# 1 CLINICAL STUDY PROTOCOL

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| **Protocol Title:** | A Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of Nemolizumab in Subjects with Chronic Kidney Disease with Associated Moderate to Severe Pruritus |
| **Protocol Number:** | RD.06.SPR.204358 |
| **IND Number:** | 117122 |
| **EudraCT Number:** | 2021-004766-35 |
| **Investigational Product:** | Nemolizumab (CD14152) |
| **Phase of Development:** | 2/3 |
| **Indication:** | Chronic Kidney Disease Associated Moderate to Severe Pruritus |
| **Sponsor:** | Galderma SA<br>Zählerweg 10<br>CH-6300 Zug<br>Switzerland<br><br>Galderma Research & Development, LLC<br>2001 Ross Avenue<br>Suite 1600<br>Dallas, TX 75201<br>United States |
| **Protocol Version:** | 6.0 |
| **Protocol Date:** | 21SEPT23 |

## 2 PROTOCOL APPROVAL SIGNATURES

**Protocol Title:** A Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of Nemolizumab in Subjects with Chronic Kidney Disease with Associated Moderate to Severe Pruritus

**Protocol Number:** RD.06.SPR.204358

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP), and applicable regulatory requirements.

**Sponsor Signatory:**

PPD

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## 3 INVESTIGATOR SIGNATURE PAGE

**Protocol Title:** A Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of Nemolizumab in Subjects with Chronic Kidney Disease with Associated Moderate to Severe Pruritus

**Protocol Number:** RD.06.SPR.204358

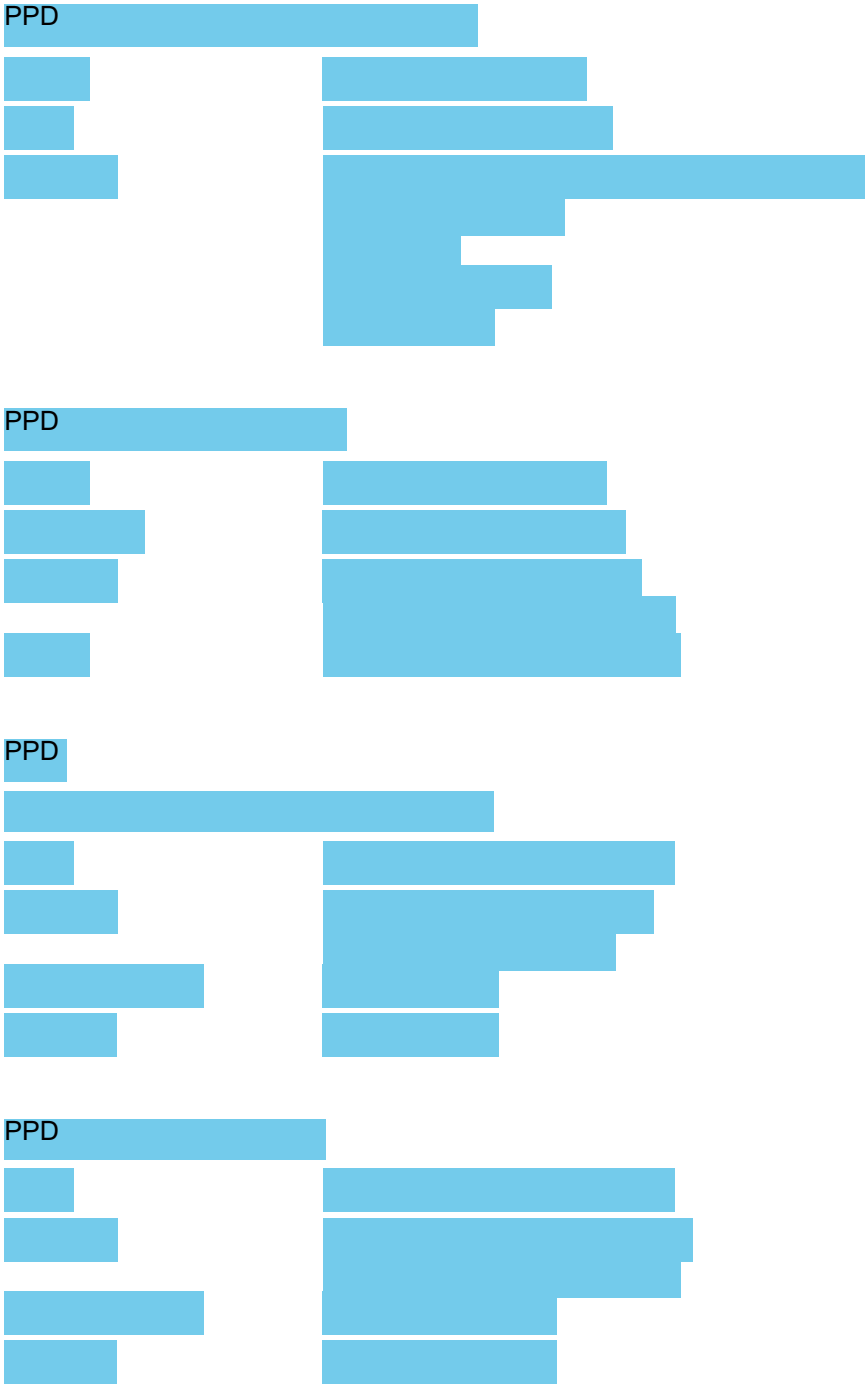
**Confidentiality and Current GCP/E6 (R2) Compliance Statement**

- I, the undersigned, have reviewed this protocol, including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), GCP, and relevant ICH guidelines.
- I am thoroughly familiar with the appropriate use of the study drug, as described in this protocol and any other information provided by Galderma SA including, but not limited to, the current Investigator's Brochure (IB).
- Once the protocol has been approved by the Independent Ethics Committee (IEC)/Institutional Review Board (IRB), I will not modify this protocol without obtaining prior approval of Galderma SA and of the IEC/IRB. I will submit the protocol amendments and/or any ICF modifications to Galderma SA and the IEC/IRB, and approval will be obtained before any amendments are implemented.
- I ensure that all persons or party assisting me with the study are adequately qualified and informed about the Galderma SA study drug and of their delegated study-related duties and functions as described in the protocol.
- I ensure that source documents and trial records that include all pertinent observations on each of the site's trial subjects will be attributable, legible, contemporaneous, original, accurate, and complete.
- I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all case report forms, laboratory samples, or source documents forwarded to the sponsor. Clinical information may be reviewed by the sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.
- Information developed in this clinical study may be disclosed by Galderma SA to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

Name, Title Investigator Signature

Institution Date (DD-Mmm-YYYY)

# 4 STUDY PERSONNEL



# 5 SYNOPSIS

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| **Title of Study:** | A Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of Nemolizumab in Subjects with Chronic Kidney Disease with Associated Moderate to Severe Pruritus |
| **Protocol Number:** | RD.06.SPR.204358 |
| **Investigators/Study Sites:** | Approximately 70 study sites are planned in North America and Europe |
| **Phase of Development:** | Phase 2/3 |
| **Objectives:** | Primary objective: The primary objective is to evaluate the efficacy of nemolizumab compared to placebo at reducing the intensity of pruritus after a 12-week treatment period in adult hemodialysis subjects with moderate to severe pruritus.<br><br>Secondary objectives: The secondary objectives are to evaluate the safety of nemolizumab compared to placebo, and to assess the CCI [redacted] and optimal dose in adult hemodialysis subjects with moderate to severe pruritus. |
| **Study Design:** | This is a randomized, double-blind, placebo-controlled, multicenter, parallel-group, phase 2/3 study to evaluate the efficacy and safety of nemolizumab in adult subjects with CKD-aP.<br><br>Subjects will be randomized in one of the three arms/groups (two different doses of nemolizumab and a placebo) in a 1:1:1 ratio:<br>• Group 1: 30 mg nemolizumab Q4W with a 60 mg loading dose at baseline;<br>• Group 2: 60 mg nemolizumab Q4W without loading dose at baseline;<br>• Group 3: placebo Q4W.<br><br>Approximately 84 subjects will be randomized in each nemolizumab group and in the placebo group for a total sample size of approximately 252 subjects.<br><br>In order to maintain the blind, all subjects will receive 2 injections at each administration (30 mg + 30 mg or 30 mg + placebo or placebo + placebo).<br><br>The study consists of a screening period (up to 4 weeks), a 12-week treatment period, and an 8-week follow up period (12 weeks after their last study drug injection).<br><br>The screening period will evaluate subject eligibility. The subjects' other (non-pruritus) complications of end-stage kidney disease (ESKD) are to be managed according to local standard of care. The use of moisturizers is encouraged to keep the skin hydrated.<br><br>At the baseline visit, subjects will receive an initial dose of nemolizumab 60 mg or placebo by two subcutaneous (SC) injections. Study drug treatment with either nemolizumab or placebo should start after completion of the hemodialysis treatment (within four hours). Then study drug (i.e., nemolizumab 30 mg, nemolizumab 60 mg, or placebo) will be administered via two SC injections (30 mg + placebo or 30 mg + 30 mg or placebo + placebo) every four weeks (Q4W) at Week 4 and 8 after completion of the hemodialysis treatment (within four hours). CCI [redacted] are to be taken before hemodialysis. Refer to the figure below. |

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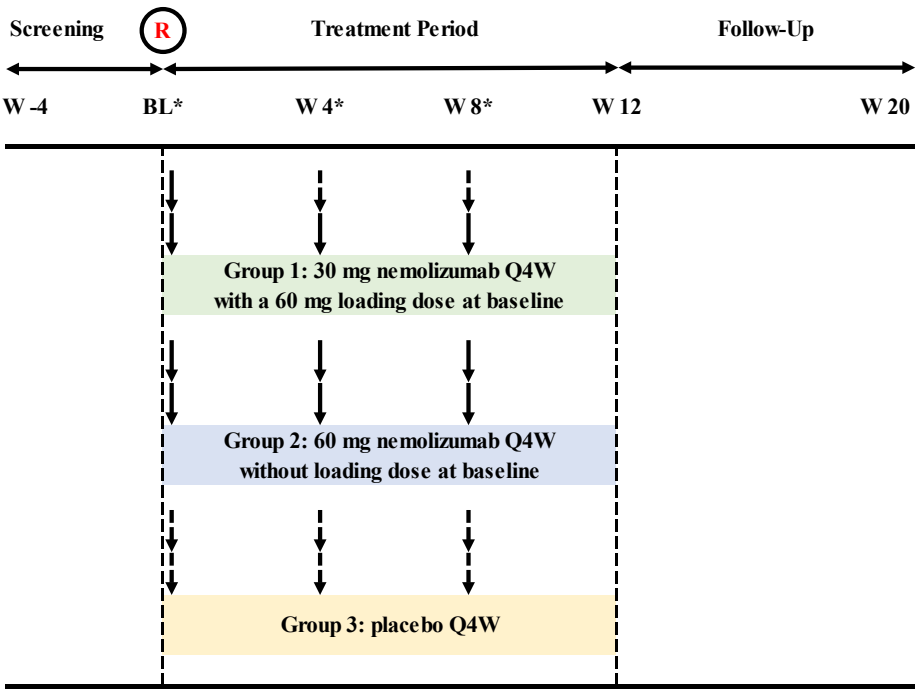
| |  <br>**R** = Randomization; * = Visits with study drug administration<br>Note: All subjects in each arm will receive 2 injections at each administration (either 30 mg + 30 mg, or 30 mg + placebo, or placebo + placebo) in order to mantain the blind<br><br>An independent data monitoring committee (IDMC) will review and monitor subject safety throughout the study. The study team will remain blinded until the end of the study.<br><br>An independent adjudication committee (IAC) will review and adjudicate all asthma-related AEs. |
| **Selection of Subjects:** | <u>Main Inclusion Criteria:</u><br><br>1. Subjects aged ≥ 18 years at the screening visit.<br><br>2. Has end-stage kidney disease (ESKD) and have been on hemodialysis three times per week for at least three months prior to the start of screening.<br><br>Note 1: Subjects who require an occasional additional hemodialysis treatment to manage fluid overload may be enrolled as long as it is anticipated that no more than one such treatment will be required in any given week.<br><br>Note 2: Subjects having received in-home hemodialysis may participate as long as they have switched to in-center hemodialysis at least two weeks prior to screening and plan to remain on in-center hemodialysis for the duration of the study.<br><br>3. Hemodialysis subjects meeting the Kidney Outcome Quality Initiative Guidelines of hemodialysis adequacy within 60 days of screening, two:<br><br>• Single-pool Kt/V measurements of at least 1.2.<br><br>4. Pruritus for ≥ three months (documented pruritus with no etiology identified other than CKD by medical record, previous physician's letter/statement, or written documentation by site investigators based on the medical history obtained from the subject).<br><br>5. WI NRS score ≥ 5.0 at the screening and baseline visit. Screening WI NRS score will be determined by a single WI NRS assessment (score ranging from 0 to 10) for the 24-hour period immediately preceding the screening visit. Baseline WI NRS score will be determined based on the weekly average of daily WI NRS scores (score ranging from 0 to 10) during the seven days immediately preceding |

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| | baseline (rounding is not permitted). A minimum of four daily scores out of the seven days immediately preceding baseline is required for this calculation.<br>6. Women of childbearing potential (WOCBP) (i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile) must agree either to commit to true abstinence throughout the study and for 12 weeks after the last study drug injection, when this is in line with the preferred and usual lifestyle of the subject, or to use an adequate and approved method of contraception throughout the study and for 12 weeks after the last study injection.<br>Adequate and approved methods of contraception applicable for the subject and/or her partner are defined below:<br>• Progestogen-only oral hormonal contraception.<br>• Combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier methods).<br>Note: "Double barrier methods" refers to simultaneous use of a physical barrier by each partner. Use of a single barrier method (e.g., condom) together with a spermicide is not acceptable.<br>• Combined (estrogen- and progestogen-containing) oral, intravaginal, or transdermal hormonal contraception.<br>• Injectable or implanted hormonal contraception.<br>• Intrauterine devices or intrauterine hormone releasing system.<br>• Bilateral tubal ligation or tube insert (such as the Essure system) at least three months before the study.<br>• Bilateral vasectomy of partner at least three months before the study.<br>7. Women are considered to be of non-childbearing potential if they meet one of the following criteria:<br>• Absence of menstrual bleeding for one year prior to screening without any other medical reason, confirmed with follicle stimulating hormone (FSH) level in the postmenopausal range.<br>• Documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy at least three months before screening.<br>Note: Bilateral tubal ligation is not accepted as reason for non-childbearing potential.<br>8. Subject willing and able to comply with all time commitments and procedural requirements of the clinical study protocol.<br>9. Understands and signs an informed consent form (ICF) before any investigational procedure(s) are performed.<br><u>Main Exclusion Criteria:</u><br>1. Body weight < 30 kg.<br>2. Pruritus caused by a concomitant condition unrelated to ESKD (e.g., dermatologic or systemic disorders such as, but not limited to atopic dermatitis (AD), psoriasis, prurigo nodularis (PN), Chronic T- cell Lymphoma, Leukemia or cholestatic liver disease).<br>3. Localized itch of only the palms of the hands and/or soles of the feet.<br>4. Pruritus present only during hemodialysis session.<br>5. History of or anticipated non-compliance with hemodialysis (i.e., such that it would adversely affect the conduct of the study or significantly change dialysis adequacy during the study) in the opinion of the investigator. |

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| | 6. New York Heart Association Class IV symptoms (see Appendix 11)or myocardial infarction within three months prior to screening.<br>7. History of stroke or transient ischemic attack within six months prior to screening.<br>8. Subjects meeting one or more of the following criteria at screening or baseline:<br>a. Had an exacerbation of asthma requiring hospitalization in the preceding 12 months.<br>b. Reporting asthma that has not been well-controlled (i.e. symptoms occurring on > two days per week, nighttime awakenings two or more times per week, or some interference with normal activities) during the preceding three months.<br>c. Asthma Control Test (ACT) ≤ 19 (only for subjects with a history of asthma).<br>9. Cutaneous infection within one week before the baseline visit, any infection requiring treatment with oral or parenteral antibiotics, antivirals, antiparasitics or antifungals within two weeks before the baseline visit.<br>Note: Subjects with chronic, stable use of prophylactic treatment for recurrent herpes viral infection can be included in this clinical study.<br>10. Any confirmed or suspected coronavirus disease (COVID-19) infection within two weeks before the screening or baseline visit. Subjects may be rescreened after the infection has resolved. Resolution of COVID-19 infection can be confirmed by recovery assessment methods, as described in the protocol.<br>11. Positive serology results (hepatitis B surface antigen [HbsAg] or hepatitis B core antibody [HbcAb], hepatitis C [HCV] antibody with positive confirmatory test for hepatitis C virus [HCV] (e.g., HCV polymerase chain reaction [PRC]), or human immunodeficiency virus [HIV] antibody) at the screening visit.<br>Note: Subjects with a positive HbcAb and a negative HbsAg can be included in this clinical study if hepatitis B surface antibody is positive (considered immune after a natural infection or vaccination). Subjects who are positive for HCV antibody and negative for HCV RNA may be enrolled.<br>In the event of rescreening, the serology tests results (e.g., HBV, HCV, HIV) from the previous screening can be used by the investigator to assess the eligibility of rescreened subjects if those tests were performed within six weeks prior to the baseline visit.<br>12. Known active or untreated latent tuberculosis (TB) infection or history of either untreated or inadequately treated active or latent TB according to the local applicable guidelines.<br>Note: Subjects who have a documented history of completion of an appropriate TB treatment regimen for latent or active TB with no history of re-exposure to TB since their treatment was completed are eligible to participate in the study.<br>13. Known or suspected immunosuppression beyond that expected due to end-stage kidney disease and its comorbidities or unusually frequent, recurrent, severe, or prolonged infections as per investigator judgment.<br>14. History of lymphoproliferative disease or history of malignancy of any organ system within the last five years, except for (1) basal cell carcinoma, squamous cell carcinoma in situ (Bowen's disease), or carcinomas in situ of the cervix that have been treated and have no evidence of recurrence in the last 12 weeks before the baseline visit, or (2) actinic keratoses that have been treated.<br>15. Pregnant women (positive serum pregnancy test result at any visits), breastfeeding women, or women planning a pregnancy during the clinical study.<br>16. In the opinion of the investigator the subject has any medical or psychological condition that could pose undue risk to the subject, prevent study completion, or |

adversely affect the validity or interpretability of the study measurements or interfered with study assessments.

17. Any clinically relevant laboratory abnormalities, such as but not limited to elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (> 3 × upper limit of normal [ULN]) in combination with elevated bilirubin (> 2 × ULN), during the screening period that may put the subject at significant risk according to the investigator's judgment, if he/she participates in the clinical study.
18. Planned or expected major surgical procedure during the clinical study, including a scheduled kidney transplant during the study. Subjects on a kidney transplant waiting list with no scheduled transplant date are not excluded.
19. Has not adhered to the restrictions in the selected medications and dialysis procedures prior to screening or is not expected to be compliant with restrictions during the study as listed in the following table.

| | **Timeframe** | |
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| **Treatment(s)** | **Before Screening** | **Screening Period and Day 1 – Week 20** |
| Systemic corticosteroids (i.e., administered by the intravenous, oral, or intramuscular route).<br>Note: Low dose prednisone (up to 10 mg per day [or equivalent other corticosteroid]) is permitted if the dose has been stable for 2 weeks prior to Screening<br>Note: Use of steroids given by other routes (inhaled, topical for indications other than itching, ophthalmic, intra-articular, etc. are permitted). | Not allowed for 4 weeks, other than stable low dose prednisone or equivalent | Prohibited, other than stable low dose prednisone or equivalent |
| Topical corticosteroids | Not allowed for 2 weeks | Prohibited |
| Topical PDE-4 inhibitor | Not allowed for 2 weeks | Prohibited |
| TCIs | Not allowed for 2 weeks | Prohibited |
| Biologics and their biosimilars (e.g. etanercept, adalimumab, infliximab, omalizumab, etc.) | Not allowed for 8 weeks or 5 half-lives (whichever is longer) | Prohibited |
| Dupilumab | Not allowed for 10 weeks | Prohibited |
| Cannabinoids | Not allowed for 2 weeks | Prohibited |
| Immunosuppressive or immunomodulatory drugs (e.g. cyclosporine A, oral tacrolimus, cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, JAK inhibitors) | Not allowed for 4 weeks or 5 half-lives (whichever is longer) | Prohibited |
| Systemic and topical antihistamines (excluding for ophthalmic use) | Stable dose for 2 weeks | Stable dose |
| Local anesthetics such as pramoxine, seed oil, capsaicin, topical ketamine, CBD oil, various lotions with anti-pruritic effects, etc. | Not allowed for 1 week | Prohibited |
| Gabapentin and pregabalin | Stable dose for 2 weeks | Stable dose |
| Phototherapy or tanning beds | Not allowed for 4 weeks | Prohibited |

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| | Selected Opioids<br>Nalbuphine or kappa opioid agonists (e.g., difelikefalin, nalfurafine) | Not allowed for 4 weeks | Prohibited |
| | All other opioids (e.g. codeine, tramadol, oxycodone, hydrocodone, methadone, buprenorphine) | Stable dose for 2 weeks | Stable dose |
| | Change in hemodialysis treatment (i.e., number of hemodialysis sessions per week, change in dialyzer or switch between hemodialysis and hemodiafiltration). Also see inclusion criterion #2 | Not allowed for 8 weeks | Prohibited |
| | Live attenuated vaccine and non-live vaccine (Seasonal vaccine (e.g., influenza), emergency vaccine (e.g., rabies or tetanus) and COVID vaccines as noted in Section 12.5.2 are permitted) | Not allowed for 4 weeks | Prohibited |

Abbreviations: PDE-4 = phosphodiesterase-4; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid.

For medications given as needed ("PRN"), stable dose during the study is defined as that without an increase or decrease by ≥75% in the total weekly dose relative to the dose during the last week of screening. For example, if the total weekly dose of 100 mg of diphenhydramine during the last week of the screening period increased to 175 mg in a given week during the study, this would be considered not a stable dose. During the Screening Period, a "stable dose" is one that has not changed (increase or decrease) by ≥ 75% during the period of required stability.

Note: Subjects should not interrupt ongoing treatment with medications important for the subject's health for the sole purpose of participating in this study.

20. Requiring rescue therapy for pruritus during the screening period or expected to require rescue therapy within 4 weeks following the baseline visit. See Section 12.5.1.2.
21. Previous treatment with nemolizumab.
22. History of hypersensitivity (including anaphylaxis) to an immunoglobulin product (plasma-derived or recombinant, e.g. monoclonal antibody) or to any of the study drug excipients.
23. Currently participating or participated in any other study of an investigational drug or device, within the past four weeks (or five half-lives of the investigational medication, whichever is longer) before the screening visit.
24. History of alcohol or substance abuse within six months of the screening visit.

**Study Endpoints:**

Data of both nemolizumab groups (30 mg and 60 mg) and placebo group and comparisons versus placebo group of both nemolizumab groups will be presented.

| **Primary Efficacy Estimand Description** | **Estimand Attributes** |
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| In adult hemodialysis patients with chronic kidney disease and associated moderate to severe pruritus, 2 nemolizumab dosing schedules[1] compared to placebo by the difference in proportions of responders where response is defined as an improvement from baseline of **WI NRS ≥ 4 at Week 12** without use of rescue therapies and without treatment discontinuation due to lack of efficacy or AE/death related to study drug | **Treatment Conditions**: initial dose of nemolizumab (60 mg) or placebo at baseline, then nemolizumab (30 mg or 60 mg) or placebo Q4W at Weeks 4 and 8 via subcutaneous injection. |
| | **Population**: adult hemodialysis patients with chronic kidney disease and associated moderate to severe pruritus (will be estimated in the Intent-to-Treat analysis set). |
| | **Variable**: a binary composite response where:<br><br>**Responder** is defined as an improvement ≥ 4 in WI NRS from baseline at Week 12 without use of rescue therapies and without treatment discontinuation due to lack of efficacy or AE/death related to study drug.<br><br>**Non-responder** is defined as an improvement < 4 in WI NRS from baseline at Week 12 or use of rescue therapies or treatment discontinuation due to lack of efficacy or AE/death related to study drug. |
| | **Strategies for Intercurrent Events**: A composite strategy was chosen for the use of rescue therapies and treatment discontinuation due to lack of efficacy or AE/death related to study drug; in case of use of rescue therapies or treatment discontinuation due to lack of efficacy or AE/death related to study drug, subjects will be considered as treatment failures in the binary composite response. In the case of treatment discontinuation for any other reason, a treatment policy strategy will be used and observed after discontinuation data (if available) will be used. |
| | **Summary measure**: treatment difference of nemolizumab from placebo in proportions of responders |

[1] Dosing schedules compared to placebo Q4W are an initial SC dose of nemolizumab (60 mg) at baseline then either 30 mg or 60 mg Q4W at Week 4 and Week 8.

Abbreviation(s): WI NRS = Worst Itch Numeric Rating Scale; Q4W = Every 4 Weeks

Key Secondary Efficacy Endpoints:

1. Proportion of subjects with an improvement of WI NRS ≥ 3 from baseline at Week 12.
2. Proportion of subjects with an improvement of WI NRS ≥ 4 from baseline at Week 4.
3. Proportion of subjects with an improvement of SD NRS ≥ 4 from baseline at Week 12.
4. Proportion of subjects with an improvement of WI NRS ≥ 3 from baseline at Week 4.
5. Proportion of subjects with an improvement of SD NRS ≥ 4 from baseline at Week 4.

CCI [redacted]

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| | CCI [redacted] |
| **Therapies:** | Investigational therapy<br>Nemolizumab 30 mg or placebo will be provided as lyophilized powder for solution for injection for SC use only after reconstitution in a dual-chamber, single-use syringe (DCS). Subjects will receive a loading dose of nemolizumab (60 mg) or placebo by two SC injections at baseline (30 mg + 30 mg, placebo + placebo) and a 30 mg or 60 mg dose of nemolizumab or placebo by two SC injections (30 mg + placebo, 30 mg + 30 mg, placebo + placebo) at Weeks 4 and 8. All the study drug treatment should be performed following the completion of the hemodialysis treatment (within four hours).<br><br>Rescue Therapies<br>If deemed to be medically necessary by the investigator (e.g. to control intolerable pruritus), rescue therapies can be prescribed to the subjects at any time during the study except during the screening period. Subjects receiving rescue therapies during the screening period are not eligible to participate in the study.<br><br>As a general guideline and per individual investigator judgment, rescue therapy should not be prescribed within the first four weeks after baseline to allow a minimum time for study drug potential effect in the presence of background therapy.<br><br>Investigator assessments of efficacy should be performed before initiating rescue therapy. Subjects requiring rescue therapy between scheduled visits should return to the clinic (unscheduled visit) for investigator assessment of efficacy before starting rescue therapy. The Investigator must contact the Medical Monitor prior to initiating rescue therapy.<br><br>As judged appropriate by the investigator and following discussion with the Medical Monitor, rescue therapies are defined as below and include the following treatments: |

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| | • Antihistamines (new or increased dose): For those given as needed ("PRN") at baseline, rescue of antihistamine is defined as that with an increase by ≥75% in the total weekly dose relative to the dose during the last week of screening administered for ≥ 1 week.<br>• Gabapentin (new or increased dose) administered for ≥ 1 week.<br>• Selected Opioids: Nalbuphine or kappa opioid agonists (e.g., difelikefalin, nalfurafine), one or more doses.<br>• Ultraviolet (UV) radiation therapy: one or more treatments.<br>Note: all new concomitant medication or increase of frequency or increase of dose will be recorded |
| **Treatment Duration:** | The expected duration of each subject's participation in the study is up to 24 weeks, including an up to 4-week screening period, a 12-week treatment period, and an 8-week follow-up period (12-weeks after the last study medication injection). |
| **Efficacy:** | The following efficacy assessments are planned according to the schedule of assessments:<br>• WI NRS<br>• SD NRS<br>CCI [redacted] |
| CCI | [redacted] |
| CCI [redacted] | [redacted] |
| **Statistical Methods and Planned Analyses:** | **Analysis Populations**<br>Statistical analyses will be performed on the following subject populations.<br>• **Intent-to-Treat Population**: The intent-to-treat (ITT) population will consist of all randomized subjects.<br>• **Modified Intent-to-Treat Population**: The modified intent-to-treat (mITT) population will consist of all ITT subjects who receive at least one dose of study drug and have at least one post baseline assessment of primary efficacy variable. |

- **Per Protocol Population**: The per protocol (PP) population will include all randomized subjects who receive all scheduled doses of study drug and have Baseline and Week 12 assessments of WI NRS and with no major deviation that could impact efficacy.
- **Safety Population**: The safety population will include all randomized subjects who receive at least one dose of study drug.
- CCI [redacted]

The ITT population will be the primary population for all efficacy analyses. The mITT and PP populations will be used for the supplementary analysis of the primary endpoint. CCI [redacted]

**Efficacy Analysis**

A summary based on observed case (OC) will be provided for all primary, secondary, and exploratory efficacy endpoints. At this case, no data will be imputed. For this summary, if any rescue medication is received or treatment is discontinued, and data are collected post-rescue receipt or treatment discontinuation, then the data post-rescue or post-discontinuation will be summarized as observed.

Proportion of subjects with WI NRS/SD NRS ≥ 4 and WI NRS ≥ 3, changes and percent changes from baseline of WI NRS/SD NRS at each week (from week 1 through week 20) will be calculated on the basis of the weekly average, obtained by averaging at least 4 daily WI NRS/SD NRS scores over 7-day periods. If fewer than 4 daily WI NRS/SD NRS scores for the 7-day period (for baseline and week 12 wider periods apply) are available, weekly average WI NRS/SD NRS will be considered missing for that period. For the aim of sensitivity analyses, weekly averages of WI NRS obtained by averaging at least 3, 2 and 1 daily scores over 7-day periods will be calculated (no period extension at baseline and week 12 applies for these weekly averages). For detailed rules, refer to section 19.3.

Data of both nemolizumab groups (30 mg and 60 mg) and placebo group and comparisons versus placebo group of both nemolizumab groups will be presented.

**Analysis of Primary Efficacy Endpoint**

The proportion of subjects with an improvement of WI NRS ≥ 4 from baseline will be analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by analysis center; strata-adjusted difference in proportions between treatment groups and the 97.5% confidence interval (CI) of the difference will be based on the large sample approximation method for binary data.

**Analysis of Key Secondary Efficacy Endpoints**

The following key secondary efficacy endpoints will be analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by analysis center; strata-adjusted difference in proportions between treatment groups and the 97.5% confidence interval of the difference will be based on the large sample approximation method for binary data.

- Proportion of subjects with an improvement of WI NRS ≥ 3 from baseline at Week 12.
- Proportion of subjects with an improvement of WI NRS ≥ 4 from baseline at Week 4.
- Proportion of subjects with an improvement of SD NRS ≥ 4 from baseline at Week 12.
- Proportion of subjects with an improvement of WI NRS ≥ 3 from baseline at Week 4.
- Proportion of subjects with an improvement of SD NRS ≥ 4 from baseline at Week 4.

CCI [redacted]

**Multiplicity Adjustment for Primary and Key Secondary Efficacy Endpoints**

In order to maintain the overall two-sided alpha of 0.05, a two-sided alpha of 0.025 will be spent for the comparison of each Nemolizumab dose group versus placebo group. A predefined hierarchal testing procedure will be implemented to test the primary and key secondary endpoints of each nemolizumab dose group versus placebo group.

**Analysis Centers**

Prior to database lock, a review of the blinded data will be performed to determine the size of each center. If there are centers with a small number of randomized subjects (i.e., centers with less than 12 randomized subjects), then these centers will be pooled in order for analyses to be carried out. The process of combining centers will be based on the ITT population, and same pooling will be repeated for mITT population and PP population.

**Handling of Missing Data**

Missing data for dichotomous efficacy endpoints will be imputed using multiple imputations (MI) under missing at random (MAR) assumption for the primary/main analyses. Dichotomous endpoints will be calculated from the underlying imputed variable.

For the sensitivity analyses of the primary endpoint, missing data will be imputed using a copy reference (CR) approach under missing not at random (MNAR) assumption

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| | (dichotomous endpoints will be calculated from the underlying imputed variable) and as "Non-responder"; moreover a Tipping Point analysis under MNAR assumption will be carried out.<br><br>For the sensitivity analyses of the key secondary efficacy endpoints, missing data will be imputed using a CR approach under MNAR assumption (dichotomous endpoints will be calculated from the underlying imputed variable) and as "Non-responder."<br><br>Missing data for continuous efficacy endpoints and Quality-of-life/Health Outcome endpoints will be imputed using MI under MAR assumption.<br><br>For the multiple imputation, the MI procedure of the SAS system will be used to generate sets of data with missing values imputed from observed data. It is expected that the pattern of missing data will be monotonic, with slight deviations being corrected by the Markov Chain Monte Carlo (MCMC) method of the MI procedure. A predictive mean matching method will be used for the continuous data with the following covariates included in the imputation model: non-missing data from earlier time points. Separate imputations by treatment group will be carried out. Changes and percent changes from baseline and dichotomous endpoints will be calculated from the imputed data.<br><br>Subjects who took rescue therapies or discontinued treatment due to lack of efficacy or AE/death related to study drug will be considered as treatment failures, efficacy data collected after the use of rescue therapies or treatment discontinuation due to lack of efficacy or AE/death related to study drug will be set to the worst possible value and subject's binary response will be imputed as "Non-responder" prior to conducting the MI and Tipping Point analysis.<br><br>**Sensitivity and Supplementary Analysis for Primary and Key Secondary Efficacy Endpoints**<br><br>For the sensitivity analyses of the primary endpoint, missing data will be imputed using a copy reference (CR) approach under missing not at random (MNAR) assumption (dichotomous endpoints will be calculated from the underlying imputed variable) and as "Non-responder"; moreover a Tipping Point analysis under MNAR assumption will be carried out. Furthermore, the analysis of the primary efficacy endpoint will be repeated using weekly averages of WI NRS with at least 3 daily scores over 7-day periods, at least 2 daily scores over 7-day periods and at least 1 daily scores over 7-day periods (no period extension at baseline and week 12 applies for these averages).<br><br>A mITT analysis, a PP analysis and an observed case analysis will be performed too as supplementary analyses for the primary efficacy endpoint.<br><br>Sensitivity analyses will be performed by imputing missing data using a CR approach under MNAR assumption (dichotomous endpoints will be calculated from the underlying imputed variable) and as "Non-responder" for the following key secondary efficacy endpoints:<br><br>• Proportion of subjects with an improvement of WI NRS ≥ 3 from baseline at Week 12.<br><br>• Proportion of subjects with an improvement of WI NRS ≥ 4 from baseline at Week 4.<br><br>• Proportion of subjects with an improvement of SD NRS ≥ 4 from baseline at Week 12.<br><br>• Proportion of subjects with an improvement of WI NRS ≥ 3 from baseline at Week 4.<br><br>• Proportion of subjects with an improvement of SD NRS ≥ 4 from baseline at Week 4. |

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| | Subjects who took rescue therapies or discontinued treatment due to lack of efficacy or AE/death related to study drug will be considered as treatment failures, efficacy data collected after the use of rescue therapies or treatment discontinuation due to lack of efficacy or AE/death related to study drug will be set to the worst possible value and subject's binary response will be imputed as "Non-responder" prior to conducting the MI and Tipping Point analysis.<br><br>**Impact of COVID-19**<br><br>To assess the impact of COVID-19 related study disruptions (e.g. treatment discontinuation, missing assessments, etc.), the primary and key secondary efficacy endpoints will also be analyzed using multiple imputations (MI) under missing at random (MAR) assumption on the ITT population excluding subjects affected by COVID-19 related study disruptions.<br><br>**Subgroup Analysis**<br><br>Descriptive summary and analysis for primary and key secondary efficacy endpoints will be produced for the following subgroups:<br>• Age group (18 to 45; >45 to 65; >65 to 80; >80)<br>• Sex (Male, Female)<br>• Race (White, Black, Asian, Other)<br>• Region (US; Excl-US)<br>• Severity of pruritus at baseline (5 to 7; >7 to 10)<br>• Duration of pruritus at baseline (≤3 months; >3 to 12 months; >12 months)<br>• Duration of hemodialysis at baseline (≤1 year; >1 year to 3 years; >3 years)<br>• With or without prior or concomitant systemic anti-pruritus treatment<br><br>**Safety Analysis**<br><br>The duration of exposure and the number of administrations per subject will be summarized by treatment group.<br><br>TEAEs, AESIs, and SAEs will be summarized using frequency tables by System Organ Class (SOC) and Preferred Term (PT) based on the Medical Dictionary for Regulatory Activities (MedDRA version 23.0 or later).<br><br>Physical examination, vital signs (including weight), clinical laboratory tests, ECG and respiratory examination and assessments will be summarized by visit using descriptive statistics/frequency tables as applicable. Shift tables from baseline by reference ranges will be presented for clinical laboratory tests.<br><br>**Dose selection**<br><br>Dose selection will be based on the final analysis by evaluating the optimal risk-benefit and considering the potential impact of body weight.<br><br>CCI [redacted]<br><br>**Safety assessment**<br><br>The IDMC will review and monitor subject safety throughout the study. |

## 6 TABLE OF CONTENTS

## LIST OF TABLES

# 7 LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ACT | Asthma Control Test |
| AD | Atopic dermatitis |
| ADA | Anti-drug antibody |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALT | Alanine aminotransferase |
| ANCOVA | Analysis of covariance |
| AR | Adverse reaction |
| AST | Aspartate aminotransferase |
| AVF | Arteriovenous Fistula |
| AVG | Arteriovenous Graft |
| BCG | Bacillus Calmette-Guérin |
| BL | Baseline |
| CDC | Center for Disease Control and Prevention |
| CDER | Center for Drug Evaluation and Research |
| CFR | Code of Federal Regulations |
| CI | Confidence interval |
| CKD | Chronic kidney disease |
| CKD-aP | Chronic kidney disease with associated pruritis |
| CMH | Cochran-Mantel-Haenszel |
| COVID-19 | Coronavirus disease 2019 |
| CP | Conditional power |
| CPK | Creatine phosphokinase |
| CR | Copy reference |
| CRO | Contract research organization |
| CS | Clinically significant |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CV | Coefficient of variation |
| CYP450 | Cytochrome P450 |
| DCS | Dual-chamber, single-use syringe |
| EASI | Eczema Area and Severity Index |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| EDC | electronic data capture |
| ELISA | Enzyme-linked immunosorbent assay |
| EMEA | Europe, Middle East, and Africa |
| ESKD | End-stage kidney disease |
| EQ-5D-5L | EuroQoL 5-dimension 5-level |
| ET | Early termination |
| FSH | Follicle-stimulating hormone |
| GCP | Good Clinical practice |
| CCI | [redacted] |

| Abbreviation | Definition |
|---|---|
| HbcAb | Hepatitis B core antibody |
| HbsAg | Hepatitis B surface antigen |
| HCV | Hepatitis C virus |
| HDL | High-density lipoprotein |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human immunodeficiency virus |
| IAC | Independent adjudication committee |
| IB | Investigator's Brochure |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IDMC | Independent Data Monitoring Committee |
| IEC | Independent Ethics Committee |
| IGA | Investigator's Global Assessment |
| IL | Interleukin |
| IRB | Institutional Review Board |
| IRR | Injection-related reaction |
| IRT | Interactive response technology |
| ITT | Intent-to-treat |
| IUG | Independent Unblinded Group |
| JAK | Janus kinase |
| Kt/V | Volume of plasma cleared of urea (Kt) relative to volume of distribution of urea (V) |
| LCL | Lower Confidence Limit |
| LSM | Least squares mean |
| MAR | Missing at random |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MNAR | Missing not at random |
| MCMC | Markov-Chain-Monte-Carlo |
| MI | Multiple imputation |
| mITT | Modified intent-to-treat |
| N | Number of subjects or sample size |
| NA | North America |
| NCS | Not clinically significant |
| NRS | Numeric rating scale |
| OC | Observed case |
| PCR | Polymerase chain reaction |
| PD | Pharmacodynamics |
| PDE | Phosphodiesterase |
| PE | Point Estimate |
| PEF | Peak expiratory flow |
| C [redacted] | [redacted] |
| Cl [redacted] | [redacted] |
| PN | Prurigo nodularis |
| popPK | Population pharmacokinetics |

| Abbreviation | Definition |
|---|---|
| PP | Per protocol |
| PRN | Pro re nata (when necessary or as needed) |
| PT | Preferred Term |
| PTC | Product technical complaint |
| Q4W | Every four weeks |
| QoL | Quality of life |
| RA | Receptor A |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SC | Subcutaneous |
| SD NRS | Sleep Disturbance Numeric Rating Scale |
| SHPT | Secondary hyperparathyroidism |
| SIN | Subject identification number |
| SOC | System Organ Class |
| SRO | Subject-reported outcome |
| SUSAR | Suspected unexpected serious adverse reaction |
| TB | Tuberculosis |
| TCI | Topical calcineurin inhibitor |
| TCS | Topical corticosteroid |
| TEAE | Treatment-emergent adverse event |
| TMF | Trial Master File |
| UCL | Upper Confidence Limit |
| ULN | Upper limit of normal |
| US | United States |
| UV | Ultraviolet |
| VAS | Visual analogue scale |
| WI NRS | Worst Itch Numeric Rating Scale |
| WOCBP | Women of childbearing potential |
| WHO | World Health Organization |

# 8 INTRODUCTION

## 8.1 Background on Chronic Kidney Disease with associated Pruritus

Chronic kidney disease with associated pruritus (CKD-aP) is a common, troubling and, in some cases, debilitating problem for patients with chronic kidney disease (CKD) and end-stage kidney disease (ESKD). It's characterized by systemic and intractable itching and is one of the diseases that troubles dialysis patients on a daily basis including adverse medical outcomes and poor quality of life (QoL).

A survey conducted in Japan in 2000 revealed that 72.8% of hemodialysis patients have experienced pruritus and that around half of these individuals have suffered from sleep disturbance (Omori 2001). Furthermore, the extent of sleeplessness among patients with CKD-aP reportedly increased as the itching became more severe (Narita 2006, Kimata 2014). The Dialysis Outcomes and Practice Patterns Study conducted in 12 countries found that approximately 41.7% of tracked patients had at least moderate pruritus and reduced sleep quality (Pisoni 2006). Severe pruritus is also a purported risk factor for poor prognosis among dialysis patients (Narita 2006).

More recently (i.e., 2012-2015), an international comparison on the prevalence of pruritis in hemodialysis patients found that 68% of survey respondents reported they were at least somewhat bothered by itchy skin (31% somewhat; 19% moderately; 11% very much; 7% extremely). Of the patients that were very much or extremely bothered by itchy skin, 84% were also bothered by dry skin, and 60% had sleep restlessness. Similar findings were reported in country specific regions such as the US and throughout Europe (Rayner 2017).

Despite a prevalence rate and a clear association with poorer psychosocial and medical outcomes including higher mortality risk (Pisoni 2006), this condition is often underreported by patients and overlooked by health care providers. In one survey, the rate of pruritis in hemodialysis patients was underestimated by medical directors by 69% (Rayner 2017). This is likely due, in part, to uncertainty regarding its pathogenesis and treatment. Conventional treatments include changing the dialysis conditions or using highly biocompatible dialysis membranes, regulating calcium and phosphorus concentrations, treating the secondary hyperparathyroidism (SHPT), topical application of moisturizers or steroid preparations, drug therapy with antihistamines or anti-allergic agents, and ultraviolet (UV) phototherapy. Nevertheless, these treatments often prove ineffective (Kfoury 2012).

The cause of CKD-aP has been attributed to various factors including accumulation of uremic substances, elevated serum calcium and phosphorus concentrations, SHPT, dialysis membrane-induced complement activation or heparin, induction of endogenous itch mediators (e.g., histamines, serotonin, substance P), immune system abnormalities, and endogenous opioid abnormalities. However, the precise mechanism of onset is still unclear.

In Japan, nalfurafine hydrochloride was launched in 2009 for the indication of improvement of pruritus in hemodialysis patients when response to conventional treatments is inadequate. However, the degree of improvement in pruritus after taking nalfurafine hydrochloride has varied among patients (Yamada 2012), and 19.4% of clinical trial subjects experienced insomnia (sleep disturbance) as an adverse reaction (AR) to the drug (Kumagai 2012). On 23 AUG 2021, the US Food and Drug Administration granted NDA approval through priority review for difelikefalin for the treatment of moderate to severe pruritus in hemodialysis

patients (Fishbane 2020), thus highlighting the need for further investigations into treatment options that possesses both adequate efficacy and a high level of safety for this population.

A 2014 study by Ko et al. investigated the relationship between CKD-aP and serum interleukin (IL-31) concentrations in 178 patients undergoing hemodialysis (Ko 2014). The study found that serum IL-31 concentrations were higher in patients with pruritus than in those without pruritus and that some of the patients with pruritus had serum IL-31 concentrations that exceeded 100 pg/mL. The study also found a correlation between serum IL-31 concentration and the Visual Analog Scale (VAS) score of pruritus intensity in patients whose serum IL-31 concentrations exceeded a certain level. This finding implies that IL-31 is involved in itching in CKD-aP and suggests that inhibition of IL-31 may have a therapeutic effect.

## 8.2 Background on Nemolizumab

Nemolizumab is a humanized anti-human IL-31 receptor A (RA) monoclonal antibody that inhibits the binding of IL-31 to IL-31RA and subsequent signal transduction. The T-cell-derived cytokine IL-31 has been suggested to be a key player in the development of pruritus, inducing severe pruritus and dermatitis in mouse models (Dillon 2004, Arai 2013). IL-31 binds to a heterodimeric receptor at TRPV1 (+)/TRPA1 (+)-Cfibres, keratinocytes, macrophages and eosinophils, and thus may be involved in transmission of pruritus and promotion of inflammation. Not limited to the skin, the densest area of this receptor seems to be at the dorsal horn of spinal cord where the cell bodies of cutaneous sensory neurons reside (Sonkoly 2006). Therefore, IL-31 may be a link between the immune and the neural system.

Nemolizumab, with its novel mechanism of action of blocking the IL-31 pathway, is expected to have a therapeutic effect in patients with CKD-aP, atopic dermatitis (AD), and prurigo nodularis (PN) not adequately controlled by existing treatments.

Nemolizumab was initially developed by Chugai Pharmaceutical Co., Ltd., a Japanese based pharmaceutical company; it was subsequently licensed to Galderma (sponsor) in 2016 worldwide except in Japan and Taiwan. Nemolizumab is an investigational agent under clinical development, and its safety and efficacy have not been fully evaluated by any regulatory authority.

## 8.3 Clinical Studies with Nemolizumab

The Investigator's Brochure (IB) contains detailed information on clinical and non-clinical studies. Summaries of completed and ongoing clinical studies of nemolizumab in CKD-aP, AD, and PN are included in the IB. The CKD-ap phase 2a study is outlined below.

### 8.3.1 Phase 2a Study in Subjects with CKD-aP

Study CIM106JP was a Phase 2a study conducted in adult hemodialysis subjects with uremic pruritus (Kinugasa 2021). The study was a randomized, double-blind, placebo-controlled, parallel four arm study with three doses of blinded study drug (CIM331; Chugai's internal code for nemolizumab) or placebo, and an open-label reference product arm (nalfurafine hydrochloride group). Study duration was 12 weeks. The population consisted of hemodialysis subjects with pruritus for which existing treatment, other than nalfurafine hydrochloride, was ineffective.

The primary endpoint was to analyse the absolute change in pruritus VAS score from baseline to four weeks. It was the pairwise comparison of each nemolizumab treatment group against placebo. Secondary endpoints included Pruritus VAS score, and the Shiratori severity score. (The Shiratori severity score is a Japanese itch severity questionnaire, which includes separate set of questions for both daytime and nighttime. Each set of questions consists of 5 grades from 0 to 4, with 4 being the worst and 0 being absent. Grade 3 or higher on each scale was considered moderate to severe pruritus). 5-D itch scale score and mean in absolute change from baseline at each evaluation time point up to week 12, and CCI [redacted]), safety. A total of 69 subjects were enrolled:15 subjects in the nemolizumab 0.125 mg/kg group, 14 subjects in the placebo and nemolizumab 2.0 mg/kg groups, and 13 subjects in the nemolizumab 0.5 mg/kg and nalfurafine hydrochloride groups). There were not statistically significant differences between the placebo group and each nemolizumab group in the absolute changes in pruritus VAS at Week 4 the primary efficacy endpoint. The LSM absolute changes in pruritus VAS (95% CI) at Week 4, the primary efficacy parameter, were −32.09 mm (−44.40 mm, −19.78 mm) in the placebo group, and −34.50 mm (−46.73 mm, −22.28 mm), −40.82 mm (−53.61 mm, −28.04 mm), and −31.74 mm (−43.97 mm, −19.51 mm) in the CIM331 0.125, 0.5, and 2.0 mg/kg groups, respectively.

In all groups including the placebo group, remarkable improvements in pruritus VAS were observed by Week 4.

In all groups including the placebo group, improvements in the secondary efficacy parameters, pruritus VAS, Shiratori severity score, and 5-D itch score, were observed by Week 4, and there was no clear difference between the placebo group and each nemolizumab group.

However, post hoc analyses conducted in the proportion of subjects achieving a pruritus VAS score of less than 30 mm (corresponding to "no or mild pruritus") showed approximately two-fold higher proportion in the 0.5 mg/kg group compared to that in the placebo group at Week 4.

The proportion of subjects with decrease in VAS ≥ 30 or ≥ 40 mm, proportion of subjects with VAS ≤ 2 or with VAS 0 -1 from baseline in all dose groups of nemolizumab were higher than that in the placebo group at week 4. Again, the 0.5 mg/kg dose provide the best efficacy profile compared to the two other tested doses.

The placebo effect of this study has been higher than expected. This could be explained by the bias of subjects expecting similar or superior effect of the blinded treatment including the blinded placebo, compared to open-label nalfurafine, the treatment subjects has received prior to randomization into the study. Therefore, the placebo effect might have been biased by expectation of higher treatment effect of the blinded treatments compared to the effect

subjects had experienced with nalfurafine before entering the study. Consistent with the explanation, open-label nalfurafine performed inferior to placebo.

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Overall, no clinically significant (CS) safety findings were reported in the nemolizumab groups.

### 8.4 Risk/Benefit Assessment

Results of previous clinical studies in adults demonstrated that treatment with nemolizumab had a marked effect on AD and PN, pruritus, and pruritus-related sleep loss. Nemolizumab was also well tolerated overall when used as monotherapy or concomitantly with a TCS.

Based on the currently available information on nemolizumab and the risks associated with biologic agents in general, the potential risks of nemolizumab treatment include local or systemic IRRs, newly diagnosed asthma or worsening of asthma, and skin or non-skin infections. Refer to the IB for the most current risk/benefits.

The following specific risk-minimization and safety follow-up measures have been planned in this clinical study:

a. In a phase 2b study for Atopic dermatitis indication (SPR.114322), a dose-dependent increase of asthma flares (1 [1.8%], 2 [3.6%], 7 [12.3%], and 10 [17.5%] in placebo, 10 mg, 30 mg, and 90 mg treatment arms, respectively) in subjects with pre-existing asthma was observed. Events were mostly mild or moderate (one severe event with highest dose), manageable, and reversible under treatment with study drug. This protocol (SPR. 204358) will exclude subjects with asthma exacerbation requiring hospitalization in the preceding 12 months before screening, subjects whose asthma has not been well controlled (i.e., symptoms > 2 days per week, nighttime awakenings two or more times per week, or some interference with normal activities) during the last three months before the screening visit, and Asthma Control Test (ACT) score ≤ 19. At all visits, all subjects will be asked about respiratory changes and a respiratory examination will be performed. At screening and baseline conduct PEF for all subjects and ACT for subjects with medical history of asthma. After baseline ACT and PEF are only required for subjects with a medical history of asthma. Subjects diagnosed with de novo asthma will perform PEF and ACT assessments at all visits starting with the visit in which the diagnosis was confirmed. Subjects with a medical history of asthma will be referred to the physician managing their asthma if ACT ≤ 19, with signs and symptoms suggestive of asthma, and/or unexpected worsening of asthma is observed or reported, PEF value is used as supplemental information. Subjects without a medical history of asthma will be referred to a respiratory specialist if respiratory changes suggestive of asthma are observed or reported. An independent adjudication committee (IAC) will review and adjudicate all asthma AEs reported during the course of the study. PEF value is used as supplemental information as well.

b. The exclusion criteria of this clinical study (i.e., restricting entry of subjects with recent/current infections or known/suspected immunosuppression or unusually frequent, recurrent, severe, or prolonged infections) will prevent non-eligible subjects at potentially higher risk of infection from receiving nemolizumab. As no data are available in pregnant or breastfeeding women, these subjects are not eligible for this study. Subjects who have recently received live vaccines may be considered for enrollment after an appropriate time has elapsed before baseline/Day 1. Administration of live attenuated vaccines and non-live vaccine is prohibited during the study.

c. A slight trend of dose-dependent increase of peripheral edema was reported in the nemolizumab study CIM003JG. Most events were mild (11 of 21), no case was serious, and none resulted in premature treatment discontinuation; no case was associated with renal or cardiac AEs. The EASI values and thymus and activation regulated chemokine levels were relatively higher in subjects with peripheral edema indicating that peripheral edema might be related to more severe AD. There were a few subjects reporting peripheral edema in study SPR.114322 (2 [3.6%], 2 [3.6%], 4 [7%], and 2 [3.5%] in placebo, 10 mg, 30 mg, and 90 mg groups, respectively). Peripheral edema will be followed as an AE of special interest (AESI) in this study. Recognizing that peripheral edema occurs commonly in dialysis patients related to their overall volume status, dialysis treatment, and other factors, peripheral edema is only to be reported as an AESI if assessed by the investigator as having a reasonable possibility for a relationship to study drug.

d. An independent data monitoring committee (IDMC) will monitor the safety data regularly throughout the study, including AESIs, which were defined based on the currently available safety information on nemolizumab and the risks associated with biologic agents in general. AESIs for this study are:

    - IRRs
        - Anaphylactic reactions
        - Acute allergic reactions requiring treatment
        - Severe injection site reactions with a duration greater than 24 hours
    - Newly diagnosed asthma or worsening of asthma
    - Infections
        - Any severe infection or any infection requiring treatment with parenteral antibiotics or with oral antibiotics/antivirals/antifungals for > 2 weeks
        - Any confirmed or suspected coronavirus disease (COVID-19) infection

- Peripheral edema: limbs, if assessed by the investigator as having a reasonable possibility for a relationship to study drug. Peripheral edema is only to be reported as an AESI if assessed by the investigator as having a reasonable possibility for a relationship to study drug.
- Facial edema
- Elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (> 3 × upper limit of normal [ULN]) in combination with elevated bilirubin (> 2 × ULN). Note: This abnormal lab findings may indicate potential severe liver injury (possible Hy's Law) and should be reported as an SAE (see Section 16.10 AESI and Section 16.12.2 Procedure for reporting a serious adverse event).

In conclusion, when taking into consideration the currently available data of nemolizumab and the risk-minimization approaches to be implemented, the benefit/risk ratio of nemolizumab is considered to be favorable in this study.

## 8.5 Drug Profile

Nemolizumab is a humanized monoclonal modified immunoglobulin G2 (IgG2) antibody comprising a structure of 2 H-chains (445 amino acid residues) and 2 L-chains (214 amino acid residues) connected by 16 disulfide bonds. The investigational product will be supplied as a lyophilized powder for solution for SC injection only after reconstitution in a pre-filled, dual-chamber, single-use syringe (DCS). The lyophilized nemolizumab powder (39 mg) and solution for reconstitution (0.595 mL) are stored in separate syringe chambers, with each DCS designed to deliver a 30 mg dose of nemolizumab. The concentration of nemolizumab in the DCS will be 61.5 mg/mL once reconstituted, with an injection volume of 0.49 mL (for the loading dose, two injections of 0.49 mL).

The placebo will be supplied as a lyophilized powder, reconstituted and administered in the same manner as the investigational product.

## 8.6 Study and Dose Selection Rationale

Based on data suggesting the role of IL-31 in the pathophysiology of CKD-aP (Ko 2014), Chugai conducted a Phase 2a study (study CIM106JP) to assess the efficacy and safety of ascending nemolizumab single doses (0.1 mg/kg, 0.5 mg/kg and 2.0 mg/kg) in subjects with CKD-aP undergoing hemodialysis. The data from this study were reviewed during an advisory board meeting held in October 2020 with experts in the field of Nephrology and Dermatology. Based on the secondary endpoints on efficacy trends, safety, and individual data analyses and post hoc analysis, the results indicated that nemolizumab was well tolerated and nemolizumab 0.5 mg/kg single dose was associated with the higher magnitude of effect on pruritus VAS. Consensual recommendation initially from the experts was to move forward with nemolizumab in subjects suffering from CKD-aP focusing first on subjects with severe pruritus as assessed by WI NRS of at least 7.0 and undergoing hemodialysis, therefore that was the approach in the original protocol.

From recently evolved data we believe that the treatment effect is unlikely driven by the severity of pruritus among the moderate and severe patients, based on the following findings: 1) Treatment effect including placebo effect observed from Difelifekalin pivotal studies are similar between severe vs. moderate plus severe pruritus HD pts and 2) Further review of the Chugai HD CKD phase 2a study (CIM106JP) 0.5mg/kg group (nemolizumab n= 12; placebo n=12), there was no different treatment pattern that could be identified between the group with VAS > 70 mm and VAS <70 mm at baseline. Thus, the protocol is amended (version 4, 08JUN22) to include Hemodialysis patients with both moderate to severe pruritus as assessed by WI NRS of at least 5.


Of note, it is acknowledged that patient population of CKD-aP is a new population and there is limited data available from the completed Phase 2a dose ranging trial to definitely conclude that there is a lack of effect of body weight on efficacy. Therefore, an additional 60 mg flat dose (without loading dose) will be assessed in this study and will provide data to decide on the need for weight-based dosing in subjects with higher body weight.

At the end of this study, dose selection will be based on the final analysis by evaluating the optimal risk-benefit and considering the potential impact of body weight.

# 9 STUDY OBJECTIVES AND ENDPOINTS

## 9.1 Study Objectives

### 9.1.1 Primary Objective

The primary objective is to evaluate the efficacy of nemolizumab compared to placebo at reducing the intensity of pruritus after a 12-week treatment period in adult hemodialysis subjects with moderate to severe pruritus.

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CCI [redacted].

## 9.2 Study Endpoints

Data of both nemolizumab groups (30 mg and 60 mg) and placebo group and comparisons versus placebo group of both nemolizumab groups will be presented.

### 9.2.1 Primary Efficacy Endpoint

| Primary Efficacy Estimand Description | Estimand Attributes |
|---|---|
| In adult hemodialysis patients with chronic kidney disease and associated moderate to severe pruritus, 2 nemolizumab dosing schedules[1] compared to placebo by the difference in proportions of responders where response is defined as an improvement from baseline of **WI NRS ≥ 4 at Week 12** without use of rescue therapies and without treatment discontinuation due to lack of efficacy or AE/death related to study drug | **Treatment Conditions**: initial dose of nemolizumab (60 mg) or placebo at baseline, then nemolizumab (30 mg or 60 mg) or placebo Q4W at Weeks 4 and 8 via subcutaneous injection. |
| | **Population**: adult hemodialysis patients with chronic kidney disease and associated moderate to severe pruritus (will be estimated in the Intent-to-Treat analysis set). |
| | **Variable**: a binary composite response where:<br><br>**Responder** is defined as an improvement ≥ 4 in WI NRS from baseline at Week 12 without use of rescue therapies and without treatment discontinuation due to lack of efficacy or AE/death related to study drug.<br><br>**Non-responder** is defined as an improvement < 4 in WI NRS from baseline at Week 12 or use of rescue therapies or treatment discontinuation due to lack of efficacy or AE/death related to study drug. |
| | **Strategies for Intercurrent Events**: A composite strategy was chosen for the use of rescue therapies and treatment discontinuation due to lack of efficacy or AE/death related to study drug; in case of use of rescue therapies or treatment discontinuation due to lack of efficacy or AE/death related to study drug, subjects will be considered as treatment failures in the binary composite response. In the case of treatment discontinuation for any other reason, a treatment policy strategy will be used and observed after discontinuation data (if available) will be used. |
| | **Summary measure**: treatment difference of nemolizumab from placebo in proportions of responders |

[1] Dosing schedules compared to placebo Q4W are an initial SC dose of nemolizumab (60 mg) at baseline then either 30 mg or 60 mg Q4W at Week 4 and Week 8.
Abbreviation(s): WI NRS = Worst Itch Numeric Rating Scale; Q4W = Every 4 Weeks

### 9.2.2 Secondary Efficacy Endpoints

#### *9.2.2.1 Key Secondary Efficacy Endpoints*

1. Proportion of subjects with an improvement of WI NRS ≥ 3 from baseline at Week 12.
2. Proportion of subjects with an improvement of WI NRS ≥ 4 from baseline at Week 4.
3. Proportion of subjects with an improvement of SD NRS ≥ 4 from baseline at Week 12.
4. Proportion of subjects with an improvement of WI NRS ≥ 3 from baseline at Week 4.
5. Proportion of subjects with an improvement of SD NRS ≥ 4 from baseline at Week 4.

CCI

CCI [redacted]

[redacted].

# 10 INVESTIGATIONAL PLAN

## 10.1 Description of Overall Study Design and Plan

This is a randomized, double-blind, placebo-controlled, multicenter, parallel-group, phase 2/3 study to evaluate the efficacy and safety of nemolizumab in adult subjects with CKD-aP.

Subjects will be randomized in one of the following three arms/groups (two different doses of nemolizumab and a placebo) in a 1:1:1 ratio:

- Group 1: 30 mg nemolizumab Q4W with a 60 mg loading dose at baseline;
- Group 2: 60 mg nemolizumab Q4W without loading dose at baseline;
- Group 3: placebo Q4W.

Approximately 84 subjects will be randomized in each nemolizumab group and in the placebo group for a total sample size of approximately 252 subjects.

In order to maintain the blind, all subjects will receive 2 injections at each administration (30 mg + 30 mg or 30 mg + placebo or placebo + placebo).

The study consists of a screening period (up to 4 weeks), a 12-week treatment period, and an 8-week follow up period (12 weeks after their last study drug injection).

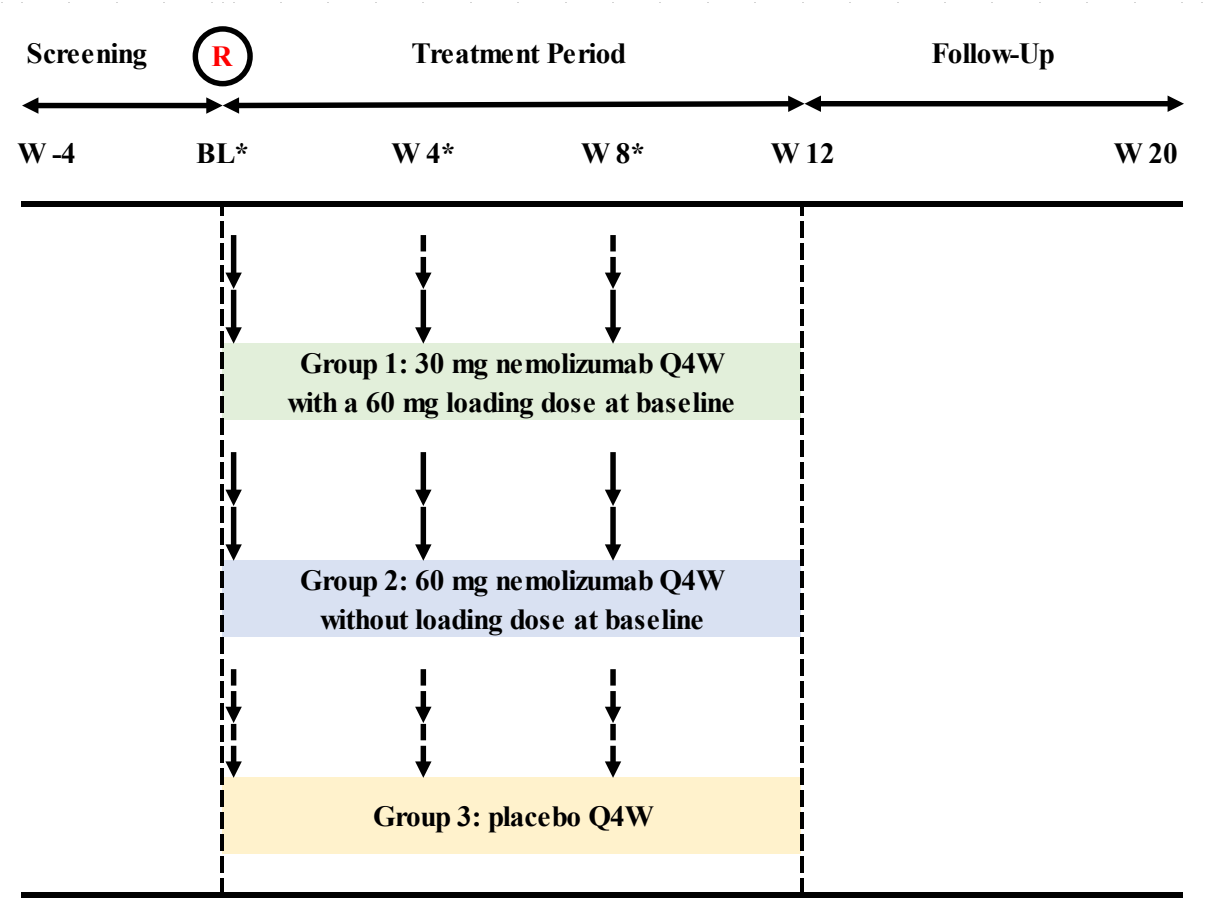
The screening period will evaluate subject eligibility. In exceptional circumstances, e.g. health reason or hemodialysis rescheduling, up to 72 hours deviation from screening window may be permitted after consultation with the Medical Monitor. The subjects' other (non-pruritus) complications of end-stage kidney disease (ESKD) are to be managed according to local standard of care. The use of moisturizers is encouraged to keep the skin hydrated.

At the baseline visit, subjects will receive an initial dose of nemolizumab 60 mg or placebo by two SC injections. Study drug treatment with either nemolizumab or placebo should start after completion of the hemodialysis treatment (within four hours). Then study drug (i.e., nemolizumab 30 mg, nemolizumab 60 mg or placebo) will be administered via two SC injections (30 mg + placebo, 30 mg + 30 mg, or placebo + placebo) Q4W at Week 4 and Week 8 after completion of hemodialysis treatment (within four hours). PK samples to be taken before hemodialysis. Refer to Section 13.1.

An IDMC will review and monitor subject safety throughout the study. The study team to remain blinded until the end of the study.

An independent adjudication committee (IAC) will review and adjudicate all asthma-related AEs.

### 10.1.1 Study Visit Schema




R = Randomization; * = Visits with study drug administration
Note: All subjects in each arm will receive 2 injections at each administration (either 30 mg + 30 mg, or 30 mg + placebo, or placebo + placebo) in order to mantain the blind

## 10.2 Discussion of Study Design

This study will evaluate the efficacy and safety of nemolizumab in adult subjects with CKD-aP undergoing hemodialysis. The rationale for the study is based on the prior Phase 2a study (study CIM106JP) conducted by the sponsor's licensing partner, and the recommendation from experts in the field of Nephrology and Dermatology to further investigate nemolizumab in subjects with CKD-aP. The rationale for the nemolizumab dose/dose regimen is provided in Section 8.6.

The subject population is selected based on the current unmet need in the management of CKD-aP, the mode of action of nemolizumab, and the need to better understand the efficacy and safety profile of nemolizumab in this indication. The study will enroll adult subjects with ESKD that have been on hemodialysis three times per week for at least three months prior to the start of screening. Other main inclusion criteria include hemodialysis adequacy (i.e., single-pool Kt/V measurements of at least 1.2), pruritis for ≥ 3 months (documented pruritus with no etiology identified other than CKD by medical record, previous physician's letter/statement, or written documentation by site investigators based on the medical history obtained from the subject), and a WI NRS score of ≥ 5.0 at the screening and baseline visit.

Following the screening period, qualified subjects will receive a loading dose of nemolizumab 60 mg or placebo by two SC injections at baseline (30 mg + 30 mg, placebo + placebo), and a 30 mg or 60 mg dose of nemolizumab or placebo by two SC injections (30 mg + placebo, 30 mg + 30 mg, placebo + placebo) at Weeks 4 and 8. All study drug treatments should be performed following the completion of the hemodialysis (within four hours). Subsequent visits will occur at Week 12 and Week 20 (end of study). A 12-week treatment period is considered adequate to evaluate the safety and efficacy of nemolizumab on pruritus based on the results of Phase 2a study and finding from other nemolizumab indications. The efficacy assessments are performed using validated scales that are commonly employed in pruritus clinical trials to capture subject-reported outcomes.

The primary endpoint is the proportion of subject with an improvement of WI NRS ≥ 4 from baseline at Week 12. The selected endpoints for assessing the CCI and safety of nemolizumab are in accordance with current standards, as are the safety endpoints of the study.

Differences may be detectable during the study drug reconstitution process between active study drug and placebo but appear similar after reconstitution is complete (approximately 10 minutes). Throughout the study, a pharmacist (or other qualified personnel) will prepare study medication for injection, including confirmation of complete reconstitution, prior to delivery of study medication for injection. The pharmacist (or other qualified personnel) preparing study medication should not be involved with any study assessments and should not discuss any aspects of study drug reconstitution with the subject/caregiver or study staff involved in subject interviews or study assessments.

If deemed to be medically necessary by the investigator (e.g. to control intolerable pruritus) and after discussion with the Medical Monitor, rescue therapies can be prescribed to the subjects at any time during the study except during the screening period. Subjects receiving rescue therapies during the screening period are not eligible to participate in the study.

As a general guideline and per individual investigator judgment, rescue therapy should not be prescribed within the first four weeks after baseline to allow a minimum time for study drug potential effect in the presence of background therapy.

Investigator assessments of efficacy should be performed before initiating rescue therapy. Subjects requiring rescue therapy between scheduled visits should return to the clinic (unscheduled visit) for investigator assessment of efficacy before starting rescue therapy. The Investigator must contact the Medical Monitor prior to initiating rescue therapy.

As judged appropriate by the investigator and following discussion with the Medical Monitor, rescue therapies include the following treatments:

- Antihistamines (new or increased dose): For those given as needed ("PRN") at baseline, rescue of antihistamine is defined as that with an increase by ≥75% in the total weekly dose relative to the dose during the last week of screening administered for ≥ 1 week.

- Gabapentin (new or increased dose) administered for ≥ 1 week.

- Selected Opioids: Nalbuphine or kappa opioid agonists (e.g., difelikefalin, nalfurafine), one or more doses

- Ultraviolet (UV) radiation therapy: one or more treatments

Note: all new concomitant medication or increase of frequency or increase of dose will be recoded

Blinding subjects and the designated study team to the treatment assignment(s) ensures objectivity and minimizes bias. Randomization through the interactive response technology (IRT) guards against selection bias. To avoid bias and to ensure the integrity of the blind, personnel directly involved with the ongoing conduct of the study from the sponsor, CRO, or other investigational study centers will not have access to any information that may lead to unblinding.

### 10.3 End of Study

A subject will have fulfilled the requirements for study completion if/when the subject has completed all study periods, including the follow-up visit at Week 20 or the last scheduled visit as indicated in the Schedule of Assessments (Table 5).

The end of the study will be the last subject's last visit as indicated in the Schedule of Assessments (Table 5).

# 11 SELECTION OF STUDY POPULATION

The study is to evaluate the efficacy and safety of nemolizumab in adult subjects with chronic kidney disease (CKD) undergoing hemodialysis with moderate to severe CKD-associated pruritus.

The subjects' other (non-pruritus) complications of End-stage kidney disease (ESKD) are to be managed according to local standard of care. The use of moisturizers is also encouraged to keep their skin hydrated.

The study allows for stable background use of the most common medications prescribed for patients with this condition (antihistamines and gabapentin) but disallows use of other treatments as well as significant changes to the hemodialysis prescription within 8 weeks prior to screening (see exclusion criterion 19). The study population consist of patients with moderate to severe CKD-associated pruritus (WI NRS ≥ 5.0 ).

Section 10.1 provides information regarding the number of subjects planned to be randomized.

Refer to Section 19.1 for the statistical considerations on which the sample size is based.

## 11.1 Number of Planned Subjects

Approximately 84 subjects will be randomized in each nemolizumab group and in the placebo group for a total sample size of approximately 252 subjects. Refer to Section 19.1 for the statistical considerations on which the sample size is based.

## 11.2 Inclusion Criteria

Individuals must meet all of the following criteria to be included in the study:

1. Subjects aged ≥ 18 years at the screening visit.

2. Has end-stage kidney disease (ESKD) and have been on hemodialysis three times per week for at least three months prior to the start of screening.

   Note 1: Subjects who require an occasional additional hemodialysis treatment to manage fluid overload may be enrolled as long as it is anticipated that no more than one such treatment will be required in any given week.

   Note 2: Subjects having received in-home hemodialysis may participate as long as they have switched to in-center hemodialysis at least two weeks prior to screening and plan to remain on in-center hemodialysis for the duration of the study.

3. Hemodialysis subjects meeting the Kidney Outcome Quality Initiative Guidelines of hemodialysis adequacy within 60 days of screening, two:

   - Single-pool Kt/V measurements of at least 1.2.

4. Pruritus for ≥ three months (documented pruritus with no etiology identified other than CKD by medical record, previous physician's letter/statement, or a written documentation by of site investigators based on the medical history obtained from the subject).

5. WI NRS score ≥ 5.0 at the screening and baseline visit. Screening WI NRS score will be determined by a single WI NRS assessment (score ranging from 0 to 10) for the 24-hour period immediately preceding the screening visit. Baseline WI NRS score will be determined based on the weekly average of daily WI NRS scores (score ranging from 0 to 10) during the seven days immediately preceding baseline (rounding is not permitted). A minimum of four daily scores out of the seven days immediately preceding baseline is required for this calculation.

6. Women of childbearing potential (WOCBP) (i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile) must agree either to commit to true abstinence throughout the study and for 12 weeks after the last study drug injection, when this is in line with the preferred and usual lifestyle of the subject, or to use an adequate and approved method of contraception throughout the study and for 12 weeks after the last study injection.

   Adequate and approved methods of contraception applicable for the subject and/or her partner are defined below:

   - Progestogen-only oral hormonal contraception.
   - Combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier methods).

     Note: "Double barrier methods" refers to simultaneous use of a physical barrier by each partner. Use of a single barrier method (e.g., condom) together with a spermicide is not acceptable.
   - Combined (estrogen- and progestogen-containing) oral, intravaginal, or transdermal hormonal contraception.
   - Injectable or implanted hormonal contraception.
   - Intrauterine devices or intrauterine hormone releasing system.
   - Bilateral tubal ligation or tube insert (such as the Essure system) at least three months before the study.
   - Bilateral vasectomy of partner at least three months before the study.

7. Women are considered to be of non-childbearing potential if they meet one of the following criteria:

   - Absence of menstrual bleeding for one year prior to screening without any other medical reason, confirmed with follicle stimulating hormone (FSH) level in the postmenopausal range.

   - Documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy at least three months before screening.

   Note: Bilateral tubal ligation is not accepted as reason for non-childbearing potential.

8. Subject willing and able to comply with all time commitments and procedural requirements of the clinical study protocol.

9. Understand and sign an informed consent form (ICF) before any investigational procedure(s) are performed.

### 11.3 Exclusion Criteria

Individuals meeting any of the following criteria at screening or baseline are ineligible to participate in this study:

1. Body weight < 30 kg.

2. Pruritus caused by a concomitant condition unrelated to ESKD (e.g., dermatologic or systemic disorders such as, but not limited to AD, psoriasis, PN, Chronic T- cell Lymphoma, Leukemia or cholestatic liver disease).

3. Localized itch of only the palms of the hands and/or soles of the feet.

4. Pruritus present only during hemodialysis session.

5. History of or anticipated non-compliance with hemodialysis (i.e, such that it would adversely affect the conduct of the study or significantly change dialysis adequacy during the study) in the opinion of the investigator.

6. New York Heart Association Class IV symptoms (see Appendix 11) or myocardial infarction within three months prior to screening.

7. History of stroke or transient ischemic attack within six months prior to screening.

8. Subjects meeting one or more of the following criteria at screening or baseline:

   a. Had an exacerbation of asthma requiring hospitalization in the preceding 12 months.

   b. Reporting asthma that has not been well-controlled (i.e. symptoms occurring on > two days per week, nighttime awakenings two or more times per week, or some interference with normal activities) during the preceding three months.

   c. ACT ≤ 19 (only for subjects with a history of asthma).

9. Cutaneous infection within one week before the baseline visit, any infection requiring treatment with oral or parenteral antibiotics, antivirals, antiparasitics or antifungals within two weeks before the baseline visit.

   Note: Subjects with chronic, stable use of prophylactic treatment for recurrent herpes viral infection can be included in this clinical study.

10. Any confirmed or suspected COVID-19 infection within two weeks before the screening or baseline visit. Subjects may be rescreened after the infection has resolved. Resolution of COVID-19 infection can be confirmed by recovery assessment methods, as described in Section 11.5.2.

11. Positive serology results (hepatitis B surface antigen [HbsAg] or hepatitis B core antibody [HbcAb], hepatitis C [HCV] antibody with positive confirmatory test for hepatitis C virus [HCV] (e.g. HCV polymerase chain reaction [PRC]), or human immunodeficiency virus [HIV] antibody) at the screening visit.

    Note: Subjects with a positive HbcAb and a negative HbsAg can be included in this clinical study if hepatitis B surface antibody is positive (considered immune after a natural infection or vaccination). Subjects who are positive for HCV antibody and negative for HCV RNA may be enrolled.

    In the event of rescreening, the serology tests results (e.g., HBV, HCV, HIV) from the previous screening can be used by the investigator to assess the eligibility of rescreened subjects if those tests were performed within six weeks prior to the baseline visit.

12. Known active or untreated latent tuberculosis (TB) infection or history of either untreated or inadequately treated active or latent TB according to the local applicable guidelines.

    Note: Subjects who have a documented history of completion of an appropriate TB treatment regimen for latent or active TB with no history of re-exposure to TB since their treatment was completed are eligible to participate in the study.

13. Known or suspected immunosuppression beyond that expected due to end-stage kidney disease and its comorbidities or unusually frequent, recurrent, severe, or prolonged infections as per investigator judgment.

14. History of lymphoproliferative disease or history of malignancy of any organ system within the last five years, except for (1) basal cell carcinoma, squamous cell carcinoma in situ (Bowen's disease), or carcinomas in situ of the cervix that have been treated and have no evidence of recurrence in the last 12 weeks before the baseline visit, or (2) actinic keratoses that have been treated.

15. Pregnant women (positive serum pregnancy test result at all visits), breastfeeding women, or women planning a pregnancy during the clinical study.

16. In the opinion of the investigator the subject has any medical or psychological condition that could pose undue risk to the subject, prevent study completion, or adversely affect the validity or interpretability of the study measurements or interfered with study assessments.

17. Any clinically relevant laboratory abnormalities, such as but not limited to elevated ALT or AST (> 3 × ULN) in combination with elevated bilirubin (> 2 × ULN), during the screening period that may put the subject at significant risk according to the investigator's judgment, if he/she participates in the clinical study.

18. Planned or expected major surgical procedure during the clinical study, including a scheduled kidney transplant during the study. Subjects on a kidney transplant waiting list with no scheduled transplant date are not excluded.

19. Has not adhered to the restrictions in the selected medications and dialysis procedures prior to screening or is not expected to be compliant with restrictions during the study as list in the following table:

**Table 1 Prior Treatments and Procedures**

| | **Timeframe** | |
|---|---|---|
| **Treatment(s)** | **Before Screening** | **Screening Period and Day 1 – Week 20** |
| Systemic corticosteroids (i.e., administered by the intravenous, oral, or intramuscular route at a dose).<br>Note: Low dose prednisone (up to 10 mg per day [or equivalent other corticosteroid]) is permitted if the dose has been stable for 2 weeks prior to Screening<br>Note: Use of steroids given by other routes (inhaled, topical for indications other than itching, ophthalmic, intra-articular, etc. are permitted). | Not allowed for 4 weeks, other than stable low dose prednisone or equivalent | Prohibited, other than stable low dose prednisone or equivalent |
| Topical corticosteroids | Not allowed for 2 weeks | Prohibited |
| Topical PDE-4 inhibitor | Not allowed for 2 weeks | Prohibited |
| TCIs | Not allowed for 2 weeks | Prohibited |
| Biologics and their biosimilars (e.g. etanercept, adalimumab, infliximab, omalizumab, etc.) | Not allowed for 8 weeks or 5 half-lives (whichever is longer) | Prohibited |
| Dupilumab | Not allowed for 10 weeks | Prohibited |
| Cannabinoids | Not allowed for 2 weeks | Prohibited |
| Immunosuppressive or immunomodulatory drugs (e.g. cyclosporine A, oral tacrolimus, cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, JAK inhibitors) | Not allowed for 4 weeks or 5 half-lives (whichever is longer) | Prohibited |

| | Timeframe | |
|---|---|---|
| **Treatment(s)** | **Before Screening** | **Screening Period and Day 1 – Week 20** |
| Systemic and topical antihistamines (excluding for ophthalmic use) | Stable dose for 2 weeks | Stable dose |
| Local anesthetics such as pramoxine, seed oil, capsaicin, topical ketamine, CBD oil, various lotions with anti-pruritic effects, etc. | Not allowed for 1 week | Prohibited |
| Gabapentin and pregabalin | Stable dose for 2 weeks | Stable dose |
| Phototherapy or tanning beds | Not allowed for 4 weeks | Prohibited |
| Selected Opioids<br>Nalbuphine or kappa opioid agonists (e.g., difelikefalin, nalfurafine) | Not allowed for 4 weeks | Prohibited |
| All other opioids (e.g. codeine, tramadol, oxycodone, hydrocodone, methadone, buprenorphine) | Stable dose for 2 weeks | Stable dose |
| Change in hemodialysis treatment (i.e., number of hemodialysis sessions per week, change in dialyzer or switch between hemodialysis and hemodiafiltration). Also see in inclusion # 2 | Not allowed for 8 weeks | Prohibited |
| Live attenuated vaccine and non-live vaccine (Seasonal vaccine (e.g., influenza), emergency vaccine (e.g., rabies or tetanus) and COVID vaccines as noted in Section 12.5.2 are permitted) | Not allowed for 4 weeks | Prohibited |

Abbreviations: PDE-4 = phosphodiesterase-4; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid.

For medications given as needed ("PRN"), stable dose during the study is defined as that without an increase or decrease by ≥75% in the total weekly dose relative to the dose during the last week of screening. For example, if the total weekly dose of 100 mg of diphenhydramine during the last week of the screening period increased to 175 mg in a given week during the study, this would be considered not a stable dose. During the screening period, a "stable dose" is one that has not changed (increase or decrease) by ≥ 75% during the period of required stability.

Note: Subjects should not interrupt ongoing treatment with medications important for the subject's health for the sole purpose of participating in this study.

20. Requiring rescue therapy for pruritus during the screening period or expected to require rescue therapy within 4 weeks following the baseline visit. Section 12.5.1.2.

21. Previous treatment with nemolizumab.

22. History of hypersensitivity (including anaphylaxis) to an immunoglobulin product (plasma-derived or recombinant, e.g. monoclonal antibody) or to any of the study drug excipients.

23. Currently participating or participated in any other study of an investigational drug or device, within the past four weeks (or five half-lives of the investigational medication, whichever is longer) before the screening visit.

24. History of alcohol or substance abuse within six months of the screening visit.

### 11.4 Rescreening

Screen failures may be allowed to rescreen up to two times. Subjects who screen fail due to disease severity inclusion criteria WI NRS will not be allowed to rescreen (note: subjects screen failed prior to protocol amendment three (version 4.0 dated 08JUN22), are allowed to rescreen if their WI NRS is ≥ 5.0).

Subjects who are rescreened must sign a new ICF and be assigned a new subject identification number (SIN). The SIN of previous screening must be documented in the eCRF.

In the event of rescreening, the serology and TB tests results from the previous screening can be used by the investigator to assess the eligibility of rescreened subjects if those tests were performed within six weeks prior to the baseline visit.

### 11.5 Removal of Subjects from Therapy or Assessments

Although the importance of completing the entire clinical study will be explained to the subjects, any subject is free to discontinue his/her participation in the study at any time and for whatever reason, specified or unspecified, and without any prejudice. No constraints are to be imposed on the subject, and when appropriate, a subject may be treated with other conventional therapy when clinically indicated once the subject is no longer in the study. Investigators or the sponsor can also withdraw subjects from the clinical study if deemed to be necessary.

Unless medically urgent, investigators are required to contact the Medical Monitor to discuss patients that are being considered for withdrawal from study drug treatment or from the study.

A subject may be withdrawn from the study treatment at any time for the following reasons:

- At the discretion of the investigator or the sponsor for safety, behavioral, compliance, or administrative reasons.
- Occurrence of AEs, including laboratory abnormalities, not compatible with the continuation of subject participation in the study, in the investigator's opinion, or unacceptable to the subject to continue, including but not limited to the following:
    - Serious immediate-type allergic manifestations including anaphylactic reaction;

- Serious new or worsening of asthma, or newly diagnosed asthma considered related to study drug administration;
- Diagnosis of a malignancy (except curatively treated in situ cervical carcinoma, squamous cell carcinoma [Bowen's disease] or basal cell carcinoma);
- Opportunistic infections such as but not limited to active TB and other infections whose nature or course suggest an immune-compromised or immune-suppressed status;
- Any serious infection or any severe infection requiring treatment with parenteral antibiotics or oral antibiotics/antivirals/antifungals for > 2 weeks considered related to study drug administration; or
- Confirmed COVID-19 infection (at least a temporary discontinuation is required, while suspected COVID-19 may be acceptable see Section 11.5.2).
- ALT or AST > 3 x ULN and TBL > 2 x ULN or INR > 1.5

- Pregnancy, for which discontinuation of study drug is mandated.
- Use of non-permitted systemic concurrent therapy (discussed and agreed upon with the investigator and medical monitor).
- Use of systemic rescue therapy, as specified in Table 4 of Section 12.5.2 and Section 12.5.1.2. (discussed and agreed upon with the investigator and medical monitor).

The main reason for withdrawal will be documented in the electronic case report form (eCRF). Subjects who have been randomized and treated will not be replaced by another subject.

Subjects who prematurely discontinue study drug and/or take rescue medication(s) will be encouraged to complete the scheduled study visits.

When a subject discontinues study drug, he/she will be fully assessed whenever possible, and followed according to guidelines presented in Section 13.2.1.

Reasonable efforts will be made to contact subjects who are lost to follow-up. These efforts must be documented in the subject's file.

The sponsor has the right to terminate the study at any time in case of SAEs or if special circumstances concerning the investigational product or the company itself occur, making further treatment of subjects impossible. In this event, the investigator(s) will be informed of the reason for study termination.

### 11.5.1 Pregnancy

The safety of nemolizumab in pregnant or lactating women has not been established.

Subjects will be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the investigator. If a subject becomes pregnant, the investigator must withdraw the subject from the study without delay. The subject must not receive any further injection(s) of the study drug.

The investigator must:

- Follow the procedures for reporting/follow-up of a pregnancy within 24 hours (see Section 16.12.4) of receipt of the information.
- Complete as fully as possible the applicable Pregnancy Surveillance Form(s) (see Section 16.12.4).
- Monitor and record the progress of the pregnancy until its outcome. Contact the subject's regular physician (general practitioner or gynecologist) or hospital staff to obtain further details and ask for regular follow-up information.
- Provide tri-monthly updates until the final outcome of the pregnancy. If the subject can no longer be reached (lost to follow-up), documentation of the non-response/ contact with two phone calls and a letter (certified with return receipt) is required.
- If the pregnancy leads to an abortion (i.e., voluntary abortion, spontaneous abortion, or therapeutic abortion), in utero death, or congenital anomaly, follow the procedure for declaration of/reporting an SAE (Section 16.12.2).

The investigator and sponsor should also be notified of pregnancy occurring during the study (and within 12 weeks [± 5 days] after the last dose of study drug) but confirmed after completion of the study. In the event that a subject is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the sponsor after delivery.

Full details will be recorded on the withdrawal page (exit form), or an SAE report will be completed if the subject has completed the study. Pregnancy is not to be considered as an AE; however, it must be monitored and reported as described in Section 16.12.4.

### 11.5.2 Coronavirus Disease 2019

Study drug administration will be discontinued in a subject in whom COVID-19 is confirmed or suspected. COVID-19 must be specified as the reason for study drug discontinuation.

Study drug administration may resume in subjects with confirmed or suspected COVID-19 based on investigator judgment after discussion with the medical monitor or Sponsor and only if the following minimum conditions are met:

- **For symptomatic subjects**: At least 14 days have passed since recovery, defined as resolution of fever without the use of fever-reducing medications and improvement in respiratory symptoms (e.g., cough, shortness of breath).
- **For asymptomatic subjects**: At least 21 days have passed since the positive PCR test and no symptoms.

Note: The above should be considered minimum criteria. Where the local guidelines are more stringent for infection resolution criteria, those must be applied.

See Appendix 1 for additional guidance for management of subjects and study conduct during the COVID-19 pandemic.

# 12 TREATMENTS

## 12.1 Details of Study Medication

### 12.1.1 Investigational Products Administered

"Study drug" or "study medication" refers to nemolizumab or placebo drug product for purposes of this double-blind study. The list of excipients is detailed in the IB.

The Sponsor has developed a lyophilized powder in a DCS which holds the lyophilized nemolizumab or placebo, and the sterile water for injection separately.

Subjects will receive a loading dose of nemolizumab (60 mg) or placebo by two SC injections at baseline (30 mg + 30 mg, placebo + placebo), and a 30 mg or 60 mg dose of nemolizumab or placebo by two SC injections (30 mg + placebo, 30 mg + 30 mg, placebo + placebo) at Weeks 4 and 8. All the study drug treatment should be performed within four hours following the completion of the hemodialysis .

### 12.1.2 Identity of Investigational Products

**Table 2 Description and Usage of Investigational Products**

| | Investigational Product | Placebo |
|---|---|---|
| Name (internal code) | Nemolizumab (CD14152) | CD14152 placebo (N/A) |
| Pharmaceutical form | Lyophilized powder for solution for injection in a DCS | Lyophilized powder for solution for injection in a DCS |
| Dosage | 30 mg (with a loading dose of 60 mg at baseline) or 60 mg | N/A |
| Dose regimen | Q4W | Q4W |
| Route [a] | SC use by subjects or clinic staff after reconstitution | SC use by subjects or clinic staff after reconstitution |
| Duration of treatment | 12 weeks: baseline to Week 12 | 12 weeks: baseline to Week 12 |

Abbreviations: DCS = dual-chamber, single-use syringe; N/A = not applicable; Q4W = every four weeks.
[a] All injections are performed at the study center. Injections by subjects are performed under supervision by clinic staff, after appropriate training.

### 12.1.3 Preparation

A pharmacist (or other qualified personnel) will prepare study medication for injection according to instructions provided in the current version of the pharmacy manual and the Instructions for Use. Study medication preparation should be conducted in a secured and clean area with limited access to only designated personnel at the time of the preparation. Good hygiene practices and clean techniques must be applied at all times.

Differences may be detectable during the study drug reconstitution, however active and placebo appear similar after reconstitution is complete (approximately 10 minutes). Throughout the study, a pharmacist (or other qualified personnel) will prepare study medication for injection, including confirmation of complete reconstitution, prior to delivery of study medication for injection. The pharmacist (or other qualified personnel) preparing study medication should not be involved with any study assessments and should not discuss any aspects of study drug reconstitution with the subject or study staff involved in subject interviews or study assessments to maintain the blind of the study.

The study drug does not contain preservatives. From a microbiological point of view, the preparation of the study drug has to be done as close to subject administration as possible, and the study drug should be used immediately (less than one hour) after reconstitution. If not used immediately, the study drug has to be used within four hours maximum after reconstitution stored at room temperature (below 30 °C) but only if the preparation has taken place applying strictly good hygiene practices and clean techniques to ensure controlled aseptic conditions.

### 12.1.4 Study Drug Injection

All study drug injections will occur at the study center, following instructions provided in the current versions of the pharmacy manual and Instruction for Use. After confirming that the study drug is fully reconstituted, the pharmacist (or other qualified personnel) will deliver the DCS to the investigator or other qualified personnel, for SC injection in the subject's abdomen or alternative injection site. A different injection site should be selected for each injection. Refer to the current versions of the Instructions for Use for further details. The site of injection should be recorded in the subject's treatment record as well as the eCRF at each time point.

For subjects willing and able to self-inject study medication and preferring to do self-inject, study center staff will provide training on study medication injections. Subjects will be allowed to inject medication at subsequent visits under supervision by study center clinic staff (with DCS preparation including reconstitution performed by the pharmacist or other qualified personnel and delivered for injection after reconstitution is complete). Study center/clinic staff can perform all injections if the subject is unwilling or unable to perform injections. The eCRF must record who performed study drug injection at each visit.

After study drug administration, subjects will be monitored closely for any signs or symptoms of hypersensitivity reaction before being discharged. For the first two visits where study drug is administered, subjects should remain at the study center for at least 30 minutes after study drug administration.

### 12.1.5 Packaging and Labeling

All IMP packaging and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products in the local language, national regulations/guidelines, and the relevant regulatory requirements, specifying that the drug is for use in a clinical study. Each DCS will be packaged in an individual carton, including a 27G ½" needle and a plunger rod (not assembled). Local adaptation of the kit design may be required; specific details for each country are provided in the pharmacy manual.

### 12.1.6 Study Drug Management

CCI

[redacted]

#### *12.1.6.2 Dosing Schedule*

Table 3 summarizes study drug dosing during the treatment period of the study.

**Table 3 Treatment Period Dosing by Treatment Group**

| Group | Treatment | Dose at Day 1/Baseline | Dose at Week 4 and Week 8 | Route | Schedule |
|---|---|---|---|---|---|
| 1 | 30 mg Nemolizumab (CD14152) | 60 mg (two 30 mg injections) | 30 mg (30 mg injection + placebo injection) | SC | Q4W |
| 2 | 60 mg Nemolizumab (CD14152) | 60 mg (two 30 mg injections) | 60 mg (two 30 mg injections) | SC | Q4W |
| 3 | Placebo | Placebo (two placebo injections) | Placebo (two placebo injections) | SC | Q4W |

Abbreviation(s): Q4W = every four weeks; SC = subcutaneous.

## 12.2 Measures to Minimize Bias: Study Treatment Assignment

### 12.2.1 Allocation Concealment and Method of Study Treatment Assignment

Subjects will be centrally randomized using an Interactive Response Technology (IRT) system. Allocation concealment will be ensured, as the system will assign the randomization number only upon confirmation of eligibility for a given subject to participate in the study. Randomization will occur individually, the randomization number will be assigned to the unique Subject Identification Number (SIN) of each randomized subject, and the simultaneous randomization of groups of subjects will be prevented.

Subjects will be randomized in a 1:1:1 ratio to:

- Group 1: 30 mg nemolizumab Q4W with 60 mg loading dose at baseline;
- Group 2: 60 mg nemolizumab Q4W without loading dose at baseline; or
- Group 3: placebo Q4W.

Randomization will be stratified by clinical site.

### 12.2.2 Blinding

All attempts will be made to keep the study center staff and subjects blinded throughout the study. Members of the study center staff, including those responsible for DCS preparation, will not have access to the randomized treatment assignment.

To ensure double-blind administration of study drug, the study center pharmacist(s) or other qualified personnel will prepare all nemolizumab or placebo treatments, according to the current versions of the pharmacy manual and the Instructions for Use, of the assigned DCS provided by the IRT system.

As there may be detectable differences between active and placebo during the reconstitution process, the DCS is delivered for injection after the reconstitution is complete. The pharmacist (or other qualified personnel) preparing study medication should not be involved with any study assessments and should not discuss any aspects of study drug reconstitution with the subject or study staff involved in subject interviews or study assessments.

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Unblinding of a subject's individual treatment code should occur only in case of a medical emergency or in the event of a serious medical condition that necessitates identification of the study drug for the welfare of that subject, as judged by the investigator. The emergency unblinding process utilizes IRT to allow the investigator to have unrestricted, immediate, and direct access to the subject's individual study treatment. When possible (i.e., when the health of the subject is not immediately at risk), the investigator or sub-investigator is encouraged to consult with the medical monitor and the sponsor before breaking the blind.

If emergency unblinding is required:

- Only the investigator will make the decision to unblind the treatment assignment.
- Only the affected subject will be unblinded.
- The IRT system will provide the treatment assignment to the investigator.

Refer to the IRT User Guide for information on the steps for breaking the blind.

When the blinding code is broken, the reason must be fully documented. If the code is broken by the investigator, the subject must be withdrawn from the study drug treatment and must also be appropriately followed for a minimum of 12 weeks after the last dose of study drug.

The reporting requirements for unblinding are the same for reporting an SAE. See also Section 16.12.2.

The randomization code will remain blinded to all study sites and study team members until completion of the study and after the study database has been locked.

The IDMC will review data at periodic intervals throughout the study as defined in the IDMC charter. The IDMC charter will specify the procedures for unblinding to ensure that treatment assignment remains undisclosed to all individuals involved in the direct execution and management of the study until the final database is locked.

## 12.3 Dosage Modifications

Dosage modification of the study drug will not be permitted during the clinical study. Any inadvertent dose modification(s) should be reported to the sponsor/CRO.

In the event of a missed dose (i.e., temporary discontinuation of the study drug), it will be documented in the eCRF that the drug has not been administered at the study visit, together with the reason (e.g., for safety). Subjects will be asked to return to the study centers for all remaining visits and complete all study assessments and procedures as described in Section 13.1.

Dosing frequency is scheduled for Q4W, based on the baseline/Day 1 visit date. If a study visit occurs outside the visit window (see Table 5), study drug can be administered provided there is a minimum of three weeks since the last injection. Future visits should be scheduled within the required windows based on the baseline/Day 1 visit date, while maintaining the minimum 3-week interval between two injections.

The rationale for the nemolizumab dose/dose regimen is provided in Section 8.6.

## 12.4 Treatment Accountability and Compliance

Study drug will be provided to the investigational site, and site personnel will acknowledge receipt of the study drug using IRT to confirm the shipment condition and content as per the current version of the pharmacy manual.

The designated personnel will also maintain accurate records of the study drug throughout the clinical study, including the inventory delivered to the study center, the use by each subject, the reconciliation of all delivered and received DCS units, and the return/destruction of unused study drug as specified in the current version of the pharmacy manual. No unauthorized use is permitted. Used DCS units will be properly documented in drug accountability records. Unless a product technical complaint (PTC) is detected or an event occurs before, during, or just after the injection, the used DCS can be disposed in an appropriate sharps container and according to waste regulation(s) in the country. A DCS involved in a malfunction or an investigator or subject complaint must be retained on site and designated personnel must proceed as defined in the current version of the pharmacy manual. Refer to Section 12.6 for PTCs.

The study monitor may check the study supplies at each study center at any time during the study. It is the responsibility of the study monitor to ensure that the investigator (or designee) has correctly documented the amount of the study drug received, dispensed, and returned/destroyed on the dispensing log that will be provided. A full drug accountability log will be maintained at the study center at all times. The study monitor will arrange collection of any unused study drug. The study monitor will also perform an inventory of study drug at the close-out visit to the study center. All discrepancies must be accounted for and documented appropriately in conjunction with the supply chain manager.

### 12.4.1 Dispensing and Return of Study Drug

All drug preparation must be appropriately performed and documented by the designated personnel. Any error in the preparation of the dose must be reported to the study monitor promptly and be properly documented. At the end of the study, the reconciliation/ return/destruction process for all unused study drug will be conducted according to the pharmacy manual.

### 12.4.2 Compliance

Treatment compliance will be assessed through the treatment records.

As study drug is administered in the clinic, treatment compliance will be overseen and documented by the investigator and study staff (using the treatment records and drug accountability records). At a minimum, date, time, dose, injector (subject or site staff), and site of injection should be accurately recorded to confirm that each dose of study treatment was properly administered.

## 12.5 Prior and Concomitant Therapy

Prior therapies are defined as therapies that have been stopped within the three months before the screening visit, unless relevant to the inclusion/exclusion criteria. Whenever possible, all prior therapies for CKD-aP should be documented.

Concomitant therapies/medications are defined as follows:

- Any existing therapies ongoing at the time of the screening visit,
- Any changes to existing therapies (such as changes in dose, formulation or application frequency) during the course of the study, or
- Any new therapies received by the subject since the screening visit.

The following two categories are to be considered for prior and concomitant therapies:

- Drugs/Therapies include but are not limited to prescription, over-the-counter, birth control pills/patches/hormonal devices, vitamins, moisturizers, sunscreens, herbal medicines/supplements, vaccines (emergency or seasonal), and homeopathic preparations.

- Medical and surgical procedures (e.g., phototherapy, exodontia). Procedures whose sole purpose is diagnosis (non-therapeutic) are not included.

Prior and concomitant therapies for drugs/therapies or for medical/surgical procedures are to be recorded in the appropriate eCRF.

Concomitant therapies are to be recorded, reviewed, and updated at each visit.

At each visit, investigators should also confirm concomitant therapies for contraception. Contraceptive counseling should occur at screening.

Any new concomitant therapy or modification of an existing therapy may be linked to an AE. In such cases, a corresponding AE form should be completed to account for the new therapy or change in therapy, except in some cases such as dose modification for a chronic condition (see Section 12.3), in which case the medication will be linked to an item in the subject's medical history.

### 12.5.1 Permitted Concomitant Therapy

Unless specified as prohibited therapies (see Section 12.5.2), all therapies are authorized, including basic skin care (cleansing and bathing), moisturizers, bleach baths, stable antihistamines, and stable TCS.

The formation of cytochrome P450 (CYP450) metabolic enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10) during chronic inflammation. Although there is no known evidence suggesting that IL-31 affects the level or activity of CYP450 enzymes, the impact of nemolizumab on such enzymes has not been studied. Therefore, investigators should consider observing for clinical or laboratory signs that might indicate a potential effect of nemolizumab in subjects using concomitant therapies that are CYP450 substrates, particularly those with a narrow therapeutic index. Typical examples of substrates with a narrow therapeutic range include warfarin, drugs that may cause torsade de pointes, almost all cytotoxic antineoplastic drugs, and aminoglycoside antibiotics. A list of representative CYP450 substrates with narrow therapeutic index can be found in Appendix 2.

#### *12.5.1.1 Moisturizer*

The subjects' current moisturizer or a moisturizer recommended by the investigator may be used. Whenever possible, subjects should use the same moisturizer throughout the study.

#### *12.5.1.2 Rescue Therapy*

If deemed to be medically necessary by the investigator (e.g. to control intolerable pruritus), rescue therapies can be prescribed to the subjects at any time during the study except during the screening period. Subjects receiving treatments defined as rescue therapies during the screening period are not eligible to participate in the study (see exclusion criterion 20 in Section 11.3).

As a general guideline and per individual investigator judgment, rescue therapy should not be prescribed within the first four weeks after baseline to allow a minimum time for study drug exposure in the presence of background therapy.

Investigator assessments of efficacy should be performed before initiating rescue therapy. Subjects requiring rescue therapy between scheduled visits should return to the clinic (unscheduled visit) for investigator assessment of efficacy before starting rescue therapy. The Investigator must contact the Medical Monitor prior to initiating rescue therapy.

As judged appropriate by the investigator, and following discussion with the Medical Monitor, rescue therapies are defined as below and include the following treatments:

- Antihistamines (new or increased dose): For those given as needed ("PRN"), at baseline, rescue of antihistamine is defined as that with an increase by ≥75% in the total weekly dose relative to the dose during the last week of screening administered for ≥ 1 week.
- Gabapentin (new or increased dose) administered for ≥ 1 week.
- Selected Opioids: Nalbuphine or kappa opioid agonists (e.g., difelikefalin, nalfurafine), one or more doses
- Ultraviolet radiation therapy: one or more treatments

Note: all new concomitant medication or increase of frequency or increase of dose will be recorded.

Whenever possible, investigators should first use topical medications as rescue therapy before escalating to systemic therapies. If subjects receive topical treatments or phototherapy as rescue therapy, study drug administration should be continued unless there is a safety concern according to the investigator's judgment. If subjects receive systemic rescue therapy, the study drug administration can be discontinued if the subject is at risk (discussed and agreed upon with investigator and medical monitor).

Further, the use of any rescue therapies should be documented in the eCRF.

### 12.5.2 Prohibited and Restricted Medication/Therapy

Treatment with the following concomitant medications/therapies is prohibited during the study unless otherwise specified in Table 4. Pro re nata (PRN) use of TCS or TCI is not permitted.

**Table 4 Prohibited and Restricted Medication/Therapy**

| | Timeframe | |
|---|---|---|
| **Treatment(s)** | **Before Screening** | **Screening Period and Day 1 – Week 20** |
| Systemic corticosteroids (i.e., administered by the intravenous, oral, or intramuscular route at a dose).<br>Note: Low dose prednisone (up to 10 mg per day [or equivalent other corticosteroid]) is permitted if the dose has been stable for 2 weeks prior to Screening.<br>Note: Use of steroids given by other routes (inhaled, topical for indications other than itching, ophthalmic, intra-articular, etc. are permitted). | Not allowed for 4 weeks, other than stable low dose prednisone or equivalent | Prohibited, other than stable low dose prednisone or equivalent |
| Topical corticosteroids | Not allowed for 2 weeks | Prohibited |
| Topical PDE-4 inhibitor | Not allowed for 2 weeks | Prohibited |
| TCIs | Not allowed for 2 weeks | Prohibited |
| Biologics and their biosimilars (e.g. etanercept, adalimumab, infliximab, omalizumab, etc.) | Not allowed for 8 weeks or 5 half-lives (whichever is longer) | Prohibited |
| Dupilumab | Not allowed for 10 weeks | Prohibited |
| Cannabinoids | Not allowed for 2 weeks | Prohibited |
| Immunosuppressive or immunomodulatory drugs (e.g. cyclosporine A, oral tacrolimus, cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, JAK inhibitors) | Not allowed for 4 weeks or 5 half-lives (whichever is longer) | Prohibited |
| Systemic and topical antihistamines (excluding for ophthalmic use) | Stable dose for 2 weeks | Stable dose |
| Local anesthetics such as pramoxine, seed oil, capsaicin, topical ketamine, CBD oil, various lotions with anti-pruritic effects, etc. | Not allowed for 1 week | Prohibited |
| Gabapentin and pregabalin | Stable dose for 2 weeks | Stable dose |
| Phototherapy or tanning beds | Not allowed for 4 weeks | Prohibited |
| Selected Opioids<br>Nalbuphine or kappa opioid agonists (e.g., difelikefalin, nalfurafine) | Not allowed for 4 weeks | Prohibited |
| All other opioids (e.g. codeine, tramadol, oxycodone, hydrocodone, methadone, buprenorphine) | Stable dose for 2 weeks | Stable dose |

| | Timeframe | |
|---|---|---|
| **Treatment(s)** | **Before Screening** | **Screening Period and Day 1 – Week 20** |
| Change in hemodialysis treatment (i.e., number of hemodialysis sessions per week, change in dialyzer or switch between hemodialysis and hemodiafiltration) Also see inclusion #2 | Not allowed for 8 weeks | Prohibited |
| Live attenuated vaccine and non-live vaccine (Seasonal vaccine (e.g., influenza), emergency vaccine (e.g., rabies or tetanus) and COVID as noted in Section 12.5.2 are permitted) | Not allowed for 4 weeks | Prohibited |

Note: Subjects should not interrupt ongoing treatment with medications important for the subject's health for the sole purpose of participating in this study.

Abbreviations: PDE-4 = phosphodiesterase-4; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid.

For medications given as needed ("PRN"), stable dose during the study is defined as that without an increase or decrease by ≥75% in the total weekly dose relative to the dose during the last week of screening. For example, if the total weekly dose of 100 mg of diphenhydramine during the last week of the Screening Period increased to 175 mg in a given week during the study, this would be considered not a stable dose. During the Screening Period, a "stable dose" is one that has not changed (increase or decrease) by ≥ 75% during the period of required stability.

Note: Subjects should not interrupt ongoing treatment with medications important for the subject's health for the sole purpose of participating in this study.

If a prohibited therapy becomes necessary for the safety of the subject, the investigator should notify the medical monitor and discuss possible alternatives. If a subject receives a prohibited therapy during the clinical study (e.g., inadvertent short-term use), the investigator should also notify the medical monitor and discuss whether or not it is acceptable for the subject to continue receiving the study drug.

If the use of systemic corticosteroids more than prednisone 10 mg per day or equivalent becomes necessary for the safety of the subject to treat conditions other than CKD-aP, the study drug should be temporarily discontinued for the duration of treatment with systemic corticosteroids plus five half-lives.

It is recommended that all subjects should be up to date with respect to standard of care vaccinations as defined by the local guidance. For subjects who have vaccination planned during the study, other than allowed vaccinations below, it will be determined after consultation with the treating physician, whether the administration of vaccine can be postponed until after the end of study, or preponed to before the start of the study, without compromising the health of the subject.

Vaccinations during the study including the screening and follow-up periods are not permitted, except for use of the following non-live vaccines:

- Seasonal vaccinations (e.g., influenza)
- Emergency vaccinations (e.g., rabies or tetanus)
- COVID-19 vaccinations

Wherever possible, it is recommended to avoid administration of seasonal and COVID-19 vaccinations +/- one week from study drug dosing. A different anatomical location should be used for study drug administration and vaccine administration.

In the event of emergency vaccination (e.g., rabies or tetanus) during the study, the study drug administration should be discontinued until the immune response to vaccination is verified. It is recommended to discuss with the medical monitor before discontinuing the study drug.

### 12.6 Product Technical Complaints

All DCS units must be inspected prior to preparation/injection by the persons performing the preparation/injection to ensure absence of visual defects that could lead to a DCS PTC. This also includes the needle and plunger rod. In case of doubt, the DCS should not be used, and the deficiency must be reported as defined in the pharmacy manual.

All PTCs should be reported to the sponsor/designee by filing the relevant form available in the Investigator Site File and the pharmacy manual and as required by local regulations. A PTC is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, reliability, safety, durability, effectiveness, or performance of a drug or delivery system. Examples may include but are not limited to appearance issues, discoloration, odor, broken/cracked syringe, missing parts, damaged stoppers, and foreign matter in lyophilized powder or diluent. These complaints may or may not represent a potential risk to the subject. For these types of events, a form must be completed as per the specific instruction by the site personnel, pictures of the defective DCS must be attached, and forwarded to the sponsor/ designee at the latest on the next working day. Reporting to health authorities will be in accordance with local regulations. The defective DCS/items must be kept in case of investigation need as defined in the pharmacy manual and may be requested to be sent to the sponsor/designee in accordance with regulations.

Refer to the current version of the pharmacy manual for further details.

# 13 STUDY PROCEDURES

A written, signed ICF, assent form, and Health Insurance Portability and Accountability Act (HIPAA) authorization is required before any study-related procedures are performed.

Upon provision of the signed ICF/assent form, each subject will be assigned a unique SIN. For the duration of the entire clinical study, the subject will be identified using the SIN in all documentations and discussion.

The planned study assessments are in Section 13.1. At each visit, assessments/procedures should be performed in the following order:

**Pre-Dialysis**

1. Sample collections for safety laboratory assessments

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3. Vital signs and pre-dialysis weight

**Recommended During Dialysis**

1. Subject-reported efficacy and safety measurements (during the first hour of dialysis treatment, whenever possible)
2. Investigator assessments (including efficacy and safety);

**Post-Dialysis**

1. 12-lead ECG. See Section 16.3.
2. PEF and respiratory examination (may also be done during the last hour of dialysis)
3. Post-dialysis weight.
4. Administration of study drug injections

If for logistical reasons, it is preferable for the ECG to be performed prior to dialysis, then all ECGs for that subject should be performed prior to dialysis.

**Assessment on Non-Dialysis Days**

Subjects will complete the WI NRS and SD NRS daily at home at approximately the same time each day on the ePRO device provided. See Sections 15.1 and 15.2. The form is to be dated, timed, and signed by the subject. Subjects will be instructed to complete the assessment on their own without consulting others. The forms will be returned to the site when the subject next returns for a dialysis treatment.

## 13.1 Schedule of Assessments

Table 5 outlines the timing of procedures and assessments to be performed throughout the study.

**Table 5 Schedule of Assessments**

| Study period | Screening period[a] | Treatment period | | | | Follow-up | Unscheduled visit[c] |
|---|---|---|---|---|---|---|---|
| Visit | V1 | V2 | V3 | V4 | V5 | V6 | (if applicable) |
| Week | W-4 | Baseline | W4 | W8 | W12/ET[b] | W20 | |
| Day | | Day 1 | Day 29 | Day 57 | Day 85 | Day 141 | |
| Visit window | | | ± 3 days | ± 3 days | ± 5 days | ±5 days | |
| Informed consent form | X | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | |
| Demographics | X | | | | | | |
| Baseline characteristics [d] | X | X | | | | | |
| Medical history, previous therapies and procedures, smoking status | X | | | | | | |
| **SUBJECT-REPORTED OUTCOME (SRO) ASSESSMENTS** | | | | | | | |
| (eDiary) Daily WI NRS/SD NRS [e,f] | X ---------- | | | | | ----------X | (X) |
| CCI [redacted] | | | | | | | |
| **INVESTIGATOR ASSESSMENT** | | | | | | | |
| IGA of CKD-aP skin status [h] | X | X | X | X | X | X | (X) |
| **SAFETY ASSESSMENTS** | | | | | | | |
| ACT [g,i] | X | X | X | X | X | X | (X) |
| PEF testing [i,j,k] | X | X | X | X | X | X | (X) |
| Respiratory exam [k,l] | X | X | X | X | X | X | (X) |
| Full physical examination | X | X | X | X | X | X | (X) |
| Height | X | | | | | | (X) |
| Pre-Dialysis and Post-Dialysis Weight | X | X | | | X | | (X) |

| Study period | Screening period[a] | Treatment period | | | | Follow-up | Unscheduled visit[c] |
|---|---|---|---|---|---|---|---|
| Visit | V1 | V2 | V3 | V4 | V5 | V6 | (if applicable) |
| Week | W-4 | Baseline | W4 | W8 | W12/ET[b] | W20 | |
| Day | | Day 1 | Day 29 | Day 57 | Day 85 | Day 141 | |
| Visit window | | | ± 3 days | ± 3 days | ± 5 days | ±5 days | |
| 12-lead ECG [k,m] | X | | | | X | | (X) |
| Vital signs [n] | X | X | X | X | X | X | (X) |
| Contraceptive counseling | X | | | | | | (X) |
| Adverse Events | X | X | X | X | X | X | (X) |
| Concomitant therapies and procedures | X | X | X | X | X | X | (X) |
| **LABORATORY ASSESSMENTS** | | | | | | | |
| Blood sample for virology (HIV, Hepatitis B, and C test) | X | | | | | | (X) |
| Blood samples for TB test | X | | | | | | (X) |
| Blood samples for hematology and biochemistry [o] | X | X | X | X | X | X | (X) |
| Urinalysis [p] | X | X | X | X | X | X | (X) |
| Pregnancy test [q] | X | X | X | X | X | X | (X) |
| FSH [r] | X | | | | | | |
| CCI [redacted] | | | | | | | |
| **RANDOMIZATION and STUDY DRUG ADMINISTRATION** | | | | | | | |
| Randomization | | X | | | | | |
| Study drug injection and training [t,u,v] | | X | X | X | | | (X) |

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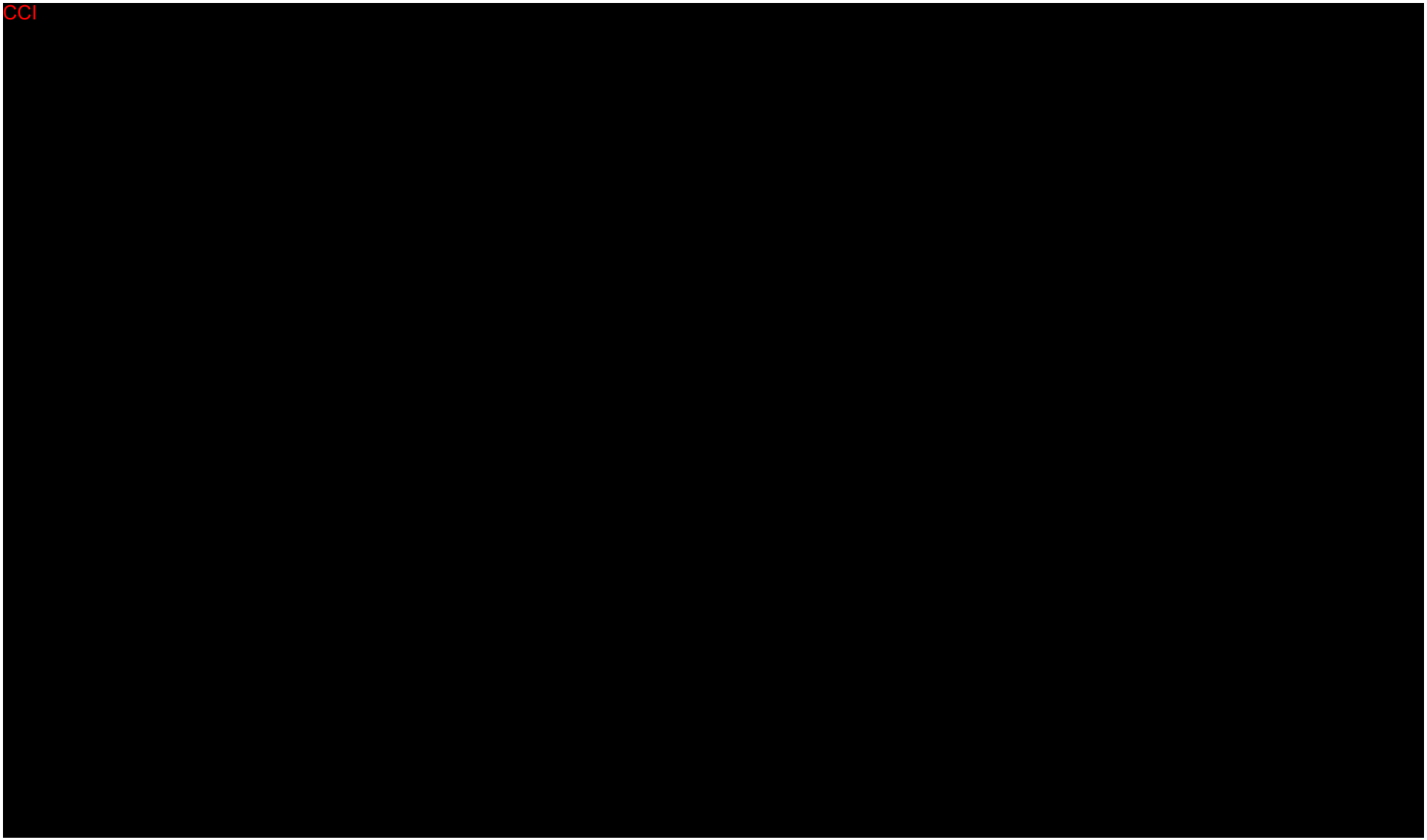

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## 13.2 Duration of Subject Participation

The expected duration of each subject's participation in the study is up to 24 weeks, including an up to 4-week screening period, a 12-week treatment period, and an 8-week follow-up period (12-weeks after the last study medication injection).

### 13.2.1 Early Termination Visit

Subjects who prematurely discontinue from the study should complete an early termination (ET) visit at the time of discontinuation. A follow-up/final visit is required 12 weeks after the last study drug administration.

Subjects who prematurely discontinue the study treatment will be asked to continue participation in the study and return for all remaining visits and assessments.

Participation will continue until the subject completes the final study visit or otherwise discontinues study participation.

### 13.2.2 Unscheduled Visit

The subject should be reminded to adhere to the study schedule. Unscheduled visits are defined as visits to repeat testing for abnormal laboratory results, for follow-up of AEs, or to conduct efficacy assessments for subjects requiring rescue medication between regularly scheduled study visits. Visits occurring outside of the visit window are not considered unscheduled visits.

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# 14 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

## 14.1 Medical History

Medical history will be recorded at screening. Investigators should document the subject's pre-existing conditions, including all prior relevant (e.g., allergic conditions such as asthma) and significant illnesses, before screening. Medical history will include alcohol consumption, if applicable and smoking history. Medical history will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA).

Additionally, demographic data will be collected for all subjects and include but are not limited to age, sex, race, etc., according to applicable regulations.

## 14.2 Height and Weight

Height and weight will be measured, according to Section 13.1.

Subject weight must be more than 30 kg at both screening and baseline visits in order to be enrolled into this clinical study.

## 14.3 Baseline Characteristics

The following baseline characteristics will be collected for all subjects:

- Duration of ESKD (months) at baseline
- Duration of hemodialysis (months) at baseline
- Hemodialysis access (AVF/AVG/Catheter)
- Kt/V at baseline
- Cause of CKD
  - Hypertension
  - Diabetes
  - Glomerulonephritis
  - Cystic disease
  - Urologic
  - Congenital/Hereditary
  - Other
- Duration of pruritus (months) at baseline

# 15 EFFICACY ASSESSMENTS

The Schedule of Assessments (Table 5) outlines the efficacy assessments to be performed throughout the study and their timing.

Efficacy measurements should be conducted by subjects (for subject-reported efficacy measurements) according to Sections 15.1 - 15.5.

Whenever possible, the same evaluator should make the investigator global assessment (IGA) throughout the study. Refer to Section 9.2 for efficacy endpoints.

## 15.1 Worst Itch Numeric Rating Scale

The WI NRS is a scale to be used by the subjects to report the intensity of their worst pruritus (itch) during the last 24 hours (see Appendix 3). The WI NRS is a validated measurement tool and has been used to assess subject-reported severity of itch in CKD-aP clinical trials (Fishbane 2020).

Subjects will be asked the following question:

- For worst itch intensity: "On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable', how would you rate your itch at the worst moment during the previous 24 hours?"

The screening WI NRS score will be determined by a single WI NRS assessment (score ranging from 0 to 10) for the 24-hour period immediately preceding the screening visit. The baseline WI NRS score will be determined based on the weekly average of daily WI NRS scores (score ranging from 0 to 10) during the seven days immediately preceding baseline (rounding is not permitted). A minimum of four daily scores out of the seven days immediately preceding baseline is required for this calculation.

Subjects will record their 24-hour worst itching assessment scores on all days. Subjects will receive instructions on how to record their WI NRS scores and will complete the assessment once daily in the evening throughout the clinical study (including the screening and the follow-up period) in an eDiary. If they cannot record it in the evening, then record it in the following morning is acceptable.

If a subject does not complete the WI NRS assessments in the evening, the subject will be allowed to complete the assessments the following morning.

## 15.2 Sleep Disturbance Numeric Rating Scale

The SD NRS is a scale to be used by the subjects to report the degree of their sleep loss related to CKD-aP (see Appendix 4). Subjects will receive instructions on how to record their SD NRS scores and will complete the assessment once daily in the morning throughout the clinical study during the screening and treatment periods.

Subjects will be asked the following question:

- "On a scale of 0 to 10, with 0 being 'no sleep loss related to the symptoms of pruritus and 10 being 'I did not sleep at all due to the symptoms of pruritus, how would you rate your sleep last night?"

If a subject does not complete the SD NRS assessment the morning of a scheduled visit, the subject will be allowed to complete the assessment at the clinic visit.

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# 16 SAFETY ASSESSMENTS

Safety assessments will be conducted for all subjects at the screening visit (upon signing of the ICF) and at every subsequent visit.

## 16.1 Vital Signs

Vital signs will be evaluated at the screening visit and at each subsequent visit according to Section 13.1. Vital signs will include pulse rate, systolic and diastolic blood pressure (after the subject has been sitting for at least five minutes), and body temperature. All abnormal values at the screening visit identified as CS by the investigator will be recorded in the medical history form. Any CS changes from the screening visit will be recorded as an AE.

## 16.2 Physical Examination

Complete physical examination should be performed at the screening, baseline, and subsequent scheduled visits, according to Section 13.1. A complete physical examination will include assessments of the head, ears, eyes, nose, throat, neck (including thyroid), skin/integumentary system, cardiovascular system, respiratory system (for additional respiratory assessments, see Section 16.8), gastrointestinal system, musculoskeletal system, lymph nodes, nervous system, and extremities.

The investigator should assess all abnormal findings for clinical significance. All CS abnormal findings at the screening visit will be recorded in the medical history form. Any CS changes from the screening visit will be recorded as an AE.

## 16.3 Electrocardiogram

A 12-lead ECG will be performed and read locally according to visits specified in Section 13.1. ECGs will be performed in the supine position at the time points described in the Schedule of Assessments, Table 5. Subjects should be monitored for potentially CS ECG results (refer to the current version of the central laboratory manual). Tests with abnormal results that are deemed CS should be repeated to ensure reproducibility of the abnormality. ECG abnormalities present at screening should be recorded in the medical history form. Any abnormalities considered by the investigator to be CS after the screening visit are to be recorded as AEs and discussed with the medical monitor, as needed.

## 16.4 Clinical Laboratory Evaluation

The hematology laboratory analyses, biochemistry laboratory analyses, and urinalyses will be performed at a central laboratory. Reference ranges will be supplied by the central laboratory and used by the investigator to assess the laboratory data for clinical significance and pathological changes.

The investigator or medically qualified sub-investigator must review and evaluate laboratory values for each subject in a timely manner. Study centers should refer to the current version of the laboratory manual for laboratory values outside of normal limits. For each out-of-range laboratory result, the investigator or designee will evaluate whether he/she considers it to be CS, defined as meeting at least 1 of the following conditions:

- The abnormality suggests a disease and/or organ toxicity, or
- The abnormality is of a degree that requires additional active management (e.g., discontinuation of the drug, close observation, more frequent follow-up assessments, or further diagnostic investigation).

If the investigator observes a CS laboratory result that meets the criteria for an adverse event or at the investigator's discretion, the test will be repeated as soon as possible, and the subject will be monitored until the value returns to normal and/or an adequate explanation for the abnormality is found.

Investigators will also be allowed to repeat specific laboratory test(s) or procedure(s) where the investigator suspects an inaccuracy or false result and that may impact the safety of the subject or the interpretation of the trial results; only after discussion with medical monitor.

All CS out-of-range laboratory values at the screening visit will be recorded in the medical history form (report a diagnosis rather than the laboratory value whenever possible). All CS out-of-range laboratory values after the screening visit are to be reported as an AE if this abnormality was not present at the screening visit or is assessed as having worsened since the screening visit (i.e., changed by a clinically significantly extent from the screening visit). Whenever possible, the investigator should provide a diagnosis of an AE when reporting the abnormal laboratory value.

Subjects should fast for at least 8 hours before the visits when blood chemistry testing is planned, except for the screening visit, if possible. The screening visit laboratory values must be available before the baseline visit. Laboratory testing conducted in a nonfasting state will not be a protocol deviation.

Total blood volumes to be drawn at each visit are provided in the clinical laboratory manual. Additional samples may be required if medically indicated (e.g., at unscheduled visits for safety reasons, when an abnormal laboratory value is observed and requires a re-test).

See Section 16.5, Section 16.6, and Section 16.7 for details regarding pregnancy testing, virology, and TB testing samples, respectively (See Section 17.1 for details regarding CCI [redacted] and Section 18.1 for ADA sampling).

The following laboratory safety tests will be performed as specified in Section 13.1.

### 16.4.1 Hematology

Hemoglobin, hematocrit, white blood cell count (with differential including eosinophils), red blood cell count, platelet count, and mean cell volume.

### 16.4.2 Biochemistry

Creatinine, AST, ALT, gamma glutamyltransferase, alkaline phosphatase, lactate dehydrogenase, total bilirubin, direct bilirubin, albumin, total protein, uric acid, sodium, potassium, calcium, chloride, glucose, urea, total cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein (HDL), CPK. CPK isoenzyme test will be performed only if CPK is elevated to > 2.5 × ULN. The investigator should also contact the medical monitor in such situations.

For postmenopausal subjects (i.e., no menses for 12 consecutive months), postmenopausal status will be confirmed with a high follicle-stimulating hormone (FSH) level in the postmenopausal range.

### 16.4.3 Urinalysis

Only applies to subjects who are able to produce urine. pH, glucose, ketones, blood, protein, leukocytes, nitrites, bilirubin, urobilinogen, and specific gravity.

## 16.5 Pregnancy Testing

All WOCBP will have a serum pregnancy test performed at all visits. Pregnancy test results must be available prior to the administration of the study drug.

Subjects with a positive serum pregnancy test result at screening must not be enrolled.

Subjects with a positive serum pregnancy test result during the trial must discontinue treatment and but remain in the study for follow-up.

## 16.6 Virology

Virology including HBsAg, HBcAb, HCV, HIV-1, and HIV-2 antibody will be assessed at the screening visit. Subjects with a positive HBcAb and a negative HBsAg will also be assessed for hepatitis B surface antibody. Subjects with positive HCV antibodies will have a confirmatory test for HCV (e.g., PCR).

## 16.7 Tuberculosis Testing

Immunosuppressant biologic treatments have been shown to increase the risk of TB infection or to cause conversion from latent to active TB in some circumstances. Because of this, subjects will be screened for active or latent TB before entry into this study. TB blood testing (using an interferon gamma release assay) may be performed at the central laboratory or at a local laboratory based on the investigator's preference.

### 16.7.1 Definitions

Active TB is a disease caused by Mycobacterium TB in any part of the body and that is in an active state as determined by either a smear or culture taken from any source in the person's body which tests positive for TB or by radiographic evidence. Individuals with active TB are symptomatic, depending upon the location of the disease (most commonly in the lungs but also possibly in the brain, kidneys, spine, or elsewhere), and can spread the infection to others.

Latent TB is said to exist when an individual is infected with Mycobacterium TB, as evidenced by a positive Interferon Gamma Release Assay, 40 such as QuantiFERON-TB Gold, but is asymptomatic and has no evidence of active infection on screening pathology or radiographic tests. Such individuals do not pass the disease to others and should commence a course of prophylactic antimycobacterial treatment to eliminate the infection and commit to completing the course of treatment.

### 16.7.2 Tuberculosis Screening

As part of the medical history, the subject should be asked if they have presented with active or latent TB in the past and whether they have received a bacillus Calmette- Guérin (BCG) vaccination. They should also be asked if they have been in contact with any individuals known to have active TB or been placed in any circumstances that may have exposed them to an increased risk of TB infection, such as travel to TB endemic regions, close contact with persons with active TB, or workplace risk (e.g., prison, hospitals).

A subject who tests positive for latent TB (with a positive QuantiFERON-TB Gold test) should be referred to the subject's treating physician for appropriate follow-up, unless the subject has a documented history of completion of an appropriate TB treatment regimen with no history of re-exposure to TB since her/his treatment was completed. If the result is indeterminate, the test may be repeated once. If confirmed indeterminate, the subject should then be managed as though he/she has a positive test result.

## 16.8 Respiratory Assessments

At screening, the investigator should specifically question all subjects about any medical history of asthma and their respiratory health (e.g., wheezing, coughing, allergies, infections). Subjects with a history of asthma will be questioned about the seasonality of their asthma and known triggers, such as allergens. Newly diagnosed asthma or worsening of asthma during the study will be reported as an AESI.

### 16.8.1 Asthma Control Test

Subjects with a medical history of asthma will take the ACT at visits according to Section 13.1 before questioning and physical examination by the investigator. Subjects with a new (de novo) diagnosis of asthma will take the ACT beginning at the visit the diagnosis was first confirmed and at all subsequent study visits thereafter. Subjects with an ACT score ≤ 19 will be referred to the physician managing their asthma.

The ACT is an assessment to determine if a subject's asthma symptoms are well controlled. The ACT is designed for adults and adolescents 12 years or older and is composed of five questions. For each question, the subject will choose the best answer out of five possible answers. The test provides a numerical score ranging from five to 25 to assess asthma control; a higher score indicates better asthma control while a score of 19 or less indicates the subject's asthma may not be under control. The ACT will also aid the investigator's questioning of subjects with a medical history of asthma. See Appendix 10.

### 16.8.2 Respiratory Examination

A respiratory examination will be required to be performed for all subjects at all scheduled visits, according to Section 13.1. After the screening visit, all subjects will be asked non-leading questions about any respiratory changes. The investigator or designee will then perform a respiratory examination of all subjects at all visits.

Subjects with a medical history of asthma will be referred to the physician managing their asthma if unexpected worsening of asthma is observed or reported. Subjects without a medical history of asthma who experience respiratory changes (examination findings or newly reported signs and/or symptoms suggestive of asthma) will be referred to a respiratory specialist.

### 16.8.3 Peak Expiratory Flow

All subjects will undergo PEF testing at screening, baseline, and specified visits according to Section 13.1. For subjects reporting a medical history of asthma, PEF testing will be conducted at all visits.

Subjects with a new (de novo) diagnosis of asthma will undergo PEF testing at all visits after the diagnosis is first made according to Section 13.1.

PEF testing during the clinical study will be performed under the supervision of qualified study personnel. PEF measurements should consist of three good efforts, with the best result documented. It is preferable that the PEF measurement be performed post-dialysis or during the last 1 hour of dialysis when most/all excess fluid has been removed. Obtained PEF values will be compared to predicted values based on the subject's age, sex, and height (Quanjer 1993, Polgar 1979).

Subjects with a medical history of asthma should be asked to withhold asthma medication, if applicable, on study visit days until after PEF testing is complete, to the extent it does not pose an undue risk to the subject, to avoid interference with PEF measurements.

### 16.8.4 Respiratory Referrals

Subjects with a medical history of asthma will be referred to the physician who manages their asthma when:

- ACT score ≤ 19 (an ACT score ≤ 19 conveys asthma that may not be adequately controlled).
- Unexpected worsening of asthma is observed or reported at any time during the study.
- At any study visit, subjects without a medical history of asthma will be referred to an appropriate specialist physician whenever:
    - Signs and/or symptoms suggestive of asthma are newly observed or reported.
    - Respiratory assessments (e.g., examination, ) suggest a worsening in the subject's respiratory health.
- PEF value is only supplemental to the clinical evaluation of respiratory signs and symptoms suggestive of asthma (de novo or worsening in patients with history of asthma) at investigators judgement.

## 16.9 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical study subject administered a medicinal product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not it is related to the medicinal (investigational) product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction, or the significant worsening of the indication under investigation that is not recorded elsewhere in the eCRF under specific efficacy assessments.

Note(s):

- Any new sign or symptom reported by the subject that appears after accidental or intentional overdose or misuse of study drug should be reported as an AE.
- Whenever possible, a diagnosis should be reported on the AE form, instead of signs, symptoms, or abnormal laboratory values.
- Pregnancy is not to be considered an AE; however, it must be monitored and reported as described in Section 16.12.4.
- Each worsening of a chronic disease from the screening visit should be reported as a new AE.

The investigator or designee will report all AEs that occur from the time the ICF is signed until the end of the study. The sponsor/CRO should be informed if the investigator becomes

aware of any safety information that appears to be drug-related, even after the subject has completed the clinical study.

At each post enrollment visit, the investigator (or sub-investigator) will question the subject about AEs using an open nonpersuasive question to elicit reporting of AEs (for example, "Have you noticed any change in your health since the last visit?"). Directed questioning and examination will then be performed as appropriate.

Any AE occurring during the AE reporting period, whether it is related to the study drug(s) or not, will be recorded immediately in the source document and described on the Adverse Event Form ("AE Form") along with the date of onset, severity, relationship to the study drug(s), and outcome, without omitting any requested and known information. Additional information will be requested under certain circumstances.

AEs assessed as related to the treatment or study procedure will be monitored until they have resolved or reached a stable condition. Other AEs will be monitored until the last visit if they have not resolved or reached a stable condition.

The investigator will obtain and maintain in the subject's files all pertinent medical records, information and medical judgment from colleagues who assisted in the treatment and follow-up of the subject. If necessary, the investigator will contact the subject's personal physician or hospital staff to obtain further details.

### 16.9.1 Assessment of Severity

Each AE will be assigned a category by the investigator as follows:

- **Mild**: An AE that is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities.
- **Moderate**: An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed.
- **Severe**: An AE that prevents normal everyday activities; treatment or other intervention usually needed.

### 16.9.2 Assessment of Causality

The investigator is to determine whether there is a reasonable causal relationship between the occurrence of the AE and exposure to the study drug (i.e., nemolizumab or placebo) and/or study procedure (e.g., injection, topical background therapy, blood sample collection). Medical judgment should be used to determine the relationship, considering all relevant factors including the pattern of the reaction, temporal relationships, relevant medical history, and confounding factors such as co-medication or concurrent diseases.

The expression "reasonable causal relationship" is meant to convey in general that there are facts or arguments to suggest a causal relationship (ICH E2A, Section IIIA 1).

The relationship assessment for an AE is to be completed using the following definitions as a guideline for all AEs occurring during this clinical study:

- **Reasonable Possibility:** According to the reporting investigator, there is a reasonable possibility (i.e., suggestive evidence or arguments) that there is a causal relationship irrespective of the dose administered:
    - Between the study drug and the AE, and/or
    - Between the clinical study protocol procedure (e.g., injection, topical background therapy, blood sample collection) and the AE.
- **No Reasonable Possibility:** No suggestive evidence or arguments can be identified regarding a causal relationship between the study drug or the clinical study protocol procedure and the AE.

### 16.9.3 Action Taken

The investigator will describe the action taken with the study drug for the AE in the appropriate section of the eCRF.

### 16.9.4 Follow-up of Adverse Event

All investigators should follow-up with subjects with AEs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Details of AE resolution must be documented in the eCRF.

Subjects should be followed up for 12 weeks (± 5 days) after receiving the last dose of study drug, and any AEs that occur during this time should be reported according to the procedures outlined above.

### 16.9.5 Documenting and Reporting of Adverse Events

AEs should be reported and documented in accordance with the procedures outlined below. All AEs occurring during the study must be documented on the relevant eCRF pages. The following data should be documented for each AE:

- Description of the symptom event
- Classification of “serious” or “not serious”
- Severity
- Date of first occurrence and date of resolution (if applicable)
- Action taken with study drug
- Other action taken (e.g., concomitant medication, other intervention)
- Causal relationship

- Outcome of event (unknown, recovered, not yet recovered, recovered with sequelae, death [with date and cause reported])

## 16.10 Adverse Events of Special Interest

An AESI is a noteworthy treatment-emergent event for the study drug that should be monitored closely and reported promptly. See Section 16.12.1 for reporting procedure. An AESI can be either serious or non-serious.

Based on the potential risks of nemolizumab and the risks associated with biologics (and their biosimilar equivalents) in general (i.e., class effects), the following AEs will be considered AESIs:

- IRRs
    - Anaphylactic reactions
    - Acute allergic reactions requiring treatment
    - Severe injection site reactions with a duration greater than 24 hours
- Newly diagnosed asthma or worsening of asthma
    - More specifically, subjects with a medical history of asthma will be referred to the physician who manages their asthma when:
        - ACT score ≤ 19: An ACT score ≤ 19 conveys asthma that may not be adequately controlled. An AESI is reported based on the investigator's clinical judgment, including consideration of the managing physician's report.
        - Unexpected worsening of asthma is observed or reported. An AESI is reported based on the investigator's clinical judgment.
    - Subjects without a medical history of asthma will be referred to an appropriate respiratory physician/specialist when:
        - Signs and/or symptoms suggestive of asthma have been observed or reported. An AESI is reported based on the investigator's clinical judgment of the specialist's report.
        - Respiratory assessments (e.g., examination) suggest a worsening in the subject's respiratory health. An AESI is reported based on the investigator's clinical judgment of the specialist's report.
    - PEF value is only supplemental to the clinical evaluation of respiratory signs and symptoms suggestive of asthma (de novo or worsening in patients with history of asthma) at investigators judgement.
- Infections

- Any severe infection or any infection requiring treatment with parenteral antibiotics or oral antibiotics/antivirals/antifungals for > 2 weeks
- Confirmed or suspected COVID-19

- Peripheral edema: limbs, bilateral, if assessed by the investigator as having a reasonable possibility for a relationship to study drug. Peripheral edema is only to be reported as an AESI if assessed by the investigator as having a reasonable possibility for a relationship to study drug.
- Facial edema
- Elevated ALT or AST (> 3 × ULN) in combination with elevated bilirubin (> 2 × ULN). These abnormal lab findings may indicate potential severe liver injury (possible Hy's Law) and should be reported as an SAE (see Section 16.12.2, procedure for reporting a serious adverse event).

## 16.11 Serious Adverse Events

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

- Results in death.
- Is life-threatening (an AE is life-threatening if the subject was at immediate risk of death from the event as it occurred, i.e., it does not include a reaction that might have caused death if it had occurred in a more serious form).
- Requires or prolongs inpatient hospitalization (Complications occurring during hospitalization are AEs and SAEs if they cause prolongation of the current hospitalization. Inpatient hospitalization is considered to have occurred if the subject has had to stay for a night at the hospital. The criterion for prolongation of hospitalization is also defined as an extra night at the hospital. Hospitalization may not constitute sufficient grounds to be considered as an SAE if it is solely for the purpose of diagnostic tests [even if related to an AE], elective hospitalization for an intervention that was already planned before subject enrollment in the clinical study, admission to a day care facility, social admission [e.g., if the subject has no place to sleep], or administrative admission [e.g., for a yearly examination]. The details of such hospitalizations must be recorded on the medical history or physical examination eCRF).
- Results in persistent or significant disability/incapacity (An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions).
- Results in a congenital anomaly/birth defect.
- An important medical event that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the safety of the subject, and may require medical

or surgical intervention to prevent 1 of the outcomes listed above in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasia, or convulsions that do not result in hospitalization.

## 16.12 Reporting Procedures

### 16.12.1 Adverse Events of Special Interest Reporting

For any AESI occurring during the clinical study, regardless of whether or not related to the treatment, the investigator must:

1. Take prompt and appropriate medical action, if necessary. The safety of subjects is the first priority.

2. Ensure that the event is evaluated as an AESI. Notify (within three days of receipt of the event) the PPD of an AESI report by fax or phone:

   PPD

   Note: AESI reporting is required by the investigator if it occurs during the clinical study following the first dose of study drug or within 12 weeks (± 5 days) of receiving the last dose of study drug, whether or not the event is considered to be related to the investigational product.

   The demographics, medical history, drugs/therapies, and medical and surgical procedures forms must also be available for review in eCRF, at that time.

3. Send any relevant information or medical records (e.g., laboratory test results) to the PPD within three days of receipt of this relevant information.

4. Monitor and record the progress of the event until it resolves or reaches a stable condition, with or without sequelae. For all additional follow-up evaluations, update the AESI form within three days of receipt of the updated information.

5. Obtain and maintain in the files all pertinent medical records, information, and medical judgments from colleagues who participate in the treatment and follow-up of the subject. If necessary, contact the subject's personal physician or hospital staff to obtain further details.

6. When the outcome of the event is known, update the AESI form, if appropriate.

### 16.12.2 Serious Adverse Event Reporting

For any SAE occurring during the clinical study, regardless of whether or not related to the study drug and/or procedure, the investigator must:

1. Take prompt and appropriate medical action, if necessary. The safety of the subject is the first priority.

2. Ensure that the event is evaluated as an SAE. Immediately notify (within 24 hours of receipt of the event) the PPD of an SAE report by fax or phone:

   PPD

   Note: Immediate SAE reporting is required by the investigator if it occurs during the clinical study or within 12 weeks (± 5 days) of receiving the last dose of study drug, whether or not the event is considered to be related to the investigational product.

   The demographics, medical history, drugs/therapies, and medical and surgical procedures forms must also be available for review in eCRF, at that time.

3. Send any relevant information or anonymized medical records (e.g., laboratory test results) to the PPD (see contact details above), within 24 hours of receipt of this relevant information.

4. Monitor and record the progress of the event until it resolves or reaches a stable condition, with or without sequelae. For all additional follow-up evaluations, complete an updated SAE report within 24 hours of receipt of the updated information.

5. Obtain and maintain in the subject files all pertinent medical records, information, and medical judgments from colleagues who participate in the treatment and follow- up of the subject. If necessary, contact the subject's personal physician or hospital staff to obtain further details.

6. When the outcome of the event is known, complete an updated SAE report, if appropriate.

7. Prompt notification of SAEs by the investigator is essential so that legal obligations and ethical responsibilities toward the safety of subjects are met. The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. The sponsor or its delegate (i.e., the CRO) will comply with country-specific regulatory requirements relating to safety

reporting to regulatory authorities, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators. Investigator safety reports are prepared for SUSARs according to local regulatory requirements and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from the sponsor or its delegate (i.e., the CRO) will file it accordingly (i.e., within the Trial Master File [TMF]), and will notify the IRB/IEC, if appropriate according to local requirements.

8. Comply with the applicable regulatory requirement(s) related to the reporting of SAEs to the IRB/IEC.

### 16.12.3 Suspected Unexpected Serious Adverse Reactions

AEs that meet all of the following criteria will be classified as SUSARs and reported to the appropriate regulatory authorities in accordance with applicable regulatory requirements for expedited reporting:

- Serious.
- Unexpected (i.e., the event is not consistent with the Reference Safety Information in the IB for nemolizumab).
- There is at least a reasonable possibility that there is a causal relationship between the event and the study treatment.

The sponsor or its delegate will comply with country-specific regulatory requirements relating to safety reporting to regulatory authorities, IRB/IEC and investigators.

Investigator safety reports are prepared for SUSARs according to local regulatory requirements and sponsor policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SUSAR or other specific safety information (e.g., summary or listing of SAEs) from the sponsor or its delegate will file it accordingly (i.e., with the TMF), and will notify the IRB/IEC, if appropriate according to local requirements.

### 16.12.4 Pregnancy Reporting

Any pregnancy occurring during clinical studies where the fetus could have been exposed to the study drug must be monitored until its outcome in order to ensure the complete collection of safety data. If a subject becomes pregnant, the investigator must:

1. Withdraw the subject from the clinical study. The subject must not receive any further injection of the study drug.

2. Complete as fully as possible the Pregnancy Surveillance Form - Part I: History and Start of Pregnancy. Send by fax along with the exit form within 24 hours of receipt of the information to the PPD

   PPD

   Note: Immediate pregnancy reporting is required by the investigator if it occurs during the clinical study or within 12 weeks (± 5 days) of receiving the last dose of study drug, whether or not the event is considered to be related to the investigational product.

3. Monitor and record the progress of the pregnancy until its outcome. Contact the subject's regular physician (general practitioner or gynecologist) or hospital staff to obtain further details and ask for regular follow-up information.

4. Provide tri-monthly updates until the final outcome of the pregnancy, by completing the Pregnancy Surveillance Form - Part II: Course and Outcome of Pregnancy. For all additional follow-up evaluations, send the form by fax to the PPD within 24 hours of receipt of the information. If the subject can no longer be reached (i.e., lost to follow-up), documentation of the non-response/contact with two phone calls and a letter (certified with return receipt) is required.

5. At the outcome of the pregnancy, complete as fully as possible the Pregnancy Surveillance Form - Part II: Course and Outcome of Pregnancy. Print and send the form by fax to the PPD within 24 hours of receipt of the information.

6. If the pregnancy leads to an abortion (i.e., voluntary abortion, spontaneous abortion, or therapeutic abortion), in utero death or congenital anomaly, follow the procedure for declaration of/reporting an SAE (see Section 16.12.2).

### 16.12.5 Overdose Reporting

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. The investigator must immediately notify the sponsor of any occurrence of overdose with study drug.

CCI

[redacted]

# 18 OTHER ASSESSMENTS

CCI

[redacted]

## 18.2 Independent Data Monitoring Committee

An IDMC will review and monitor subject safety throughout the study. The IDMC will provide recommendations on the safety of subjects.

Details on the IDMC, including the plan of analysis for IDMC outputs, the composition of the IDMC, the procedures, roles, responsibilities, and their communications are provided in the IDMC charter.

## 18.3 Independent Adjudication Committee

An IAC will review all asthma-related AEs throughout the study. Details on the IAC, including the plan of analysis for IAC outputs, the composition of the IAC, the procedures, roles, responsibilities, and their communications are provided in the IAC charter.

# 19 STATISTICAL ANALYSIS

A statistical analysis plan (SAP) will be prepared after the protocol is approved. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a complement to the protocol and supersedes it in case of differences.

The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed. All primary, secondary, and exploratory efficacy endpoints, and safety endpoints will be summarized. Summary statistics will be presented by treatment group. For continuous variables, data will be summarized with the number of subjects (n), mean, standard deviation, median, first quartile, third quartile, minimum, and maximum by treatment group. For categorical variables, data will be tabulated with the number and proportion of subjects for each category by treatment group.

## 19.1 Determination of Sample Size

The sample size calculation is based on providing enough subjects to enable the detection of treatment difference in the primary endpoint at Week 12. Approximately 84 subjects will be randomized in each nemolizumab group and in the placebo group for a total sample size of approximately 252 subjects. 84 subjects per treatment group will have power ≥ 90% to detect difference between placebo group (expected success proportion 20%) and nemolizumab group (30 mg or 60 mg, expected success proportion 50%) at the overall two-sided alpha of 0.05. A two-sided alpha of 0.025 will be spent for the comparison of each nemolizumab dose group versus placebo group.

## 19.2 Analysis Populations

Statistical analyses will be performed on the following subject populations.

- **Intent-to-Treat Population**: The intent-to-treat (ITT) population will consist of all randomized subjects.
- **Modified Intent-to-Treat Population**: The modified intent-to-treat (mITT) population will consist of all ITT subjects who receive at least one dose of study drug and have at least one post baseline assessment of primary efficacy variable.
- **Per Protocol Population**: The per protocol (PP) population will include all randomized subjects who receive all scheduled doses of study drug and have Baseline and Week 12 assessments of WI NRS and with no major deviation that could impact efficacy.
- **Safety Population**: The safety population will include all randomized subjects who receive at least one dose of study drug.
- CCI [redacted]

The ITT population will be the primary population for all efficacy analyses. The mITT and PP populations will be used for the supplementary analysis of the primary endpoint. CCI [redacted] and all safety data will be summarized based on the safety population.

### 19.3 Efficacy Analysis

A summary based on observed case (OC) will be provided for all primary, secondary, and exploratory efficacy endpoints. At this case, no data will be imputed. For this summary, if any rescue medication is received or treatment is discontinued, and data are collected post-rescue receipt or treatment discontinuation, then the data post-rescue or post-discontinuation will be summarized as observed.

Proportion of subjects with WI NRS/SD NRS ≥ 4 and WI NRS ≥ 3, changes and percent changes from baseline of WI NRS/SD NRS at each week (from week 1 through week 20) will be calculated on the basis of the weekly average, obtained by averaging at least 4 daily WI NRS/SD NRS scores over 7-day periods.

For baseline weekly average, if fewer than 4 daily WI NRS/SD NRS scores for the 7-day period are available, the interval lower bound will be extended up to 7 additional days, one day at a time, until 4 daily WI NRS/SD NRS scores are available. If after the interval extension fewer than 4 daily WI NRS/SD NRS scores are available, the baseline weekly average WI NRS/SD NRS will be considered missing. The interval extension for the baseline weekly average calculation applies to the statistical analysis only. For eligibility, 4 daily WI NRS/SD NRS scores for the 7-day period are required (see inclusion criterion 5).

For week 12 weekly average, if fewer than 4 daily WI NRS/SD NRS scores for the 7-day period are available, the interval upper bound will be extended for 5 additional days, one day at a time, until 4 daily WI NRS/SD NRS scores are available. If after extending the upper bound fewer than 4 daily WI NRS/SD NRS scores available, the interval lower bound will be extended for 5 additional days, one day at a time, until 4 daily scores are available. If after the interval extension fewer than 4 daily WI NRS/SD NRS scores are available, the week 12 weekly average WI NRS/SD NRS will be considered missing.

For all the other weekly averages, if fewer than 4 daily WI NRS/SD NRS scores for the 7-day period are available, the weekly average WI NRS/SD NRS will be considered missing for that period.

For the aim of sensitivity analyses, weekly averages of WI NRS obtained by averaging at least 3 daily scores over 7-day periods, at least 2 daily scores over 7-day periods and at least 1 daily score over 7-day periods will be calculated. No period extension at baseline and week 12 applies for these weekly averages. If fewer than 3, 2 or 1 daily WI NRS scores for the 7-day period are available, the corresponding weekly average of WI NRS will be considered missing for that period.

Data of both nemolizumab groups (30 mg and 60 mg) and placebo group and comparisons versus placebo group of both nemolizumab groups will be presented.

### 19.3.1 Analysis of Primary Efficacy Endpoint

Primary efficacy endpoint and related estimand are the following:

| Primary Efficacy Estimand Description | Estimand Attributes |
|---|---|
| In adult hemodialysis patients with chronic kidney disease and associated moderate to severe pruritus, 2 nemolizumab dosing schedules[1] compared to placebo by the difference in proportions of responders where response is defined as an improvement from baseline of **WI NRS ≥ 4 at Week 12** without use of rescue therapies and without treatment discontinuation due to lack of efficacy or AE/death related to study drug | **Treatment Conditions**: initial dose of nemolizumab (60 mg) or placebo at baseline, then nemolizumab (30 mg or 60 mg) or placebo Q4W at Weeks 4 and 8 via subcutaneous injection. |
| | **Population**: adult hemodialysis patients with chronic kidney disease and associated moderate to severe pruritus (will be estimated in the Intent-to-Treat analysis set). |
| | **Variable**: a binary composite response where:<br><br>**Responder** is defined as an improvement ≥ 4 in WI NRS from baseline at Week 12 without use of rescue therapies and without treatment discontinuation due to lack of efficacy or AE/death related to study drug.<br><br>**Non-responder** is defined as an improvement < 4 in WI NRS from baseline at Week 12 or use of rescue therapies or treatment discontinuation due to lack of efficacy or AE/death related to study drug. |
| | **Strategies for Intercurrent Events**: A composite strategy was chosen for the use of rescue therapies and treatment discontinuation due to lack of efficacy or AE/death related to study drug; in case of use of rescue therapies or treatment discontinuation due to lack of efficacy or AE/death related to study drug, subjects will be considered as treatment failures in the binary composite response. In the case of treatment discontinuation for any other reason, a treatment policy strategy will be used and observed after discontinuation data (if available) will be used. |
| | **Summary measure**: treatment difference of nemolizumab from placebo in proportions of responders |

[1] Dosing schedules compared to placebo Q4W are an initial SC dose of nemolizumab (60 mg) at baseline then either 30 mg or 60 mg Q4W at Week 4 and Week 8.
Abbreviation(s): WI NRS = Worst Itch Numeric Rating Scale; Q4W = Every 4 Weeks

The estimand for the primary endpoint will be analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by analysis center; strata-adjusted difference in proportions between treatment groups and the 97.5% confidence interval of the difference will be based on the large sample approximation method for binary data.

### 19.3.2 Analysis of Secondary Efficacy Endpoints

#### *19.3.2.1 Analysis of Key Secondary Efficacy Endpoints*

The following key secondary efficacy endpoints will be analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by analysis center; strata-adjusted difference in proportions between treatment groups and the 97.5% confidence interval of the difference will be based on the large sample approximation method for binary data.

- Proportion of subjects with an improvement of WI NRS ≥ 3 from baseline at Week 12.
- Proportion of subjects with an improvement of WI NRS ≥ 4 from baseline at Week 4.
- Proportion of subjects with an improvement of SD NRS ≥ 4 from baseline at Week 12.

- Proportion of subjects with an improvement of WI NRS ≥ 3 from baseline at Week 4.
- Proportion of subjects with an improvement of SD NRS ≥ 4 from baseline at Week 4.

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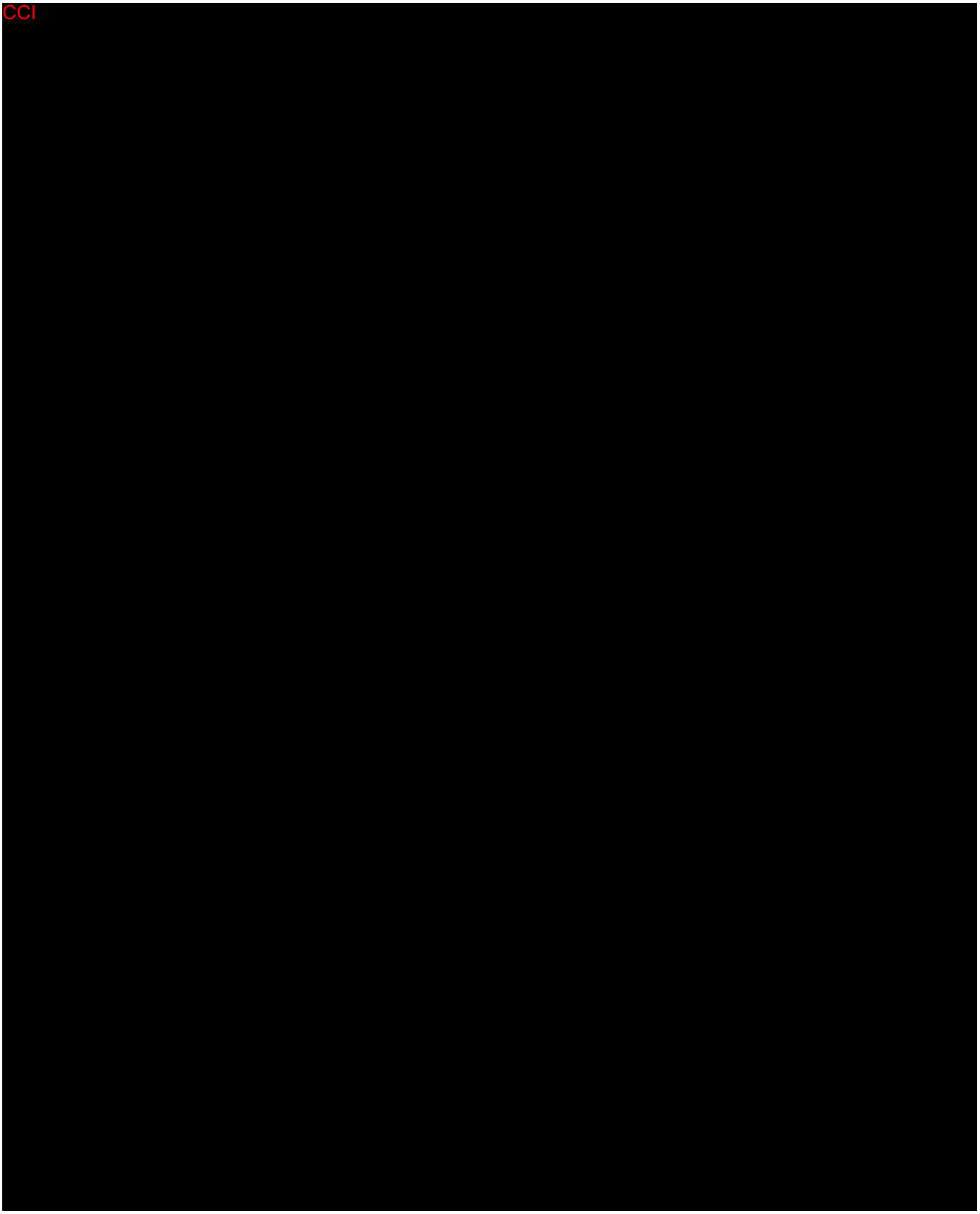

### 19.3.4 Multiplicity Adjustment for Primary and Key Secondary Efficacy Endpoints

In order to maintain the overall two-sided alpha of 0.05, a two-sided alpha of 0.025 will be spent for the comparison of each Nemolizumab dose group versus placebo group. A predefined hierarchal testing procedure will be implemented to test the primary and key secondary endpoints of each nemolizumab dose group versus placebo group.

The following hypothesis test will be evaluated for the primary endpoint at the two-sided alpha of 0.025:

$$\begin{cases} H_0: \pi_{Nemolizumab} = \pi_{Placebo} \\ H_a: \pi_{Nemolizumab} \neq \pi_{Placebo} \end{cases}$$

where $p_{Nemolizumab}$ is the proportion of subjects in nemolizumab group with an improvement of WI NRS $\geq 4$ from baseline at Week 12 and $p_{Placebo}$ is the proportion of subjects in placebo group with an improvement of WI NRS $\geq 4$ from baseline at Week 12.

The hypothesis tests for the key secondary efficacy endpoints are conditional on the success of the primary endpoint. The hypothesis tests for the key secondary efficacy endpoints will be evaluated on the ITT population according to the following predefined order, all at the same two-sided alpha of 0.025, moving to the next hypothesis test only after a success on the previous hypothesis test. This approach does not inflate the type I error rate as long as the hypothesis tests for the key secondary efficacy endpoints are conditional on the success of the primary, there is a prospective specification of the testing sequence and no further testing is performed once the sequence breaks, that is, further testing stops as soon as there is a failure of a hypothesis test in the sequence to show significance at the predefined alpha level.

Key Secondary Efficacy Endpoints:

1. Proportion of subjects with an improvement of WI NRS $\geq 3$ from baseline at Week 12.
2. Proportion of subjects with an improvement of WI NRS $\geq 4$ from baseline at Week 4.
3. Proportion of subjects with an improvement of SD NRS $\geq 4$ from baseline at Week 12.
4. Proportion of subjects with an improvement of WI NRS $\geq 3$ from baseline at Week 4.
5. Proportion of subjects with an improvement of SD NRS $\geq 4$ from baseline at Week 4.

## 19.4 Safety Analysis

### 19.4.1 Extent of Exposure

The duration of exposure and the number of administrations per subject will be summarized by treatment group.

### 19.4.2 Adverse Events

All reported AEs will be coded according to the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs, defined as those AEs occurring or worsening after the first administration of study treatment until last visit be tabulated in frequency tables by system organ class and preferred term. Additional summary tables will be provided for SAEs, AEs related to the study drug(s) (reasonable possibility, no reasonable possibility), AEs related to the study procedure, AESIs, and AEs leading to treatment discontinuation and study withdrawal. For a given AE, a subject will be counted once even if he/she has experienced multiple episodes of that particular AE.

Pre-treatment AEs will be listed separately.

### 19.4.3 Clinical Laboratory

Laboratory data (absolute values and change from baseline) will be summarized by visit and treatment group. In addition, the number and percentage of subjects below, within, and above the laboratory reference ranges and/or pre-defined threshold according to the Common Terminology Criteria for Adverse Events (CTCAE) and the number and percentage of subjects who met criteria of potential clinically significant value will be summarized by treatment group. Shift tables will be generated using the reference ranges. Reference ranges will be provided in the laboratory manual. Details of any potential clinically significant ranges will be provided in the SAP.

### 19.4.4 Vital Signs

All vital signs and weight data (absolute values and change from baseline) will be summarized by visit and treatment group. In addition, the number and percent of subjects with clinically significant abnormal values (of clinical concern as identified by the investigator) will be summarized by treatment group.

### 19.4.5 12-Lead Electrocardiogram

The number and percentage of subjects who have ECGs that are normal, abnormal NCS and abnormal CS will be summarized by visit and treatment group. Heart Rate and PR, QRS, RR, QT, QTcB and QTcF intervals and their changes from baseline will be summarized by visit and treatment group.

### 19.4.6 Physical Examination

The number and percentage of subjects who are normal, abnormal CS, and abnormal not clinically significant (NCS) will be displayed by treatment at each visit.

### 19.4.7 Respiratory Assessments

The results (absolute values and change from baseline) from PEF testing and respiratory exam will be summarized by visit and treatment group. ACT for subjects with a medical history of asthma will be listed.

### 19.4.8 Prior and Concomitant Medications

Prior and concomitant medications will be coded according to the most recent version of the World Health Organization (WHO) Drug Dictionary Enhanced for Concomitant Medication and summarized. Summary and analysis of rescue medications will be described in the SAP.

## 19.5 Pharmacokinetic and Anti-drug Antibody Analysis

Descriptive statistics (arithmetic and geometric mean, standard deviation [SD], coefficient of variation [CV%], median, first quartile, third quartile, minimum [min.], maximum [max.]) will be used to summarize the observed nemolizumab $C_{trough}$ in serum.

In addition, individual and mean serum concentration versus time curves will be presented for both linear and semi-log scales. Treatment related positive ADA subjects and positive ADA subject will be identified in the graphs.

Descriptive statistics (n, arithmetic mean, standard deviation, Coefficient of Variation (CV)%, geometric mean, minimum, median, maximum) will be calculated for all individual CCI derived parameters.

Incidence of positive ADA results will be summarized (absolute occurrence, percent of subjects, and treatment-related ADA). The ADA results presentation will be detailed in the SAP.

## 19.6 Dose selection

Dose selection will be based on the final analysis by evaluating the optimal risk-benefit and considering the potential impact of body weight.

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Safety assessment:

The IDMC will review and monitor subject safety throughout the study.

## 19.7 Handling of Missing Data

Missing data for dichotomous efficacy endpoints will be imputed using multiple imputations (MI) under missing at random (MAR) assumption for the primary/main analysis. Dichotomous endpoints will be calculated from the underlying imputed variable.

For the sensitivity analyses of the primary endpoint, missing data will be imputed using a copy reference (CR) approach under missing not at random (MNAR) assumption (dichotomous endpoints will be calculated from the underlying imputed variable) and as "Non-responder"; moreover a Tipping Point analysis under MNAR assumption will be carried out.

For the sensitivity analyses of the key secondary efficacy endpoints, missing data will be imputed using a CR approach under MNAR assumption (dichotomous endpoints will be calculated from the underlying imputed variable) and as "Non-responder".

Missing data of continuous efficacy endpoints and QoL/Health Outcome endpoints will be imputed using MI under MAR assumption.

For the multiple imputation, the MI procedure of the SAS system will be used to generate sets of data with missing values imputed from observed data. It is expected that the pattern of missing data will be monotonic, with slight deviations being corrected by the Markov Chain Monte Carlo (MCMC) method of the MI procedure. A predictive mean matching method will be used for the continuous data with the following covariates included in the imputation model: non-missing data from earlier time points. Separate imputations by treatment group will be carried out. Changes and percent changes from baseline and dichotomous endpoints will be calculated from the imputed data.

Subjects who took rescue therapies as defined in Section 12.5.1.2 or discontinued treatment due to lack of efficacy or AE/death related to study drug will be considered as treatment failures, efficacy data collected after the use of rescue therapies or treatment discontinuation due to lack of efficacy or AE/death related to study drug will be set to the worst possible value and subject's binary response will be imputed as "Non-responder" prior to conducting the MI and Tipping Point analysis.

Further details will be provided in the SAP.

## 19.8 Analysis Centers

Prior to database lock, a review of the blinded data will be performed to determine the size of each center. If there are centers with a small number of randomized subjects, then these centers will be pooled in order for analyses to be carried out. The process of combining centers will be based on the ITT population, and same pooling will be repeated for mITT population and PP population.

A small center is defined as a center which randomizes less than 12 subjects. First, centers will be sorted by geographic region, number of randomized subjects (descending order) and center number (ascending order). Pooling will start with combining the largest of the set of small centers of a geographic region with the smallest center within the same geographic region. If there is a further need to combine data (the size of the pooled centers includes less

than 12 subjects), the next smallest center will be combined with the next largest of the small centers, until the criterion of a minimum of 12 subjects is met. The process will continue until all pooled centers have a minimum of 12 subjects within the same geographic region. Any remaining small centers of a geographic region will be pooled with the last pooled center within the same geographic region. The pooled centers and the remaining original unpooled clinical centers will be referred to as 'analysis centers' and will be used as stratification factor in the statistical analyses.

If at the start of pooling any geographic region has less than 12 subjects in the ITT population in total, then centers will be added to the list of small centers in another geographic region and then combined as above. This decision will be documented in clinical report.

### 19.9 Sensitivity and Supplementary Analysis for Primary and Key Secondary Efficacy Endpoints

For the sensitivity analyses of the primary endpoint, missing data will be imputed using a copy reference (CR) approach under missing not at random (MNAR) assumption (dichotomous endpoints will be calculated from the underlying imputed variable) and as "Non-responder"; moreover a Tipping Point analysis under MNAR assumption will be carried out. Furthermore, the analysis of the primary efficacy endpoint will be repeated using weekly averages of WI NRS with at least 3 daily scores over 7-day periods, at least 2 daily scores over 7-day periods and at least 1 daily scores over 7-day periods (no period extension at baseline and week 12 applies for these averages).

A mITT analysis, a PP analysis and an observed case analysis will be performed too as supplementary analyses for the primary efficacy endpoint.

Sensitivity analyses will be performed by imputing missing data using a CR approach under MNAR assumption (dichotomous endpoints will be calculated from the underlying imputed variable) and as "Non-responder" for the following dichotomous secondary endpoints:

- Proportion of subjects with an improvement of WI NRS ≥ 3 from baseline at Week 12.
- Proportion of subjects with an improvement of WI NRS ≥ 4 from baseline at Week 4.
- Proportion of subjects with an improvement of SD NRS ≥ 4 from baseline at Week 12.
- Proportion of subjects with an improvement of WI NRS ≥ 3 from baseline at Week 4.
- Proportion of subjects with an improvement of SD NRS ≥ 4 from baseline at Week 4.

Subjects who took rescue therapies as defined in Section 12.5.1.2 or discontinued treatment due to lack of efficacy or AE/death related to study drug will be considered as treatment failures, efficacy data collected after the use of rescue therapies or treatment discontinuation due to lack of efficacy or AE/death related to study drug will be set to the worst possible value and subject's binary response will be imputed as "Non-responder" prior to conducting the MI and Tipping Point analysis.

Further details will be provided in the SAP.

## 19.10 Impact of COVID-19

To assess the impact of COVID-19 related study disruptions (e.g. treatment discontinuation, missing assessments, etc.), the primary and key secondary efficacy endpoints will also be analyzed using multiple imputations (MI) under missing at random (MAR) assumption on the ITT population excluding subjects affected by COVID-19 related study disruptions.

Further details will be provided in the SAP.

## 19.11 Subgroup Analysis

Descriptive summary and analysis for primary and key secondary efficacy endpoints will be produced for the following subgroups:

- Age group (18 to 45; >45 to 65; >65 to 80; >80)
- Sex (Male, Female)
- Race (White, Black, Asian, Other)
- Region (US; Excl-US)
- Severity of pruritus at baseline (5 to 7; >7 to 10)
- Duration of pruritus at baseline (≤3 months; >3 to 12 months; >12 months)
- Duration of hemodialysis at baseline (≤1 year; >1 year to 3 years; >3 years)
- With or without prior or concomitant systemic anti-pruritus treatment

# 20 STUDY MANAGEMENT

## 20.1 Approval and Consent

### 20.1.1 Regulatory Guidelines

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the United States (US) Code of Federal Regulations (CFR), in compliance with International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines, and according to the appropriate regulatory requirements in the countries where the study was conducted.

### 20.1.2 Institutional Review Board/Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted IRB/IEC. Approval is required for the study protocol, protocol amendments (if applicable), IB, ICFs, recruitment material and subject information sheets and other subject-facing material.

### 20.1.3 Informed Consent

For each study subject, written informed consent will be obtained before any protocol- related activities. As part of this procedure, the principal investigator or designee must explain orally and in writing the nature of the study, its purpose, procedures, expected duration, alternative therapy available, and the benefits and risks involved in study participation. The subject should be informed that he/she may withdraw from the study at any time, and the subject will receive all information that is required by local regulations and guidelines for ICH. The principal investigator will provide the sponsor or its representative with a copy of the IRB/IEC approved ICF before the start of the study.

## 20.2 Data Management

The designated CRO will be responsible for activities associated with the data management of this study. This will include, but is not limited to, setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. All data management activities will be detailed in the data management plan.

Study centers will enter data directly into an electronic data capture (EDC) system by completing the eCRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study center. Data to be recorded directly on the eCRF will be identified and the eCRF will be considered the source document. Any changes to the data entered into the EDC system will be recorded in the audit trail.

## 20.3 Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. The investigator will provide direct access to source documents and/or source data in the facilitation of trial-related monitoring, audits, review by IECs/IRBs, and regulatory inspections.

The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects.

Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, not obscure the original entry, and be explained if necessary.

Sponsor monitors, auditors, and regulatory inspectors should have direct access to source data.

## 20.4 Record Retention

Study records and source documents must be preserved for at least 25 years after the completion or discontinuation of/withdrawal from the study, at least two years after the drug being studied has received its last approval for sale, or at least two years after the drug development has stopped, and in accordance with the applicable local privacy laws, whichever is the longer period.

## 20.5 Monitoring

The study will be monitored according to the monitoring plan to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

Monitoring visits and contacts will be made at appropriate times during the study. The principal investigator will assure he/she and adequate site personnel are available throughout the study to collaborate with clinical monitors. Clinical monitors must have direct access to source documentation in order to check the completeness, clarity, and consistency of the data recorded in the eCRFs for each subject.

The investigator will make available to the clinical monitor all source documents and medical records necessary to review protocol adherence and eCRFs. In addition, the investigator will work closely with the clinical monitor and, as needed, provide them appropriate evidence that the study is being conducted in accordance with the protocol, applicable regulations, and GCP guidelines.

## 20.6 Quality Control and Quality Assurance

The sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, security, and reliability of the study data presented to the sponsor lies with the investigator generating the data.

The sponsor will arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, standard operating procedures, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at study sites and during data management to assure that safety and efficacy data are adequate and well documented.

## 20.7 Protocol Amendment and Protocol Deviation

### 20.7.1 Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no effect on the safety of subjects or the conduct of the study will be classed as administrative amendments and will be submitted to the IEC/IRB for information only. The sponsor will ensure that acknowledgment is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate regulatory authorities and the IECs/IRBs for approval and will not be implemented at sites until such approvals are received other than in the case of an urgent safety measure.

### 20.7.2 Protocol Deviations

Should a protocol deviation occur, the sponsor must be informed as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. Protocol deviations will be reported to the IRB/IEC and in accordance with applicable regulatory authority mandates.

Changes that involve only logistical or administrative changes to the clinical study protocol are authorized. The investigator should document and explain any deviation from the clinical study protocol. Major deviations are categorized into the following categories:

- Eligibility deviations (inclusion/exclusion criteria).
- Improper reconstitution and administration of study medication.
- Non-compliance with study medication per the investigator’s discretion.
- Non-compliance with study procedures if the consequence of non-compliance would compromise either the subject’s safety and/or the study integrity, primary endpoint, and/or is not in line with GCP/ICH guidelines.
- Use of prohibited concomitant therapies.

All protocol deviations will be identified, evaluated, and closed before the respective database lock and will be described in the clinical study report. Protocol deviations incurred as a direct result of the COVID-19 pandemic should be specifically recorded as a COVID-19 deviation. Further details of protocol deviations will be provided in the Protocol Deviation and Non-Compliance Management Plan.

### 20.8 Ethical Considerations

This study will be conducted in accordance with this protocol, the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the CFR; EU 536/2014, Annex 1, D, 17 (a); and in compliance with GCP guidelines.

IECs/IRBs will review and approve this protocol and the ICF. All subjects are required to give written informed consent before participation in the study.

### 20.9 Financing and Insurance

Before the study commences, the sponsor (or its designee) and the investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the investigator (or the institution signatory) and the sponsor (or its designee).

The investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The sponsor will provide no-exclusion insurance coverage for the clinical study as required by national regulations.

### 20.10 Publication Policy/Disclosure of Data

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the institution and the sponsor or their designee.

With respect to such rights, the sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. In order to facilitate such ownership, investigators will be required to assign all such inventions either to their institution or directly to the sponsor or its designee, as will be set forth in the clinical study agreement.

### 20.11 Subject Confidentiality

Monitors, auditors, and other authorized agents of the sponsor and/or its designee, the IEC(s) approving this research, as well as that of any other applicable agency(ies), will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent

permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identities will remain confidential.

All personal data collected and processed for the purposes of this study should be managed by the investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the applicable national and/or local laws and regulations on personal data protection.

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