Adverse event definition

An AE is any untoward medical occurrence in a patient or clinical study patient, temporally associated with the use of IMP, whether or not considered related to the IMP.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of IMP.

### Events meeting the AE definition:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after IMP administration even though it may have been present before the start of the study. This includes any physical examination finding that is judged by the investigator as a potentially clinically significant change (worsening) compared with a baseline value will be considered an adverse event, recorded on the CRF, and monitored as described below.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either IMP or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Signs, symptoms, or the clinical sequelae of a suspected error, misuse or abuse of either IMP

The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE.

### Events NOT meeting the AE definition:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient’s condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

## Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study unless more severe than expected for the patient's condition, hospitalization for social reason in the absence of any deterioration in the patient's general condition).

A SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
    - The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
    - In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
    - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
    - Routine treatment or monitoring of the studied indication, not associated with deterioration of symptoms related to IgAN is not considered an AE.
- Results in persistent disability/incapacity
    - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
    - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Other situations:
    - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, 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.

## Recording and follow-up of AEs and/or SAEs

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant AE/SAE information in the eCRF. SAEs/AESIs have to be recorded in the eCRF within 24 hours of awareness. If there is a system failure, the investigator will complete a paper SAE Report Form instead (please see below under the heading "Reporting of SAEs/AESIs").

It is not acceptable for the investigator to send photocopies of the patient's medical records to the sponsor in lieu of completion of the AE/SAE eCRF page. There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all patient identifiers, except the patient number, will be redacted on the copies of the medical records before submission to the sponsor or designee.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

## Assessment of intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

## Assessment of severity (toxicity grade)

The toxicity grade of AEs will be graded according to the NCI-CTCAE version 5.0 of 27-Nov-2017 using the following definitions:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

- Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

## Assessment of causality

The investigator is obligated to assess the relationship between IMP and each occurrence of each AE/SAE.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IMP administration will be considered and investigated and documented, if applicable.

The investigator will also consult the Investigator's Brochure of felzartamab (MOR202) in his/her assessment.

For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE/AESI has occurred, and the investigator has minimal information to include in the initial report in the eCRF or/and on the SAE report form. However, it is very important that the investigator always assess causality for every event before the initial transmission of the SAE data.

The investigator may change his/her opinion of causality based on follow-up information and send a SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

## Follow-up of AEs and SAEs

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a patient dies during participation in the study or during a recognized follow-up period, the investigator will provide a copy of any post mortem findings including histopathology.

The investigator will submit any updated SAE/AESI data within 24 hours of receipt of the information.

## Reporting of SAEs/AESIs

The primary mechanism for reporting an SAE will be the eCRF. If the electronic system is unavailable, then the site will use the back-up paper SAE report form in the ISF to report the event within 24 hours. The site will enter the SAE/AESI data into the electronic system as soon as it becomes available. After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE/AESI from a study patient or receives updated data on a previously reported SAE/AESI after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (provided in the Investigator site file).

Contacts for SAE reporting can be found on the SAE report form.

# 12.5 Appendix 5: Contraceptive guidance/pregnancy information

## Definitions:

Female of childbearing potential (FCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of IMP, additional evaluation should be considered.

Women in the following categories are not considered FCBP

- Premenarchal
- Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
- Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level (usually above 35 IU/L) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity. Genetic abnormality like Turner syndrome), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the patient's medical records, medical examination, or medical history interview.

## Contraception guidance

Female patients of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 12-3.

For Czech Republic and Germany: Sexually active male patients should at least use one method of contraception (as a minimum in form of a condom) during treatment and until 3 months after the last dose of felzartamab.

FCBPs and non-vasectomized males will be counselled for pregnancy risks.

**Table 12-3 Highly effective contraceptive methods**

| |
|---|
| **Highly effective contraceptive methods that are user dependent [a]**<br>Failure rate of <1% per year when used consistently and correctly.<br>Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation<br>• Oral<br>• Intravaginal[+]<br>• Transdermal[+]<br>Progestogen only hormonal contraception associated with inhibition of ovulation[+] Oral<br>• Injectable |
| **Highly effective methods that are user independent [a]**<br>Implantable progestogen only hormonal contraception associated with inhibition of ovulation[+]<br>• Intrauterine device (IUD)<br>• Intrauterine hormone-releasing system (IUS)<br>• Bilateral tubal occlusion |
| **Vasectomized partner**<br>A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the FCBP and the absence of spermatocytes has been confirmed. If not, an additional highly effective method of contraception should be used. |
| **Sexual abstinence**<br>Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment and for at least 90 days after cessation of treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient[b]. |
| NOTE:<br>a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for patients participating in clinical studies.<br>b) Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a study, and withdrawal are not acceptable methods of contraception.<br>[+] These methods of contraception are not approved in Japan |

## Collection of pregnancy information

## Male patients with partners who become pregnant

The investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant during the period the male patient receives IMP and 3 months beyond the last dose.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 3 months following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

## Female patients who become pregnant

The investigator will collect pregnancy information on any female patient who becomes pregnant within 3 months after the last dose. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a patient's pregnancy.

The patient will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the patient and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 3 months beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any post-study pregnancy related SAE considered reasonably related to the IMP by the investigator will be reported to the sponsor as described in Section 9.3.6. While the investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.

Any female patient who becomes pregnant while participating in the study will discontinue IMP.

## 12.6 Appendix 6: Data handling and quality assurance

### Completing and signing case report forms

Trained clinical trial site personnel will enter the data into the eCRF. For any missing data a reason should be given. Any errors should be corrected within the electronic system and source documents. The audit trail will record all changes made, the date and time of the correction, and the person correcting the error. The appropriate electronic signature will be provided. The investigators will receive a copy of their eCRF in a readable format after database lock for archiving.

### Clinical monitoring

The sponsor or designee will monitor the clinical trial conduct at the clinical trial sites to ensure data quality (accurate and complete data collection), and protection of the patient's safety and rights.

### Audit and inspection

The sponsor or regulatory authorities may audit the investigational site. The sponsor's Quality Assurance Unit or Sponsor's authorized representative or CRO`s Quality Assurance Unit, independent of the Clinical Development and Clinical Operations Department, is responsible for auditing the trial.

The investigator(s) must accept that regulatory authorities may decide to conduct an inspection to verify compliance of the trial with GCP.

### Clinical data management

The sponsor or designee will be responsible for the processing and quality control of the data. The handling of data, including data quality control, will comply with all applicable regulatory guidelines. Adverse events and concomitant medications terms will be coded with the current MedDRA version and World Health Organization (WHO) medication dictionary. At the end of the trial all MedDRA codes will be updated to the newest versions.

### Archiving

All trial documentation at the sites and Sponsor site will be archived in accordance with International Council for Harmonization (ICH) E6-Good Clinical Practice (GCP) and the sponsor's quality standards and SOPs.

## 12.7 Appendix 7: MEST-C Score for IgAN

**Table 12-4 Pathological variables used in MEST-C Score**

| Variable | Definition | Score |
|---|---|---|
| Mesangial hypercellularity | < 4 Mesangial cells/mesangial area=0<br>4–5 Mesangial cells/mesangial area=1<br>6–7 Mesangial cells/mesangial area=2<br>>8 Mesangial cells/mesangial area=3<br>The mesangial hypercellularity score is the mean score for all glomeruli. Mesangial score should be assessed in periodic acid-Schiff-stained sections. | M0 ≤ 0.5<br>M1 > 0.5<br>If more than half the glomeruli have more than three cells in a mesangial area, this is categorized as M1. Therefore, a formal mesangial cell count is not always necessary to derive the mesangial score. |
| Segmental glomerulosclerosis | Any amount of the tuft involved in sclerosis, but not involving the whole tuft or the presence of an adhesion | S0: absent<br>S1: present |
| Endocapillary hypercellularity | Hypercellularity due to increased number of cells within glomerular capillary lumina causing narrowing of the lumina | E0 – absent<br>E1 – present |
| Tubular atrophy/ interstitial fibrosis | Percentage of cortical area involved by the tubular atrophy or interstitial fibrosis, whichever is greater | T0: 0–25% –<br>T1: 26–50% –<br>T2: >50% – |
| Crescents | Cellular and fibrocellular crescents | C0: no crescents<br>C1: crescents in < 25 % of glomeruli<br>C2: crescents in > 25 % of glomeruli |

Source: Trimarchi et al 2017

## 12.8 Appendix 8: Corticosteroid Equivalence

**Table 12-5 Corticosteroid Equivalence Chart**

| Substance | Equivalent dose (mg) |
|---|---|
| Hydrocortisone | 20 |
| Cortisone acetate | 25 |
| Prednisone/ Prednisolone | 5 |
| Methylprednisolone | 4 |
| Triamcinolone | 4 |
| Dexamethasone | 0.75 |
| Betamethasone | 0.75 |
| Beclometasone | 0.75 |

Note: Cortisol (hydrocortisone) is the standard of comparison for glucocorticoid potency. Hydrocortisone is the name used for pharmaceutical preparations of cortisol.

## 12.9 Appendix 9: Guidance on Monitoring Patients with Elevated Liver Function Tests

This appendix provides guidance on monitoring of patient with clinically significant elevated liver enzymes defined as elevation of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST) to ≥3 × ULN.

Liver enzymes (ALT, AST, gamma glutamyl-transpeptidase [GGT], and serum alkaline phosphatase [ALP]) as well as total bilirubin will be measured at each study visit.

In case elevated ALT or AST is detected in a patient enrolled in the clinical trial, a thorough medical history and physical examination with a focus on liver disease should be undertaken. This includes: history of liver disease (family or personal); history of a systemic disease with potential liver involvement; alcohol consumption, medications (prescription or over-the-counter), herbal preparations, dietary supplements, recreational drugs, special diets, or environmental chemical agents; potential exposure to infectious agents (e.g. travel to developing countries, history of potential exposure to blood or blood products, high-risk sexual relations); and any additional information deemed relevant by the investigator. A physical examination should also be performed (including signs of chronic liver disease). Clinical symptoms such as fatigue, nausea, abdominal pain and immune-allergic signs (e.g. fever, rash and adenopathy) provides strong evidence for a potential DILI. Therefore, the presence or absence of symptoms needs to be investigated and documented.

In case of symptoms suggestive of drug-induced liver injury, patients will be instructed to return to the trial site for an unscheduled visit or to go to the emergency room to measure liver enzymes and to perform an urgent clinical assessment as soon as possible.

Solitary elevations of bilirubin, not accompanied by elevations of ALT or AST should be managed according to the discretion of the treating physician.

**Table 12-6 Algorithm for Monitoring and Management of Patients with Elevated Liver Function Tests**

| **Elevation of Either ALT or AST to ≥3 × ULN** | |
|---|---|
| • Confirmation is required in cases of elevation of either ALT or AST ≥3 × ULN and <8 × ULN. In cases of elevation of ALT or AST ≥8 × ULN, no confirmation is required, but the assessments below should be performed.<br>• The day in which the abnormal value is received from the laboratory will be considered as day 0 for follow-up of liver enzyme elevation.<br>• In cases where a local laboratory is used, the results should be recorded in the eCRF, accompanied by the reference range of the relevant measurements. | |
| Confirmation | The investigator should repeat/perform the following mandatory testing for confirmation purposes within 24 hours: ALT, AST, ALP, R value |

| | |
|---|---|
| | (ALT/ULN÷ALP/ULN), bilirubin (total, direct, and indirect), CBC (with differential for eosinophil count), and INR. |
| | The abnormality will be regarded as confirmed in each of the following scenarios:<br>• The baseline value was within the normal range and ALT or AST is still ≥3 × ULN.<br>• The baseline value was above the ULN and ALT or AST is ≥2 × the baseline value. |
| Additional Tests/ Evaluations | Upon confirmation of the abnormality as noted above, the following additional evaluations should be performed and results should be recorded in the eCRF:<br>• Serology for hepatitis A (antibody and immunoglobulins M and G), B (core antibody total, core immunoglobulin M, and surface antigen), and C viruses.<br>• Serology for autoimmune hepatitis: anti-nuclear antibodies (titer), anti-smooth muscle antibodies, and anti-liver kidney microsomal antibodies; further testing may be required in case of a positive result for hepatitis B or C.<br>• Ultrasound examination of the liver and biliary tract at the investigator's discretion.<br>• Other diagnostic tests/consultations as deemed necessary by the investigator (e.g. serology for hepatitis E virus in case of travel to endemic geography).<br>• Observation and follow-up (to be performed after the abnormality was confirmed as above). |
| Continuous Monitoring | 1. The following values are to be monitored during the further course:<br>• Alanine aminotransferase, AST, GGT, ALP, R value (ALT/ULN÷ALP/ULN), total bilirubin, direct bilirubin, indirect bilirubin, CBC and differential count (to assess for eosinophilia), and INR. |
| | For **ALT or AST ≥3 × ULN but ≤5 × ULN**, monitor the above values on days 5 (±2 days), 8 (±2 days), 14 (±3 days), and 28 (±3 days).<br>Should the abnormality (≥3 × ULN in case baseline was within the normal range or ≥ 2 × ULN in case the baseline value was above ULN but still ≤5 × ULN) persist further, the patient will be followed according to the investigator's discretion, but a blood sample for ALT, AST, GGT, ALP, R value (ALT/ULN÷ALP/ULN), and total bilirubin, direct bilirubin, indirect bilirubin should be sent to the local laboratory at least once a month. |
| | 2. For **ALT or AST >5 × ULN**, monitor the above values twice a week until resolution or stabilization of the abnormality. |

3. **NOTE:** ALT or AST > 5 × ULN is defined as Grade 3 as per CTCAE. Therefore, felzartamab needs to be interrupted as per Section 7.8 of this Clinical Trial Protocol, unless the increased liver enzymes are considered unrelated to the IMP.

**Stopping Rules**

In the following circumstances, the study drug will be discontinued immediately unless the increased liver enzymes are considered unrelated to the IMP:

- Any increase in ALT or AST to ≥3 × ULN, combined with INR >1.5 or total bilirubin >2 × ULN.
- Any increase in ALT or AST to >5 × ULN, which is accompanied by symptoms clearly associated with impaired liver function (e.g. vomiting, fatigue, abdominal pain, nausea, fever, rash, adenopathy, and eosinophilia) and not deemed related to other diseases.
- Any increase in ALT or AST to levels >5 × ULN, which is persistent for ≥2 weeks of repeated measurements.
- Any increase in ALT or AST to levels >8 × ULN.
- In any case where monitoring of liver enzymes cannot be performed according to the protocol guidance.

**Follow-Up of Liver Enzymes After Stopping Rules Are Met**

- For a patient who meets the above criteria for discontinuation of the study drug, data as per the EOT visit need to be collected as soon as possible. Please refer to Section 8.1 of the clinical trial protocol for additional guidance.
- Liver enzymes should be monitored until normalization or stabilization of the abnormality, according to the discretion of the investigator.
- In any case, the minimal follow-up period will be 28 days and will include measurement of liver enzymes at least once weekly.
- Every effort should be made to complete the additional tests/evaluations, as described above.

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