**Galderma S.A.**

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# 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

**19FEB2024**

Final Statistical Analysis Plan

**Version 1.0**

Prepared by: PPD

PPD

## Galderma Approval and Acknowledgement Signatures

### Galderma Study Biostatistician (for approval and acknowledgement)

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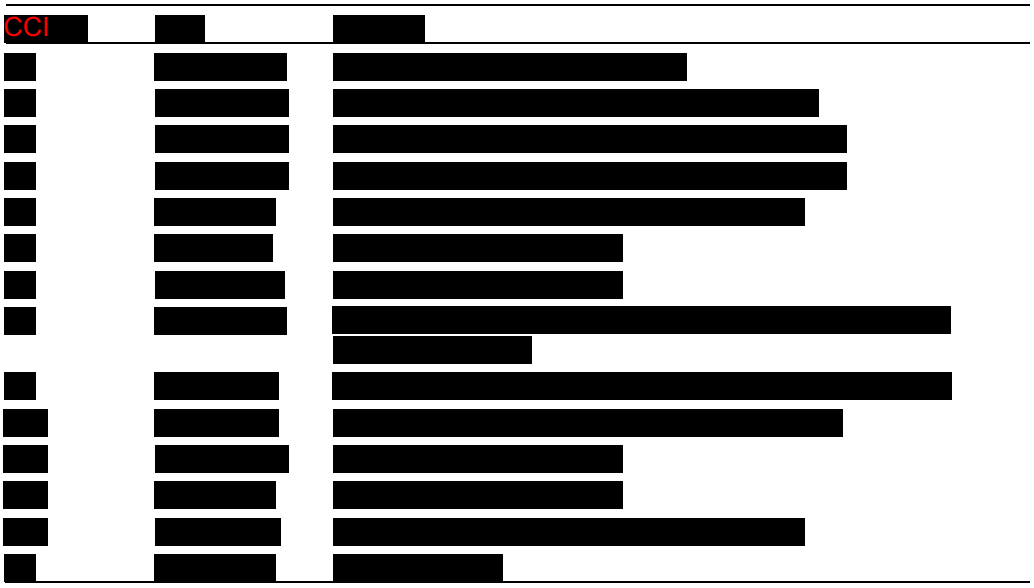
## Document History - Changes compared to previous versions of SAP



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**List of Abbreviations**

| | |
|---|---|
| ACT | Asthma control test |
| AD | Atopic dermatitis |
| ADA | Anti-drug antibody |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| ATC | Anatomical therapeutic chemical |
| CCI | [redacted] |
| AVF | Arteriovenous fistula |
| AVG | Arteriovenous graft |
| CI | Confidence interval |
| CKD | Chronic kidney disease |
| CKD-aP | Chronic kidney disease with associated pruritus |
| Cl/F | Apparent total body clearance |
| CMH | Cochran-Mantel-Haenszel test |
| COVID-19 | Coronavirus disease 2019 |
| CPK | Creatinine phosphokinase |
| CCI | [redacted] |
| EASI | Eczema Area and Severity Index |
| ECG | Electrocardiogram |
| ECLIA | Electro-chemi-luminescence immunoassay |
| eCRF | Electronic Case Report Form |
| eDISH | Evaluation of drug-induced serious hepatotoxicity |
| CCI | [redacted] |
| ESKD | End-stage kidney disease |
| CCI | [redacted] |
| HBcAb | Hepatitis B core antibody |
| HBsAg | Hepatitis B surface antigen |
| HCV | Hepatitis C virus |

| | |
|---|---|
| HDL | High-density lipoprotein |
| HIV | Human immunodeficiency virus |
| IAC | Independent adjudication committee |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IDMC | Independent data monitoring committee |
| IGA | Investigator's global assessment |
| IRT | Interactive response technology |
| ITT | Intent-to-treat |
| IUG | Independent Unblinded Group |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| LDL | Low-density lipoprotein |
| LS | Least-Squares |
| MAR | Missing at random |
| MCMC | Markov Chain Monte Carlo |
| MedDRA | Medical dictionary for regulatory activities |
| MI | Multiple imputation |
| mITT | Modified intent-to-treat |
| MNAR | Missing not at random |
| NRS | Numeric rating scale |
| OC | Observed cases |
| PCR | Polymerase chain reaction |
| PEF | Peak expiratory flow |
| [redacted] | [redacted] |
| PN | Prurigo nodularis |
| PP | Per Protocol |
| PT | Preferred term |
| PTAE | Pre-treatment adverse events |
| Q1 | First quartile |
| Q3 | Third quartile |

| | |
|---|---|
| QoL | Quality of life |
| RA | Receptor A |
| RSE | Relative standard error |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SC | Subcutaneous |
| SD | Standard deviation |
| SD NRS | Sleep disturbance numeric rating scale |
| SOC | System organ class |
| SOP | Standard operating procedure |
| CC | [redacted] |
| TB | Tuberculosis |
| TCS | Topical corticosteroid |
| TEAE | Treatment-emergent adverse events |
| TLFs | Tables, Listings and Figures |
| CCI | [redacted] |
| WI NRS | Worst itch numeric rating scale |

# 1 Introduction

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[1]. Recently, an international comparison on the prevalence of pruritus in hemodialysis patients found that 68% of survey respondents reported they were at least somewhat bothered by itchy skin. 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[2]. Despite a prevalence rate and a clear association with poorer psychological and medical outcomes including higher mortality risk[3], this condition is often underreported by patients and overlooked by health care providers[2].

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. 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. 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 topical corticosteroid (TCS).

The purpose of this Statistical Analysis Plan (SAP) is to describe the analyses and data presentations used in determining the efficacy and safety of nemolizumab in the treatment of moderate to severe pruritus in adult CKD subjects undergoing hemodialysis. This SAP outlines the types of analyses that will address the study objectives and explains in detail how the data will be handled and analyzed. It contains the definitions of analysis sets and statistical methods for the analysis of endpoints.

This statistical analysis plan was written in accordance with ICH E9, ICH E9 (R1) and PPD (SOPs) and using the study protocol version 6.0 dated 21st September 2023.

# 2 Objectives

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.

The secondary objectives are to evaluate the safety of nemolizumab compared to placebo, and to assess the CCI and optimal dose in adult hemodialysis subjects with moderate to severe pruritus.

# 3 Investigational Plan

## 3.1 Overall Study Design and Plan

This is a randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of nemolizumab in adult subjects with moderate to severe 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:

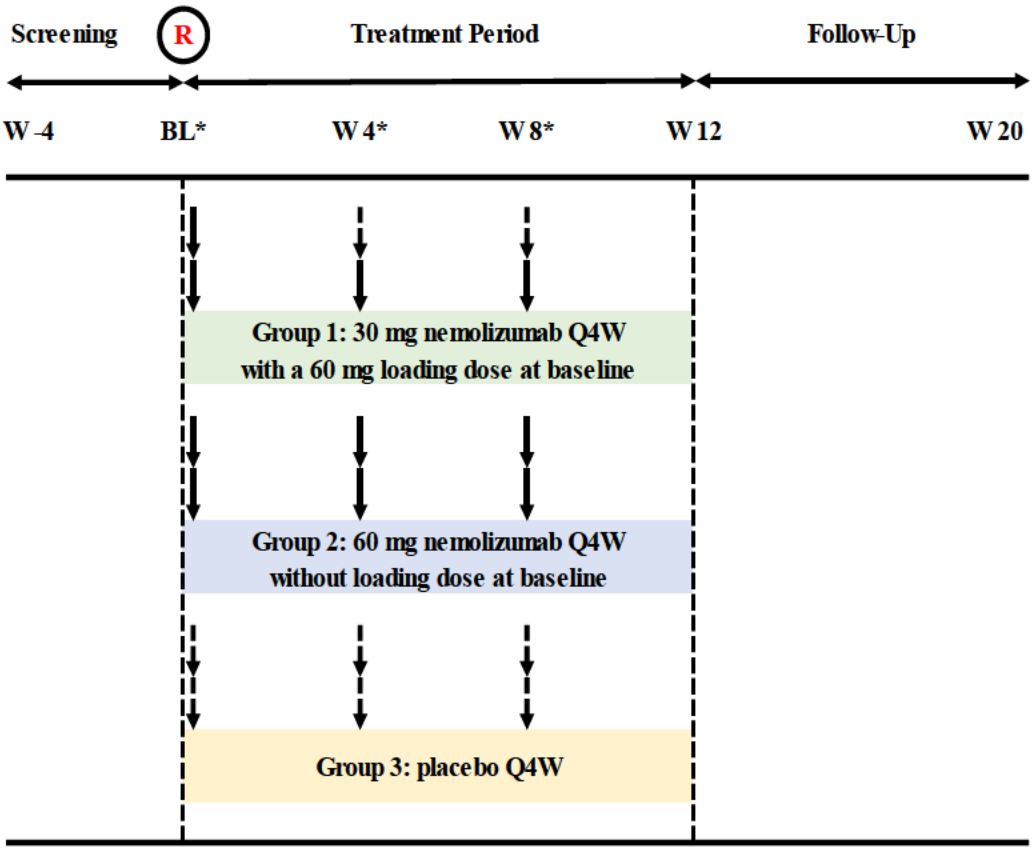
- Group 1: 30 mg Nemolizumab Q4W with a 60 mg loading dose at baseline;
- Group 2: 60 mg Nemolizumab Q4W without loading dose at baseline;
- Group 3: Placebo Q4W.

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 the last study drug injection). The screening period will evaluate subject eligibility. At the baseline visit, subjects will receive an initial dose of nemolizumab 60 mg or placebo by two subcutaneous (SC) injections (30 mg + 30 mg, or placebo + placebo). 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) at Week 4 and Week 8 after completion of hemodialysis treatment (within four hours). CCI are to be taken before hemodialysis. Figure 1 below presents the study design:

**Figure 1**




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

The schedule of assessments is summarized in Appendix A.

## 3.2 Study Endpoints

### 3.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with an improvement of Worst Itch Numeric Rating Scale (WI NRS) ≥ 4 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. Subjects who took rescue therapies or discontinued treatment due to lack of efficacy or AE/death related to study drug will be considered treatment failures (see Table 6 for full details of the primary estimand). Note that this combines the outcome with intercurrent events by defining a binary composite response.

### 3.2.2 Secondary Efficacy Endpoints

The key secondary efficacy endpoints are defined as follows:

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 Sleep Disturbance Numeric Rating Scale (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]

### 3.2.6 Other Safety Measurements

Other safety measurements are as follows:

1. Physical examination and vital signs.
2. Clinical laboratory tests.

3. Electrocardiogram (ECG) results.
4. Respiratory examination and assessments.

### 3.3 Treatments

This study has three treatment arms at a ratio of 1:1:1. 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 Week 4 and at Week 8. All the study drug treatment should be performed following the completion of the hemodialysis treatment (within four hours). Table 1 below summarizes the study drug dosing during the treatment period of the study.

**Table 1 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.

## 4 General Statistical Considerations

All summaries and results in Tables, Listings and Figures (TLFs) should be presented for the following groups:

**Table 2 Treatment Group Labels in TLFs**

| Treatment Groups | Label in TLFs |
|---|---|
| 60 mg loading dose of nemolizumab by two SC injections of 30 mg at Baseline, followed by one SC injection of 30 mg of nemolizumab + one SC injection of placebo at Week 4 and at Week 8 | Nemolizumab 30 mg |
| Two SC injections of 30 mg of Nemolizumab at Baseline, at Week 4 and at Week 8 | Nemolizumab 60 mg |
| Two SC injections of placebo at Baseline, at Week 4 and at Week 8 | Placebo |
| Nemolizumab 30 mg, Nemolizumab 60 mg, and Placebo treatment groups combined | Total |

The reference date for the calculation of study days will be the date of the first treatment injection on Day 1/Baseline for subjects randomized and treated or the date of randomization for subjects randomized but not treated (if any).

For events/assessments on or after the reference date, the study day of events/assessments is calculated as the date of event minus the reference date + 1. For events/assessments before the reference date, the study day of the events/assessments is calculated as the date of assessment minus the reference date.

Baseline is defined as the last non-missing measurement prior to the first treatment injection at Day 1/Baseline for subjects randomized and treated or prior to the randomization for subjects randomized but not treated (if any). Change from baseline and percent change from baseline are defined as follows:

$$\text{Change from Baseline} = \text{PostBaseline} - \text{Baseline}$$

$$\text{Percent Change from Baseline} = \begin{cases} \text{Baseline} \neq 0 \Rightarrow 100 \cdot \dfrac{\text{PostBaseline} - \text{Baseline}}{\text{Baseline}} \\ \text{Baseline} = 0 \Rightarrow \text{Missing} \end{cases}$$

All by-visit summaries and analyses will use the analysis visit (see section 4.10).

Continuous data will be summarized using the following descriptive statistics: number of subjects (n), mean, standard deviation (SD), median, first and third quartiles (Q1 and Q3), minimum and maximum. Categorical data will be summarized using the frequency count (n) and percentage (%) of subjects for each category. For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean, median, Q1 and Q3 will be displayed to one level of precision greater than the data collected. Standard deviation will be displayed to two levels of precision greater than the data collected.

P-values will be displayed in the following format, 0.9999. Any p-value less than 0.0001 will be displayed as <0.0001. Any p-value greater than 0.9999 will be displayed as >0.9999.

The following flagging conventions will be applied for the p-values of all statistical testing:

- 0.01 ≤ p-values < 0.025 will be flagged with one asterisk (e.g. “0.0249 *”).
- 0.001 ≤ p-value < 0.01 will be flagged with two asterisks (e.g. “0.0099 **”).
- 0.0001 ≤ p-value < 0.001 will be flagged with three asterisks (e.g. “0.0009 ***”).
- p-value < 0.0001 will be flagged with four asterisks (e.g. “<0.0001 ****”).

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. The denominator for all percentages will be the number of subjects in that treatment within the analysis set of interest, unless otherwise specified. Percentages will be presented to one decimal place.

All proportions will be presented as percentages (not as fraction of unit).

Any imputed data will be used in analysis tables and figures (as applicable) and the original collected data will be used in summary tables and figures and displayed in listings.

Unless specified otherwise, all the summary tables will be presented overall and by treatment, and all the collected data will be presented in the listings. Data displayed in the listings will be sorted by treatment and subject identifier.

All analyses will be conducted using SAS Version 9.4 or higher.

## 4.1 Date Imputations

For the purpose of inclusion in prior and/or concomitant medication/procedure and AE tables, incomplete AEs and medications/procedures start and end dates will be imputed as follows:

- Start Date Imputation of Adverse Events:
  - Imputation of adverse event end date has to be done before imputation of event start date.
  - Completely missing: For subjects treated, impute to the date of first treatment injection. For subject randomized but not treated, impute to the date of randomization. For subjects not randomized, impute to the date of informed consent.
  - Missing day and month: For subjects treated, impute to January 1$^{st}$, unless year is the same as year of first treatment injection then impute to the date of first treatment injection. For subject randomized but not treated, impute to January 1$^{st}$, unless year is the same as year of randomization then impute to the date of randomization. For subjects not randomized, impute to January 1$^{st}$, unless year is the same as year of informed consent then impute to the informed consent date.
  - Missing day: For subjects treated, impute to the 1$^{st}$ of the month, unless month and year are the same as month and year of first treatment injection then impute to the date of first treatment injection. For subject randomized but not treated, impute to the 1$^{st}$ of the month, unless month and year are the same as month and year of randomization then impute to the date of randomization. For subjects not randomized, impute to the 1$^{st}$ of the month, unless month and year are the same as month and year of informed consent then impute to the informed consent date.
  - If event end date (imputed or not) is not missing and imputed event start date is after event end date (imputed or not), set the event start date to the event end date (imputed or not).
- Start Date Imputation of Prior/Concomitant Therapies and Medical/Surgical Procedures:
  - Imputation of therapy/procedure end date has to be done before imputation of therapy/procedure start date.

  - Completely missing: For subjects treated, impute to the date of first treatment injection. For subject randomized but not treated, impute to the date of randomization. For subjects not randomized, impute to the date of informed consent.
  - Missing day and month: For subjects treated, impute to January 1st, unless year is the same as year of first treatment injection then impute to the date of first treatment injection. For subject randomized but not treated, impute to January 1st, unless year is the same as year of randomization then impute to the date of randomization. For subjects not randomized, impute to January 1st, unless year is the same as year of informed consent then impute to the informed consent date.
  - Missing day: For subjects treated, impute to the 1st of the month, unless month and year are the same as month and year of first treatment injection then impute to the date of first treatment injection. For subject randomized but not treated, impute to the 1st of the month, unless month and year are the same as month and year of randomization then impute to the date of randomization. For subjects not randomized, impute to the 1st of the month, unless month and year are the same as month and year of informed consent then impute to the informed consent date.
  - If therapy/procedure end date (imputed or not) is not missing and imputed therapy/procedure start date is after therapy/procedure end date (imputed or not), set the therapy/procedure start date to the therapy/procedure end date (imputed or not).

- Stop Date Imputation of Adverse Events, Prior/Concomitant Therapies and Medical/Surgical Procedures:
  - Completely missing and with outcome 'Not Recovered/Not Resolved' or 'Unknown' (Adverse Events): Leave it missing.
  - Completely missing and flagged as being ongoing (Prior/Concomitant Therapies and Medical/Surgical Procedures): Leave it missing.
  - Completely missing and with an outcome different from 'Not Recovered/Not Resolved' and 'Unknown' (Adverse Events): Impute to the date of end of participation.
  - Completely missing and not flagged as being ongoing (Prior/Concomitant Therapies and Medical/Surgical Procedures, Medical History Diseases): Impute to the date of end of participation.
  - Missing day and month: Impute to December 31st, unless year is the same as date of end of participation then impute to the date of end of participation.
  - Missing day: Impute to the last day of the month, unless year and month are the same as year and month of date of end of participation then impute to the date of end of participation.

## 4.2 Sample Size

The sample size calculation is planned to enroll 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.

Eighty-four (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.

## 4.3 Randomization, Stratification, and Blinding

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.

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;
- Group 3: Placebo Q4W.

Randomization will be stratified by clinical site.

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.

## 4.4 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 $\pi_{\text{Nemolizumab}}$ is the proportion of subjects in nemolizumab group with an improvement of WI NRS ≥ 4 from baseline at Week 12 and $\pi_{\text{Placebo}}$ is the proportion of subjects in placebo group with an improvement of WI NRS ≥ 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 Set 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 ≥ 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.

## 4.5 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 Set, and same pooling will be repeated for the mITT Set and the PP Set.

A small center is defined as a center which randomizes less than 15 subjects. First, centers will be sorted by geographic region, country, 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 country with the smallest center within the same country (if applicable) or within the same geographic region. If there is a further need to combine data (the size of the pooled centers includes less than 15

subjects), the next smallest center will be combined with the next largest of the small centers, until the criterion of a minimum of 15 subjects is met. The process will continue until all pooled centers have a minimum of 15 subjects within the same geographic region. Any remaining small centers of a country/geographic region will be pooled with the last pooled center within the same country/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 15 subjects in the ITT Set 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 Study Report.

### 4.6 Adjustments for Covariates


### 4.7 Handling of Missing Data

Missing data of the following dichotomous efficacy endpoints:

- Proportion of subjects with an improvement of WI NRS ≥ 4 from baseline at Week 12
- 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
- Proportion of subjects with an improvement of WI NRS ≥ 4 from baseline at Week 1

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 (i.e., weekly averages of WI NRS and SD NRS, as applicable).

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 (see Appendix C for details about Multiple Imputation and Tipping Point analysis).

Multiple imputation will be based on data collected up to Week 12. A further sensitivity analysis based on MI using all data collected up to Week 20 may be performed.

Similarly, sensitivity analyses will be performed by imputing missing data using a CR approach under MNAR assumption and as "Non-responder" for the key secondary efficacy endpoints based on WI NRS and SD NRS.

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 in the endpoints defined for Estimands 1 to 6 (see section 5). The values of the variable of interest 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.

Missing data of the following dichotomous efficacy endpoint:


will be imputed using MI under MAR assumption for the main analysis; changes and percent changes from baseline will be calculated from the imputed variables (i.e. questionnaires' scores and weekly averages of WI NRS and CCI 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. The values of the variable of interest 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 prior to conducting the MI. See Appendix C for details of the multiple imputation process.

### 4.8 Use of an Efficacy Subset of Subjects

The classification of the protocol deviations and the exclusion of subjects from the Per Protocol (PP) Set will be determined prior to breaking the study blind (see section 6.2).

The analysis on the PP Set will allow evaluating the impact of major protocol deviations on the estimation of the treatment effect.

### 4.9 Examination of Subgroups

Descriptive summaries and analyses 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 group (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)
- Subjects with or without prior or concomitant systemic anti-pruritus treatment

Prior or concomitant systemic anti-pruritus treatments will be identified based on a list provided by Galderma medical experts.

### 4.10 Analysis Visit Windows

All by-visit summaries and analyses will use the analysis visits. Scheduled, unscheduled and early termination visits will be windowed based on the following analysis visit windows which are based on study day. Details of the analysis visit window of efficacy and safety assessments/measurements collected during clinical visits are in the table below.

**Table 3 Analysis visit windows for efficacy and safety assessments or measurements collected during clinical visits**

| Analysis Visit | Target Study Day | CCI | Analysis Windows for ACT, PEF testing, Respiratory exam, Full physical examination, Vital signs, Blood samples for hematology and biochemistry, Urinalysis, Pregnancy test | Analysis Windows for 12-lead ECG, Pre-Dialysis and Post-Dialysis Weight | Analysis Windows for Height, Blood sample for virology and TB test, FSH | CCI |
|---|---|---|---|---|---|---|
| Baseline | 1 | | ≤ 1 | ≤ 1 | ≤ 1 | |
| Week 4 | 29 | | 2 to 42 | NA | NA | |
| Week 8 | 57 | | 43 to 70 | NA | NA | |
| Week 12 | 85 | | 71 to 113 | ≥ 2 | NA | |
| Week 20 | 141 | | ≥ 114 | NA | NA | |

If multiple assessments/measurements are taken within the same window, then all assessments will be listed, and the following rules will be applied for determining the values to be used for the summaries and analyses:

- Efficacy assessments: the assessment/measurement closer to the target study day will be used for the summaries and analyses. If there are multiple measurements with same difference from target day, the latest assessment will be used for the summaries and analyses.
- Safety assessments, excluding clinical laboratory tests: the assessment/measurement closer to the target study day will be used for the summaries and analyses. If there are multiple measurements with same difference from target day, the latest assessment will be used for the summaries and analyses.

- Clinical laboratory tests: the latest assessment will be used for the summaries and analyses.

CCI

Analysis visits of ePRO data will be defined depending on the data collection as below.

For the evening assessments of WI NRS, the daily data collected up to Week 20 will be classified into analysis visits considering the data during the 7 days immediately preceding the target study day of analysis visit. Similarly, for the morning assessment of WI NRS (if the WI NRS assessment in the evening is missed, the subjects are allowed to complete the assessment the following morning) and SD NRS, the 7 days data up to the target study day will be classified into analysis visit. Details of the analysis visit window of ePRO data are in the table below.

**Table 4 Analysis Visit Windows for calculation of Weekly Average of WI NRS and SD NRS**

| Analysis Visit | Target Study Day | Analysis Windows for WI NRS Evening Assessments | Analysis Windows for WI NRS Following Morning Assessments * | Analysis Windows for SD NRS Morning Assessments |
|---|---|---|---|---|
| Baseline [a] | 1 | -7 to -1 | -6 to 1 before dosing | -6 to 1 before dosing |
| Week 1 | 8 | 1 to 7 | 2 to 8 | 2 to 8 |
| Week 2 | 15 | 8 to 14 | 9 to 15 | 9 to 15 |
| Week 3 | 22 | 15 to 21 | 16 to 22 | 16 to 22 |
| Week 4 | 29 | 22 to 28 | 23 to 29 | 23 to 29 |
| Week 5 | 36 | 29 to 35 | 30 to 36 | 30 to 36 |
| Week 6 | 43 | 36 to 42 | 37 to 43 | 37 to 43 |
| Week 7 | 50 | 43 to 49 | 44 to 50 | 44 to 50 |
| Week 8 | 57 | 50 to 56 | 51 to 57 | 51 to 57 |
| Week 9 | 64 | 57 to 63 | 58 to 64 | 58 to 64 |
| Week 10 | 71 | 64 to 70 | 65 to 71 | 65 to 71 |
| Week 11 | 78 | 71 to 77 | 72 to 78 | 72 to 78 |
| Week 12 [b] | 85 | 78 to 84 | 79 to 85 | 79 to 85 |
| Week 13 | 92 | 85 to 91 | 86 to 92 | 86 to 92 |
| Week 14 | 99 | 92 to 98 | 93 to 99 | 93 to 99 |
| Week 15 | 106 | 99 to 105 | 100 to 106 | 100 to 106 |
| Week 16 | 113 | 106 to 112 | 107 to 113 | 107 to 113 |
| Week 17 | 120 | 113 to 119 | 114 to 120 | 114 to 120 |
| Week 18 | 127 | 120 to 126 | 121 to 127 | 121 to 127 |

| Analysis Visit | Target Study Day | Analysis Windows for WI NRS Evening Assessments | Analysis Windows for WI NRS Following Morning Assessments * | Analysis Windows for SD NRS Morning Assessments |
|---|---|---|---|---|
| Week 19 | 134 | 127 to 133 | 128 to 134 | 128 to 134 |
| Week 20 | 141 | 134 to 140 | 135 to 141 | 135 to 141 |

*: If the WI NRS assessment in the evening is missed, the subjects are allowed to complete the assessment the following morning.
a: 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.
b: 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.

## 4.11 Analysis Sets

A summary of the analysis sets including the number and percentage of subjects for the following categories: subjects in the ITT Set, subjects in the mITT Set, subjects in the PP Set, subjects in the Safety Set, and subjects in the CCI will be presented. All percentages will be based on the number of subjects randomized. A corresponding listing will be displayed.

### 4.11.1 Intent-to-treat (ITT) Set

The Intent-to-treat (ITT) Set consist of all randomized subjects. The ITT Set will be the primary set for all efficacy analysis. Subjects will be summarized and analyzed according to their randomized treatment group.

### 4.11.2 Modified Intent-to-Treat (mITT) Set

The Modified Intent-to-treat (mITT) Set 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. The mITT Set will be used for the supplementary analysis of the primary endpoint. Subjects will be summarized and analyzed according to their randomized treatment group.

### 4.11.3 Per Protocol (PP) Set

The Per Protocol (PP) Set 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. The PP Set will be used for the supplementary analysis of the primary endpoint. Subjects will be summarized and analyzed according to their randomized treatment group.

### 4.11.4 Safety Set

The Safety Set includes all randomized subjects who receive at least one dose of study drug. All safety data will be summarized based on the Safety Set. Subjects will be summarized according to their actual treatment group.


## 5 Estimands

The estimands for primary and key secondary endpoints provide precise descriptions of the treatment effect reflecting the clinical questions posed by the trial objectives. They summarize at a population level what the outcomes would be in the same patients under different treatment conditions being compared.

The intercurrent events are events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. It is necessary to address intercurrent events when describing the clinical question of interest in order to precisely define the treatment effect that is to be estimated.

The intercurrent events identified for this study and the estimands for primary and key secondary endpoints are defined in the following tables.

**Table 5 List of Intercurrent Events**

| Intercurrent Event | Strategy to Deal With Intercurrent Event Within Analysis | Assessment of Subjects |
|---|---|---|
| Rescue therapy | Composite strategy | Subjects will be considered as treatment failures. The values of the variable of |

| Intercurrent Event | Strategy to Deal With Intercurrent Event Within Analysis | Assessment of Subjects |
|---|---|---|
| | | interest collected after the use of rescue therapies will be set to the worst possible value and subject's binary response will be imputed as "Non-responder" |
| Treatment discontinuation due to lack of efficacy or AE/death related to study drug | Composite strategy | Subjects will be considered as treatment failures. The values of the variable of interest collected after 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" |
| Treatment discontinuation due to any other reason | Treatment-policy strategy | The values of the variable of interest are used regardless of the occurrence of treatment discontinuation |

**Table 6 Estimand of Primary Efficacy Endpoint**

| Primary Efficacy Estimand Description | Estimand Attributes |
|---|---|
| **Estimand 1:** 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>**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>**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 versus 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.

Summary of estimation is provided in section Appendix B.

Composite binary response variables are defined in a similar manner as in the primary efficacy estimand for the following key secondary estimands where all estimands attributes are as per Estimand 1 except for the variable definition as reported below.

**Table 7 Estimands for Key Secondary Efficacy Endpoints**

| Efficacy Estimand Description | Estimand Attributes |
|---|---|
| **Estimand 2:** 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 ≥ 3 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>**Responder** is defined as an improvement ≥ 3 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>**Non-responder** is defined as an improvement < 3 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 versus placebo in proportions of responders |
| **Estimand 3:** 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 4** without use of | **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>**Responder** is defined as an improvement ≥ 4 in WI NRS from baseline at Week 4 without use of rescue therapies and without treatment discontinuation due to lack of efficacy or AE/death related to study drug.<br>**Non-responder** is defined as an improvement < 4 in WI NRS from baseline at Week 4 or use of rescue therapies or treatment discontinuation due to lack of efficacy or AE/death related to study drug. |

| Efficacy Estimand Description | Estimand Attributes |
|---|---|
| rescue therapies and without 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 versus placebo in proportions of responders |
| **Estimand 4:** 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 **SD 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>**Responder** is defined as an improvement ≥ 4 in SD 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>**Non-responder** is defined as an improvement < 4 in SD 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 versus placebo in proportions of responders |
| **Estimand 5:** 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 ≥ 3 at Week 4** without use of | **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>**Responder** is defined as an improvement ≥ 3 in WI NRS from baseline at Week 4 without use of rescue therapies and without treatment discontinuation due to lack of efficacy or AE/death related to study drug.<br>**Non-responder** is defined as an improvement < 3 in WI NRS from baseline at Week 4 or use of rescue therapies or treatment discontinuation due to lack of efficacy or AE/death related to study drug. |

| Efficacy Estimand Description | Estimand Attributes |
|---|---|
| rescue therapies and without 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 versus placebo in proportions of responders |
| **Estimand 6:** 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 **SD NRS ≥ 4 at Week 4** 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>**Responder** is defined as an improvement ≥ 4 in SD NRS from baseline at Week 4 without use of rescue therapies and without treatment discontinuation due to lack of efficacy or AE/death related to study drug.<br>**Non-responder** is defined as an improvement < 4 in SD NRS from baseline at Week 4 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 versus 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.

# 6 Subject Disposition

## 6.1 Disposition

Subject disposition including the number and percentages of subjects for the following categories will be summarized in a table:

- screen failure/not assigned subjects
- screen failure/not assigned subjects due to COVID-19

- randomized subjects
- treated subjects
- subjects who completed the treatment
- subjects who terminated treatment early
- subjects who terminated treatment early due to COVID-19
- subjects who completed the treatment period
- subjects who terminated treatment period early
- subjects who terminated treatment period early due to COVID-19
- subjects who completed the study
- subjects who terminated study early
- subjects who terminated study early due to COVID-19

The reasons for screen failure, early treatment termination and early study termination will be summarized. Subjects affected by COVID-19 related study disruptions, COVID-19 related study disruptions impacting efficacy and COVID-19 related study disruptions impacting safety will be summarized. The percentages of screen failure and subjects randomized will be calculated based on number of subjects screened and other percentages will be based on the number of subjects in the ITT Set.

The reasons for study and treatment discontinuation will also be summarized in the aforementioned table.

Subject disposition data will be presented in a listing. A corresponding listing will be provided for screen failures, subjects with early treatment termination and for subjects with early study termination. Subjects affected by COVID-19 related study disruptions will be presented in a listing. A summary of inclusion/exclusion criteria not met will be presented for all screened subjects. Details of inclusion/exclusion criteria not met will be provided in a listing for the screened set.

## 6.2 Protocol Deviations

All deviations will be identified, evaluated, and closed prior to database lock. Deviations from the protocol will be assessed as “Major” (or equivalently “Significant”) and “Minor” (or equivalently “Not Significant”) in cooperation with the sponsor. A case-by-case decision regarding exclusions of subjects from the PP Set will be made in a blind data review meeting which will take place prior to database lock and study unblinding.

All major protocol deviations will be summarized by category and by treatment in a table for the ITT Set. The major deviations which lead to exclusion from the PP Set will be summarized in a separate table. All protocol deviations (major and minor) will be listed with major protocol deviations which would lead to exclusion from the PP Set being flagged. All major COVID-19 related protocol deviations will be summarized by

category and all COVID-19 related protocol deviations will be flagged in the corresponding listing.

# 7 Demographics and Baseline Characteristics

## 7.1 Demographics

The demographics will be summarized by treatment group in the ITT Set, Safety Set and CCI The following variables will be included:

- Age (Years)
- Age group (18 to 45; >45 to 65; >65 to 80; >80)
- Sex (Male, Female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown or Not reported)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, Multiple or Not reported)
- Race group (White, Black, Asian, Other)
- Region (US; Excl-US)
- Pre-dialysis weight (kg), Height (cm) at baseline

Status of habitual tobacco use (Never, Former, Current), status of habitual alcohol use (Never, Former, Current), and history of tuberculosis in the past will also be summarized by treatment in the same table as Demographics.

Subject demographics will be presented in a listing.

## 7.2 Baseline Disease Characteristics

The following baseline disease characteristics will be summarized by treatment group in the ITT Set, Safety Set and CCI :

- Duration of end-stage kidney disease (ESKD) (months)
- Duration of hemodialysis (months)
- Duration of hemodialysis (≤1 year; >1 year to 3 years; >3 years)
- Hemodialysis access location (AVF/AVG/Catheter)
- Kt/V result
- Duration of pruritus (months)
- Duration of pruritus (≤3 months; >3 to 12 months; >12 months)
- With or without prior or concomitant systemic anti-pruritus treatment

- Cause of chronic kidney disease (CKD) (Hypertension, Diabetes, Glomerulonephritis, Cystic disease, Urologic, Congenital/hereditary, Other)
- Investigator's global assessment (IGA) of CKD-aP skin status
- Weekly Average of WI NRS score
- Severity of pruritus/WI NRS group (5 to 7; >7 to 10)
- Weekly Average of SD NRS score
- CCI [redacted]
- [redacted]
- [redacted]
- [redacted]

Baseline disease characteristics will be also presented in a listing.

### 7.3 Alcohol and Tobacco Usage

Smoking status and alcohol consumption status will be summarized together with demographics characteristics (see section 7.1).

### 7.4 Childbearing Potential Status, Methods of Contraception and Reproductive Status

Childbearing Potential Status, Methods of Contraception and Reproductive Status will be listed and summarized.

### 7.5 Medical History

The number and percentage of subjects with any medical history will be summarized by treatment and for each body system by system organ class (SOC) and preferred term (PT). SOC will be sorted in decreasing order of frequency based on the total number of subjects of all treatment groups and within each SOC, PT will be presented in decreasing order of frequency. Percentages will be calculated based on number of subjects in the ITT Set.

Subject medical history data including specific details will be presented in a listing. Body systems will be included as recorded on the CRF.

Medical Dictionary for Regulatory Authorities (MedDRA) dictionary Version 24.1 or higher will be used for reporting and will be described in the relevant table and listing footnotes.

# 8 Treatments and Medications

## 8.1 Prior and Concomitant Medications

All medications used within 3 months prior to the date of screening through to the end of study will be collected on the CRF. All medications will be coded according to the World Health Organization drug dictionary Global B3 September 2021 or higher. The medication names will be coded according to the Anatomical Therapeutic Chemical (ATC) class level 4, and preferred terms provided in the dictionary.

A prior medication is defined as any medication that is taken within 3 months prior to the date of the first treatment injection, that is stopped prior to the date of the first treatment injection. A concomitant medication is defined as any existing therapy ongoing at the time of the first treatment injection, or any changes to existing therapies during the course of the study, or any new therapies the subject received since the date of the first treatment injection.

For missing start or end dates, the rules stated in section 4.1 will be followed. Though note that, for treated subjects, if the start date is completely missing and end date is not prior to the first treatment injection, then the medication will be classified as concomitant. If the end date is missing, then the medication will be classified as ongoing. Medications for which the start and end dates are missing will be classified as concomitant. All medications of not treated subjects will be classified as prior.

Prior medications will be summarized by providing the number and percentage of subjects by ATC class level 2, ATC class level 4 and preferred term overall and for each treatment. ATC class level 2 and ATC class level 4 will be sorted in decreasing order of frequency based on the total number of subjects who take each medication in the total column. In the same way, preferred terms within each drug class will be presented in decreasing order of frequency based on the total of all treatment groups. In addition, the total number of prior medications and the number and percentage of subjects receiving at least one prior medication will also be presented in this table. If a subject has multiple medications for a given preferred term the subject will only be counted once. A similar table will be presented for concomitant medications.

All summaries will be performed using the ITT Set. Prior and concomitant medications will be presented in a listing for the ITT Set.

## 8.2 Prior and Concomitant Medical and Surgical Procedures

All relevant medical and surgical procedures done within 3 months prior to the date of screening through to the end of study will be collected on the CRF. Medical and surgical procedures will be coded according to MedDRA version 24.1 or higher.

For analysis purpose, a prior medical or surgical procedure is defined as any medical or surgical procedure that is done within 3 months prior to the date of first treatment

injection. A concomitant medical or surgical procedure is defined as any medical or surgical procedure started or changed since the first treatment injection.

For missing start or end dates, the rules stated in section 4.1 will be followed. Though note that, for treated subjects, if the start date is completely missing and end date is not prior to the first treatment injection, then the medical or surgical procedure will be classified as concomitant. If the end date is missing, then the medical or surgical procedure will be classified as ongoing. Medical or surgical procedures for which the start and end dates are missing will be classified as concomitant. All medical/surgical procedures of not treated subjects will be classified as prior.

Prior medical or surgical procedures will be summarized by providing the number and percentage of subjects by system organ class (SOC) and preferred term (PT) overall and for each treatment group. In addition, the total number of prior medical or surgical procedures and the number and percentage of subjects undergoing at least one prior medical or surgical procedures will also be presented in this table. A similar table will be presented for concomitant medical and surgical procedures.

All summaries will be performed using the ITT Set. Prior and concomitant medical or surgical procedures will be presented in a listing for the ITT Set.

### 8.3 Rescue Therapies

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.

For the purpose of efficacy analyses (including sensitivity and supplementary analyses), that are not based on Observed Case (OC), subjects receiving any rescue therapies will be considered as treatment failures. Efficacy data collected after the use of rescue therapies will be set to the worst possible value for continuous variables and subject's binary response will be imputed as "Non-responder" prior to conducting the MI and Tipping Point analysis.

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.

Rescue medications will be summarized for the ITT Set, by rescue therapy type (topical, systemic) and, within each rescue type, by ATC class level 2, ATC class level 4 and preferred term overall and for each therapy. ATC class level 2 and ATC class level 4 will be sorted in decreasing order of frequency based on the total number of subjects of all treatment groups and within each drug class, preferred terms will be presented in decreasing order of frequency.

Rescue procedures will be summarized for the ITT Set, by rescue therapy type (phototherapy) and by SOC and PT overall and for each therapy. SOC will be sorted in decreasing order of frequency based on the total number of subjects of all treatment groups and within each SOC, PT will be presented in decreasing order of frequency.

Rescue therapies data including specific details will be presented in a listing.

The time to first rescue therapy will be analyzed using Kaplan-Meier survival functions that will be compared between treatment groups by using the log-rank test. The number and proportion of events and censoring, point estimates of the median, Q1 and Q3 with the corresponding 97.5% CI will be presented and Kaplan-Meier curves will also be provided. Subjects who do not use any rescue therapy during the study will be censored and date of end of participation will be used as censoring date.

## 8.4 Study Treatments

### 8.4.1 Extent of Exposure

The duration of treatment (in days), the duration of treatment period (in days), the duration of study (in days), the total dose administered (in mg), the number of injections per subject, the number of missed injections per subject, the number of missed injections per subject due to COVID-19, the proportion of subjects who missed at least one injection, the proportion of subjects who missed at least one injection due to COVID-19 will be summarized by treatment group for the Safety Set.

The duration of treatment (in days) is defined as the number of days from the date of first treatment injection through the date of the last treatment injection, inclusive, adding 1 day (i.e. date of last treatment injection – date of first treatment injection + 1).

The duration of treatment period (in days) is defined as the number of days from the date of first treatment injection through the date of the end of treatment period as collected in the CRF, inclusive, adding 1 day (i.e. date of end of treatment period – date of first treatment injection + 1).

The duration of study (in days) is defined as the number of days from the date of signature of first informed consent (across all screening occurrences) through the date of the end of participation (across all screening occurrences), inclusive, adding 1 day (i.e. date of end of participation – date of signature of first informed consent + 1).

### 8.4.2 Treatment Compliance and Modifications

Dosage modifications of the study drug will not be permitted during the clinical study. Any inadvertent dose modifications should be reported to the sponsor/Contract Research Organization (CRO).

Treatment compliance will be assessed through the treatment record and drug dispensation logs. Dosing frequency is scheduled for every 4 weeks, based on the baseline/Day 1 visit date. If a study visit occurs outside the visit window, 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 overall compliance in percent will be calculated as the ratio of the total number of actual injections during the treatment period divided by the total number of expected injections during the treatment period multiplied by 100.

Dose compliance will be documented in the CRF, with the total volume (mL) of the study drug that was properly administered. Total volume injected in mL is converted into total dose administered in mg following the correspondence below:

| **Volume injected (mL)** | **Dose administered (mg)** |
|---|---|
| 0.49 mL | 30 mg dual-chamber, single-use syringe (DCS) |

Injected volume is assumed to be proportional to the dose administered.

Subjects are considered as compliant when their compliance is $\geq 80\%$ and $\leq 120\%$.

The overall compliance until Week 8, the compliance by visit and the number of injections received and missed per subject will be presented in a table by treatment for the Safety Set. The number of missing injections will be based on the full treatment period (six injections) and will not be adjusted for subjects that terminate treatment early (i.e. a subject that received 2 injections at baseline and then discontinued before Week 4 will be counted as missing 4 injections). A corresponding listing will be provided for exposure and compliance. Details of study drug administration at each visit will also be listed.

## 9 Efficacy Analysis

Efficacy assessments will be conducted for all subjects at the screening visit (upon signing of the ICF) and at every subsequent visit as described in schedule of assessments in Appendix A. All efficacy assessments will be listed in by-subject listing.

All efficacy analyses will be performed in the ITT Set. The primary efficacy analysis will be repeated in the mITT Set and PP Set as supportive evidence and to assess robustness of efficacy findings.

Subjects will be summarized and analyzed according to their randomized treatment group.

Summaries based on observed case (OC) will be provided for all primary, secondary, and exploratory efficacy endpoints without imputation of any missing data. For the OC summaries, if any rescue therapy 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 $\geq 4$ and WI NRS $\geq 3$, 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.

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.

## 9.1 Analysis of Primary Efficacy Endpoint

An overview of the analyses for primary efficacy is given in Appendix B.

### 9.1.1 Primary Analysis of the Primary Efficacy Endpoint (Estimand 1)

A summary will be provided for the primary efficacy endpoint without any imputation of missing data. Note that subjects who took rescue therapies at any point up to and including Week 12 are considered as treatment failures in this endpoint.

In the main statistical analysis described below, missing WI NRS weekly average values will be imputed for the ITT set using multiple imputations (MI) under missing at random (MAR) assumption. Worst values are assumed after use of rescue therapy or treatment discontinuation due to lack of efficacy or AE/death related to study drug prior to imputation. Dichotomous endpoints will be calculated from the underlying imputed variable. See Appendix C for details about Multiple Imputation.

The proportion of subjects with an improvement at Week 12 of WI NRS $\geq 4$ from baseline without use of rescue therapies and without treatment discontinuation due to lack of efficacy or AE/death related to study drug will be analyzed in the ITT Set for each multiply imputed dataset, using the Cochran-Mantel-Haenszel (CMH) test stratified by analysis center; strata-adjusted difference in proportions between treatment groups (Nemolizumab – Placebo) and the 97.5% confidence interval (CI) of the difference will be based on the large sample approximation method for binary data using Mantel-Haenszel strata weights[8] and the Sato variance estimator[9]. This analysis will be performed for both dosing schedules compared to placebo using the "Commonriskdiff" and "CL=MH" options in SAS PROC FREQ. Proportions and strata-adjusted difference in proportions will be pooled using Rubin's method. Results from the CMH analysis will be combined using the Wilson-Hilferty transformation as described in the Bohdana Ratitch, et al. paper[10] to produce a pooled CMH test p-value.

### 9.1.2 Sensitivity and Supplementary Analyses of the Primary Efficacy Endpoint (Estimand 1)

The following sensitivity analyses will be conducted for the robustness of the primary analysis of the primary efficacy endpoint:

- Sensitivity Analysis 1: MI using a copy reference (CR) approach under MNAR assumption (dichotomous endpoints will be calculated from the underlying imputed variable);
- Sensitivity Analysis 2: "Non-responder" analysis;
- Sensitivity Analysis 3: Tipping Point analysis;
- Sensitivity Analysis 4: the primary analysis at Week 12 as per section 9.1.1 will be repeated in the ITT Set using weekly averages of WI NRS obtained by averaging at least 3 daily scores over 7-day periods. No period extension at baseline and week 12 applies for these weekly averages. MI under MAR will be repeated using the weekly averages obtained by averaging at least 3 daily scores over 7-day periods;
- Sensitivity Analysis 5: the primary analysis at Week 12 as per section 9.1.1 will be repeated in the ITT Set using weekly averages of WI NRS obtained by averaging at least 2 daily scores over 7-day periods. No period extension at baseline and week 12 applies for these weekly averages. MI under MAR will be repeated using the weekly averages obtained by averaging at least 2 daily scores over 7-day periods;
- Sensitivity Analysis 6: the primary analysis at Week 12 as per section 9.1.1 will be repeated in the ITT Set using weekly averages of WI NRS obtained by averaging at

least 1 daily score over 7-day periods. No period extension at baseline and week 12 applies for these weekly averages. MI under MAR will be repeated using the weekly averages obtained by averaging at least 1 daily scores over 7-day periods.

See Appendix C for details about Multiple Imputation and Tipping Point analysis.

The primary analysis imputes all missing data using MI under MAR assumption. The sensitivity analyses and tipping point will investigate the robustness of results to assumptions made for missing data.

In all these sensitivity analyses, subjects who took rescue therapies or discontinued treatment due to lack of efficacy or AE/death related to study drug are considered as treatment failure as defined for this estimand (i.e., the values of the variable of interest collected after the intake 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").

In addition, the following supplementary analyses will be conducted:

- Supplementary Analysis 1: the primary analysis at Week 12 as per section 9.1.1 will be repeated in the mITT Set; subjects who took rescue therapies or discontinued treatment due to lack of efficacy or AE/death related to study drug are considered as treatment failure as defined for this estimand; MI will not be repeated on the mITT Set and missing values will be imputed using the values of MI under MAR assumption on the ITT Set (dichotomous endpoints will be calculated from the underlying imputed variable);
- Supplementary Analysis 2: the primary analysis at Week 12 as per section 9.1.1 will be repeated in the PP Set; subjects who took rescue therapies are considered as treatment failure as defined for this estimand; subjects who discontinued treatment for any reason will not be included in the PP set; subjects with missing data at Baseline or Week 12 will not be included in the PP set and thus no imputation of missing data is needed;
- Supplementary Analysis 3 (Treatment Policy Adaptation): the primary analysis at Week 12 as per section 9.1.1 will be repeated in the ITT Set using observed cases only, without any imputation of missing data and without considering either rescue therapies or treatment discontinuation.

### 9.1.3 Impact of COVID-19 on the Primary Efficacy Endpoint (Estimand 1)

To assess the impact of COVID-19 related study disruptions (e.g. treatment discontinuation, missing assessments, etc.), the primary efficacy endpoint will also be analyzed on the ITT Set excluding subjects affected by COVID-19 related study disruptions. Missing values will be imputed using MI under MAR assumption (dichotomous endpoints will be calculated from the underlying imputed variable). Subjects affected by COVID-19 related study disruptions will not be included in the MI.

### 9.1.4 Subgroup Analysis for Primary Efficacy Endpoint (Estimand 1)

A summary based on the primary efficacy endpoint (without imputation of missing data) will be repeated in the subgroups defined in section 4.9.

The primary analysis for the primary efficacy endpoint will be repeated in the subgroups defined in section 4.9. The strata-adjusted difference in proportions of responders with 97.5% CI, pooled CMH test p-value will be derived as described in section 9.1.1.

MI will not be repeated on each subgroup and missing values will be imputed using the values of MI under MAR assumption on the ITT Set (dichotomous endpoints will be calculated from the underlying imputed variable).

A Forest plot with the result of primary analysis and all subgroup analysis of primary efficacy endpoint will be presented.

## 9.2 Analysis of the Key Secondary Efficacy Endpoints

An overview of the analyses for key secondary efficacy is given in Appendix B.

### 9.2.1 Main Analysis of Key Secondary Efficacy Endpoints CCI

A summary will be provided for the key secondary efficacy endpoints without any imputation of missing data.

Analysis will be as for the main estimation of Estimand 1 with missing values imputed using MI under MAR assumption. Worst values are assumed after use of rescue therapy or treatment discontinuation due to lack of efficacy or AE/death related to study drug prior to imputation. Dichotomous endpoints will be calculated from the underlying imputed variable. The strata-adjusted difference in proportions of responders with 97.5% CI, pooled CMH test p-value will be derived as described in section 9.1.1.

The same MI output dataset as used for the primary endpoint will be used to derive the other dichotomous endpoints from WI NRS (Estimand 2, 3, and 5). CCI

### 9.2.2 Sensitivity Analysis of Key Secondary Efficacy Endpoints CCI

The following sensitivity analyses will be conducted for the robustness of the main analysis of the key secondary efficacy endpoints:

- Sensitivity Analysis 1: MI using a copy reference (CR) approach under MNAR assumption (dichotomous endpoints will be calculated from the underlying imputed variable); the same MI output dataset for WI NRS using a copy reference (CR) approach under MNAR assumption will be used to derive the other dichotomous

endpoints CCI [redacted]. Similarly, the same CR output dataset for SD NRS will feed into all dichotomous endpoints derived from that CCI [redacted]

- Sensitivity Analysis 2: "Non-responder" analysis.

See Appendix C for details about Multiple Imputation.

### 9.2.3 Impact of COVID-19 on the Key Secondary Efficacy Endpoints CCI [redacted]

To assess the impact of COVID-19 related study disruptions (e.g. treatment discontinuation, missing assessments, etc.), the key secondary efficacy endpoints will also be analyzed on the ITT Set excluding subjects affected by COVID-19 related study disruptions. Missing values will be imputed using MI under MAR assumption (dichotomous endpoints will be calculated from the underlying imputed variable). Subjects affected by COVID-19 related study disruptions will not be included in the MI.

### 9.2.4 Subgroup Analysis of the Key Secondary Efficacy Endpoints CCI [redacted]

Summaries for the key secondary endpoints (without imputation of missing data) will be repeated in the subgroups defined in section 4.9.

The main analysis for the key secondary efficacy endpoint will be repeated in the subgroups defined in section 4.9. The strata-adjusted difference in proportions of responders with 97.5% CI, pooled CMH test p-value will be derived as described in section 9.1.1.

MI will not be repeated on each subgroup and missing values will be imputed using the values of MI under MAR assumption on the ITT Set (dichotomous endpoints will be calculated from the underlying imputed variable).

Forest plots with the result of primary analysis and all subgroup analysis of the key secondary efficacy endpoints will be presented.

C [redacted]
CI

[redacted]

CCI [redacted]

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, and all scores after the intake of rescue therapies or treatment discontinuation due to lack of efficacy or AE/death related to study drug will be assigned the worst possible value. 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.

These continuous endpoints will be analyzed using an ANCOVA with treatment group and analysis center as factors and baseline score as covariate. Missing data will be imputed using MI under MAR assumption (see Appendix C for details about Multiple Imputation).

CCI [redacted]

Time to onset of effect on pruritus from baseline (defined as the day when the weekly average of WI NRS shows a change from baseline ≥ 4) will be analyzed using Kaplan-Meier survival functions that will be compared between treatment groups by using the log-rank test. The number and proportion of events and censoring, point estimates of the median, Q1 and Q3 with the corresponding 97.5% CI will be presented and Kaplan-Meier curves will also be provided.

The following censoring rules will be applied:

- Subjects who took rescue therapy before achieving onset of effect on pruritus from baseline will be censored and the date of decision to put subject under rescue therapies will be used as censoring date.
- Subjects who discontinued treatment due to lack of efficacy or AE/death related to study drug before achieving onset of effect on pruritus from baseline will be censored and the date of treatment discontinuation will be used as censoring date.
- Subjects who discontinued treatment for any other reason, did not take rescue therapies and did not achieve onset of effect on pruritus from baseline during the study will be censored and date of end of participation will be used as censoring date.
- Subjects who did not take rescue therapies, did not discontinue treatment and did not achieve onset of effect on pruritus from baseline during the study will be censored and date of end of participation will be used as censoring date.

In case of occurrence of both intake of rescue therapy and treatment discontinuation due to lack of efficacy or AE/death related to study drug, the earlier date will be used for censoring purposes.

The following rules will be applied:

| 1st Intercurrent Event | 2nd Intercurrent Event | Censoring Rule |
|---|---|---|
| Intake of rescue therapies | Treatment discontinuation due to lack of efficacy or AE/death related to study drug | Subjects will be censored and the date of decision to put subject under rescue therapies will be used as censoring date |
| Intake of rescue therapies | Treatment discontinuation for any other reason | Subjects will be censored and the date of decision to put subject under rescue therapies will be used as censoring date |
| Treatment discontinuation due to lack of efficacy or AE/death related to study drug | Intake of rescue therapies | Subjects will be censored and the date of treatment discontinuation will be used as censoring date |
| Treatment discontinuation for any other reason | Intake of rescue therapies | Subjects will be censored and the date of decision to put subject under rescue therapies will be used as censoring date |

In order to investigate the impact of rescue medication intake and treatment discontinuation, cumulative incidence functions for competing-risks data will be presented and compared between treatment groups by using Gray's test.

Proportion of subjects with an improvement WI NRS $\geq 4$ from baseline at Week 1 will be analyzed in the ITT Set, using the Cochran-Mantel-Haenszel (CMH) test stratified by analysis center. The strata-adjusted difference in proportions of responders with 97.5% CI, pooled CMH test p-value will be derived as described in section 9.1.1. Subjects who took rescue therapies will be considered as treatment failures, efficacy data collected after the use of rescue therapies will be set to the worst possible value and subject's binary response will be imputed as "Non-responder". Treatment discontinuation due to lack of efficacy, AE/death related to study drug or any other reason is not a factor at this early timepoint since the second administration is not due until Week 4. Missing subject's binary response will be imputed using MI under MAR assumption (dichotomous endpoints will be calculated from the underlying imputed variable). See Appendix C for details about Multiple Imputation.

CCI

CCI

CCI

# 11 Immunogenicity Analyses

The immunogenicity endpoint is nemolizumab immunogenicity in adult hemodialysis subjects with moderate to severe pruritus.

Anti-drug antibodies assessments using a validated electro-chemiluminescence immunoassay (ECLIA) (screening, confirmatory, titer, Nab) and incidence of positive ADA results (absolute occurrence, percent of subject, and treatment-related ADA) will be summarized by visit and by treatment group. A treatment-related ADA is defined when at baseline, the screening or confirmatory ADA result is negative, and the post-baseline confirmatory ADA result is positive. A corresponding listing will be provided.

Summaries will be based on the Safety Set. Subjects will be summarized according to their actual treatment group.

# 12 Safety Analysis

Safety assessments/measurements will be conducted for all subjects at the screening visit (upon signing of the ICF) and at every subsequent visit as described in schedule of assessments in Appendix A. All safety assessments/measurements will be listed in by-subject listing.

Subjects will be summarized according to their actual treatment group.

TEAEs will be summarized descriptively overall and by treatment and other safety information will be summarized descriptively by treatment.

All safety analyses will be based on the Safety Set.

## 12.1 Adverse Events

A TEAE is defined as any AE with a start date/time on or after the date/time of the first injection (Baseline/Day 1) through the last study visit (follow-up visit), whether or not it is considered causally related to the study drug.

Treatment Emergent/Non-Treatment Emergent:

- Complete Missing Dates:
  - If both the start date and the end date are totally missing, then the AE is assumed to be treatment emergent.
- Partial Missing Dates:
  - If the start date is missing and the non-missing end date is prior to first injection (Baseline/Day 1) date, then the AE is not considered treatment emergent.

  - If the start date is missing and the partial end date can be assumed to be prior to first injection (Baseline/Day 1) date (month and/or year before infusion date), then the AE is not considered treatment emergent.
  - If the start date is missing and the end date is after the first injection (Baseline/Day 1) date or the partial end date cannot be assumed to be prior to the first injection (Baseline/Day 1) date (based on month and/or year), then the AE is assumed to be treatment emergent.
  - If the start date is partial and can be assumed to be prior to the first injection (Baseline/Day 1) date (based on the month and/or year) and the non-missing end date is prior to the injection date, then the AE is not considered treatment emergent.
  - If the partial start date cannot be assumed to be prior to the first injection (Baseline/Day 1) date, then the AE is assumed to be treatment emergent.
- Complete Dates:
  - If the start date is prior to the first injection (Baseline/Day 1) date, then the AE is not considered treatment emergent.
  - If the start date is equal to the first injection (Baseline/Day 1) date and the start time is missing, then the AE is considered treatment emergent.
  - If the start date is equal to the first injection (Baseline/Day 1) date and the start time is prior to the first injection time, then the AE is not considered treatment emergent.
  - If the start date is equal to the first injection (Baseline/Day 1) date and the start time is on or after the first injection time, then the AE is considered treatment emergent.
  - If the start date is after the first injection (Baseline/Day 1) date, then the AE is considered treatment emergent.

For the imputation of missing start or end dates, the rules stated in Section 4.1 will be followed.

All AEs will be coded according to MedDRA 24.1 or higher.

### 12.1.1 Incidence of Adverse Events

An overall summary table with count and percentage of subjects with TEAEs and count of events will include:

- TEAEs
- TEAEs by greatest severity
- TEAEs by closest relationship to study drug
- TEAEs by closest relationship to study procedures

- TEAEs leading to treatment discontinuation
- TEAEs leading to study discontinuation
- TEAEs of special interest
- TEAEs of special interest by greatest severity
- TEAEs due to COVID-19
- Asthma-related TEAEs adjudicated by IAC
- Asthma-related TEAEs adjudicated by IAC by greatest severity
- Asthma-related TEAEs adjudicated by IAC by closest relationship to study drug
- Serious TEAEs (both fatal and non-fatal)
- Non-fatal serious TEAEs
- TEAEs leading to death
- Serious TEAEs by closest relationship to study drug
- Serious TEAEs by closest relationship to study procedures
- Serious TEAEs leading to treatment discontinuation
- Serious TEAEs leading to study discontinuation

The incidence of AEs will be summarized in tables with count and percentage of subjects with AEs and count of events by system organ class (SOC) and preferred term (PT). Unless otherwise specified, at each level of SOC or preferred term, a subject with multiple events will only be counted once per SOC or preferred term. AEs will be displayed by treatment for the Safety Set.

The following categories of AE will be summarized by SOC and PT:

- TEAEs
- TEAEs by greatest severity
- TEAEs related to study drug
- TEAEs related to study procedures
- TEAEs leading to treatment discontinuation
- TEAEs leading to study discontinuation
- TEAEs of special interest
- TEAEs of special interest by greatest severity
- TEAEs due to COVID-19
- Asthma-related TEAEs adjudicated by IAC

- Asthma-related TEAEs related to study drug adjudicated by IAC
- Asthma-related TEAEs reported by Investigator with adjudication outcome by IAC
- Asthma-related TEAEs related to study drug reported by Investigator with adjudication outcome by IAC
- Asthma-related TEAEs adjudicated by IAC by greatest severity
- Asthma-related TEAEs related to study drug adjudicated by IAC by greatest severity
- Serious TEAEs (both fatal and non-fatal)
- Non-fatal serious TEAEs
- TEAEs leading to death
- Serious TEAEs related to study drug
- Serious TEAEs related to study procedures
- Serious TEAEs leading to treatment discontinuation
- Serious TEAEs leading to study discontinuation

At each level of SOC or PT, if a subject experiences more than 1 occurrence of the same AE, the occurrence with the greatest severity, the closest relationship with the study drug and the closest relationship with the study procedures will be used in the corresponding summary tables. All AEs will be presented in tables in descending order from the SOC with the highest total incidence (across all treatment groups) to the SOC with the lowest total incidence. Within each SOC, AEs will be sorted in descending order of PT based on the total of all treatment groups.

TEAEs, TEAEs leading to death, serious TEAEs, non-fatal serious TEAEs, severe TEAEs, TEAEs of special interest, TEAEs leading to treatment discontinuation, TEAEs leading to study discontinuation and TEAEs due to COVID-19 will be listed separately.

Pre-treatment AEs (PTAEs) will be listed separately.

### 12.1.2 Relationship of Adverse Events to Study Drug and/or Study Procedures

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 procedures (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 relationship assessment for an AE is to be completed using the following definitions 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 procedures (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 procedures and the AE.

If the relationship to study drug information is missing, then the corresponding AE is assumed to be related with reasonable possibility to the study drug. If a subject experiences more than 1 occurrence of the same AE, the occurrence with the closest relationship to study drug will be used in summary tables.

### 12.1.3 Severity of Adverse Event

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.

If the severity is missing, then the AE is assumed to be severe. If a subject experiences more than 1 occurrence of the same AE, the occurrence with the greatest severity will be used in summary tables.

## 12.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed according to the schedule of assessments in Appendix A.

The safety laboratory assessments include the following parameters:

Hematology:

- Hemoglobin (g/L)
- Hematocrit (L/L)
- White blood cell count (with differential including eosinophils) (10^9/L)
- Red blood cell count (10^12/L)
- Platelet count (10^9/L)
- Erythrocytes Mean Corpuscular Volume (fL)

Urinalysis:

- pH
- Bacteria
- Glucose
- Casts
- Crystals
- Epithelial Cells
- Erythrocytes
- Ketones
- Occult Blood
- Protein
- Leukocytes
- Leukocytes Esterase
- Mucous Threads
- Nitrites
- Bilirubin
- Urobilinogen
- Specific gravity
- Yeast Cells

Serum chemistry:

- Creatinine (umol/L)
- Aspartate Amino Transferase (AST) (U/L)
- Alanine Amino Transferase (ALT) (U/L)
- Gamma glutamyltransferase (U/L)
- Alkaline Phosphatase (U/L)
- Lactate Dehydrogenase (U/L)
- Total Bilirubin (umol/L)
- Direct Bilirubin (umol/L)
- Albumin (g/L)
- Total Protein (g/L)
- Urate (mmol/L)
- Sodium (mmol/L)
- Potassium (mmol/L)
- Calcium (mmol/L)
- Chloride (mmol/L)
- Glucose (mmol/L)
- Urea Nitrogen (mmol/L)
- Total Cholesterol (mmol/L)
- Triglycerides (mmol/L)
- Low-density lipoprotein (LDL) Cholesterol (mmol/L)

- High-density lipoprotein (HDL) Cholesterol (mmol/L)
- Creatine Kinase (CK) (U/L)

Summary statistics of the observed values and change from baseline for all laboratory parameters will be provided by visits and treatment groups.

For quantitative parameter, results will be presented for each parameter by treatment in a shift table, using above, below, within normal range, between baseline and visits at Week 4, Week 8, Week 12 and Week 20. Results will be presented for each parameter by treatment group in a shift table, using normal, abnormal not clinically significant and abnormal clinically significant categorization based on the current version of Central Lab Manual and Alert Report Specification, between baseline and visits at Week 4, Week 8, Week 12 and Week 20.

Last post-baseline and worst post-baseline results (derived using both scheduled and unscheduled measurements) will also be included in summaries and shift tables. For each parameter, worst post-baseline value will be defined as the highest or lowest value relative to the reference range.

All post-baseline (both scheduled and unscheduled) measurements will be used for Potentially Clinically Significant Values (PCSV) determination (criteria are available in Appendix D).

Number and proportions of subjects with Potentially Clinically Significant Values will be summarized by visits and treatment groups.

All laboratory data will also be presented in listings for each parameter with abnormal values, clinically significant values and potentially clinically significant values (PCSV) flagged. Moreover, abnormal values and potentially clinically significant values will be presented in separate listings.

For statistical or graphical summaries of the laboratory tests, values above or below the limit of detection will be substituted with the lower limit of detection minus 1%, or the upper limit of detection plus 1% (e.g. ‘<3’ is substituted by 2.97). In the data listings, the values are shown including the ‘<’ or ‘>’ sign.

Boxplots presenting the distribution of AST, ALT, ALP, Total Bilirubin and CPK over the visits will be displayed by treatment. An additional boxplot will be presented on the figure considering the maximum post-baseline value. Additionally, individual plots presenting the distribution of AST, ALT, ALP, Total Bilirubin and CPK, for subjects with abnormal values, over the visits will be displayed by treatment. An evaluation of drug-induced serious hepatotoxicity (eDISH) plot will be displayed in addition.

### 12.3 Pregnancy Testing

Pregnancy tests will be performed on female subjects of child-bearing potential. Serum pregnancy tests will be performed at all visits according to the schedule of assessments summarized in Appendix A. Pregnancy test results will be presented in a listing.

### 12.4 Virology

Virology including Hepatitis B Surface Antigen (HBsAg), Hepatitis B Core Antibody (HBcAb), Hepatitis C Virus (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. Polymerase Chain Reaction (PCR) test). These data will be presented in a listing.

### 12.5 Tuberculosis (TB) 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. The data will be presented in a listing.

### 12.6 Vital Sign Measurements

Vital signs including pulse rate (beats/min), systolic and diastolic blood pressure (mmHg), body temperature (C), pre-dialysis weight (kg) and post-dialysis weight (kg) will be assessed over time during the study according to the schedule of assessments in Appendix A. Descriptive statistics of observed values and change from baseline will be summarized by visit and by treatment.

Results from overall interpretation of vital signs assessments will be summarized by visit and treatment group and will be presented by treatment group in a shift table, using normal, abnormal not clinically significant and abnormal clinically significant categorization, between baseline and visits at Week 4, Week 8, Week 12 and Week 20.

All post-baseline (both scheduled and unscheduled) measurements will be used for Potentially Clinically Significant Values (PCSV) determination (criteria are available in Appendix E).

Number and proportions of subjects with Potentially Clinically Significant Values will be summarized by visits and treatment groups.

A corresponding listing with potentially clinically significant values (PCSV) flagged will also be provided.

### 12.7 Physical Examination

A complete physical examination including assessments of the head, ears, eyes, nose, throat, neck (including thyroid), skin/integumentary system, cardiovascular system, respiratory system, gastrointestinal system, musculoskeletal system, lymph nodes, nervous system, and extremities will be performed at screening, baseline/Day 1, and

subsequent scheduled visits. All physical examinations will be summarized in a table by visit and by treatment group. Results of physical examinations are categorized into normal, abnormal, and not done. If abnormal, results will be categorized with or without clinical significance. A corresponding listing will be provided with abnormal values flagged.

### 12.8 Electrocardiogram

A 12-lead ECG will be performed at specific visits according to the schedule of assessments in Appendix A. Electrocardiogram results are categorized into normal, and abnormal. If abnormal, results will be categorized with or without clinical significance. Results will be summarized by visit and treatment group and will be presented by treatment group in a shift table, using normal, abnormal not clinically significant and abnormal clinically significant categorization, between baseline and visit at Week 12. Heart rate (beats/min) and PR, QRS, RR, QT, QTcB and QTcF intervals (msec) and their changes from baseline will be summarized by visit and treatment group. A corresponding listing will be provided with abnormal values flagged.

### 12.9 Respiratory Assessments

PEF and ACT will be performed according to subjects' asthma history as follows:

1) If subjects have no asthma history, PEF will be performed at Screening and Baseline.

2) If subjects have asthma history, PEF and ACT will be performed at all visits according to the schedule of assessments in Appendix A.

3) If subjects have a new (de novo) diagnosis of asthma PEF and ACT will be performed at all subsequent visits (considering that some subjects will have performed some PEF testing at prior visits as per point 1).

ACT and PEF (observed values and changes from baseline) will be summarized by visit and treatment group. A corresponding listing will be also provided for both assessments.

For ACT, the numbers and percentages of subjects with an ACT score <=19 will be summarized by visit and treatment group.

For PEF, the numbers and percentages of subjects with PEF<80% of the predicted value will be presented by visit and treatment group and percent change from baseline will be classified as follows

- <= -20%
- <= -15% and > -20%
- <= -10% and > -15%
- < 0% and > -10%
- >= 0% and < 10%

- >= 10% and < 15%
- >= 15% and < 20%
- >= 20%

and will be presented by visit and treatment group.

All PEF summaries will be presented for subjects with/without asthma history.

Additionally, individual plots presenting the distribution of ACT and PEF for subjects with abnormal values, over the visits will be displayed by treatment.

A listing with all known asthma triggers will be provided.

## 13 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (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.

## 14 Interim Analysis

No interim analysis is planned for this study.

## 15 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.

# 16 Changes from the Protocol Analysis Plan

Any change from the protocol will be justified and fully documented.

If the blind review suggests changes to the principal features stated in the protocol, these have to be documented in a protocol amendment. Otherwise, it will suffice to update the statistical analysis plan with the considerations suggested from the blind review.

No changes have been made to the intent of protocol text.

The following clarification has been made:

- Addition of Appendix C for details about Multiple Imputation and Tipping Point analysis. Note that this clarifies that the tipping point approach is using the delta-adjustment multiple imputation framework under Missing Not at Random (MNAR) assumption.

# 17 General Features of Tables, Listings and Figures

TLF have to be printed in A4 page size with landscape orientation and with the following margins:

- Top: 2.0 cm (i.e. headers at 2.0 cm from page edge)
- Bottom: 2.0 cm (i.e. footers at 2.0 cm from page edge)
- Left: 0.8 cm
- Right: 0.8 cm

Courier New, 8-point font will be used for TLF contents (excluding column headers) and TLF footnotes.

Courier New, 8-point, bold font will be used for page headers and footers, TLF title, TLF headers, column headers and figures' axis labels.

A clear, accurate and complete programming code will be developed to generate the statistical analyses, summary tables, figures and listings to be integrated in the Clinical Study Report. The use of precise titles and footnotes will be made to improve the understanding of summaries and document any assumption. Details of analysis specifications including but not limited to the SAS code will be documented on the shells.

The final list of TLF is available in Appendix F. The final mock TLF shells for the reporting of this study will be available in a separate document that will be developed and will be finalized before database lock.

## 18 References

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11. Victoria Liublinska and Donald B. Rubin, "Sensitivity analysis for a partially missing binary outcome in a two-arm randomized clinical trial", 2014, Stat Med.

# 19 Appendices

## 19.1 Appendix A: Schedule of Study Procedures

| 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] | | | | | | | |
| **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) |

| 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 | |
| Height | X | | | | | | (X) |
| Pre-Dialysis and Post-Dialysis Weight | X | X | | | X | | (X) |
| 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] | | | | | | | |

| 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 | |
| **RANDOMIZATION and STUDY DRUG ADMINISTRATION** | | | | | | | |
| Randomization | | X | | | | | |
| Study drug injection and training [t,u,v] | | X | X | X | | | (X) |

CCI [redacted]


CCI

CCI

[redacted]


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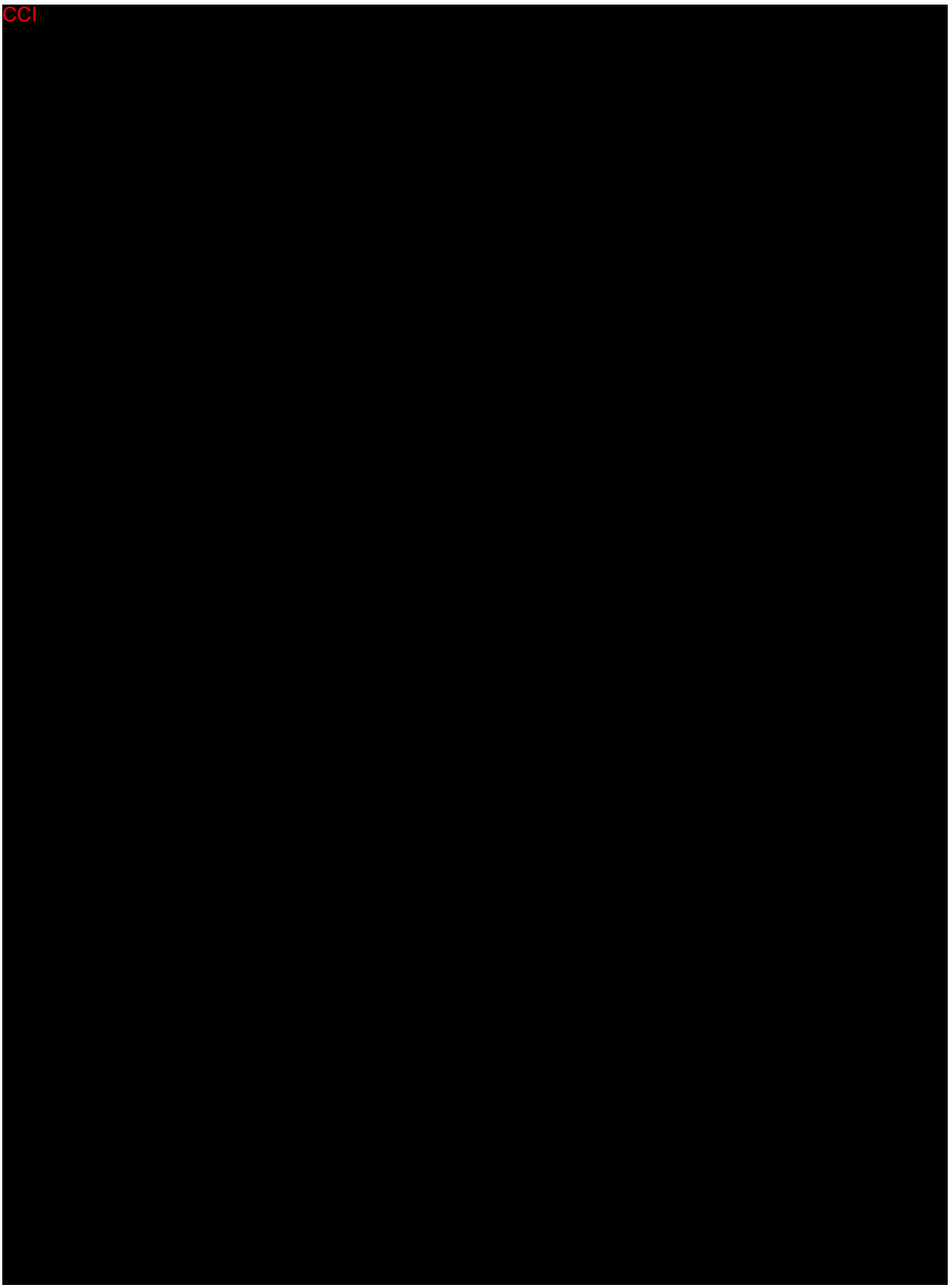
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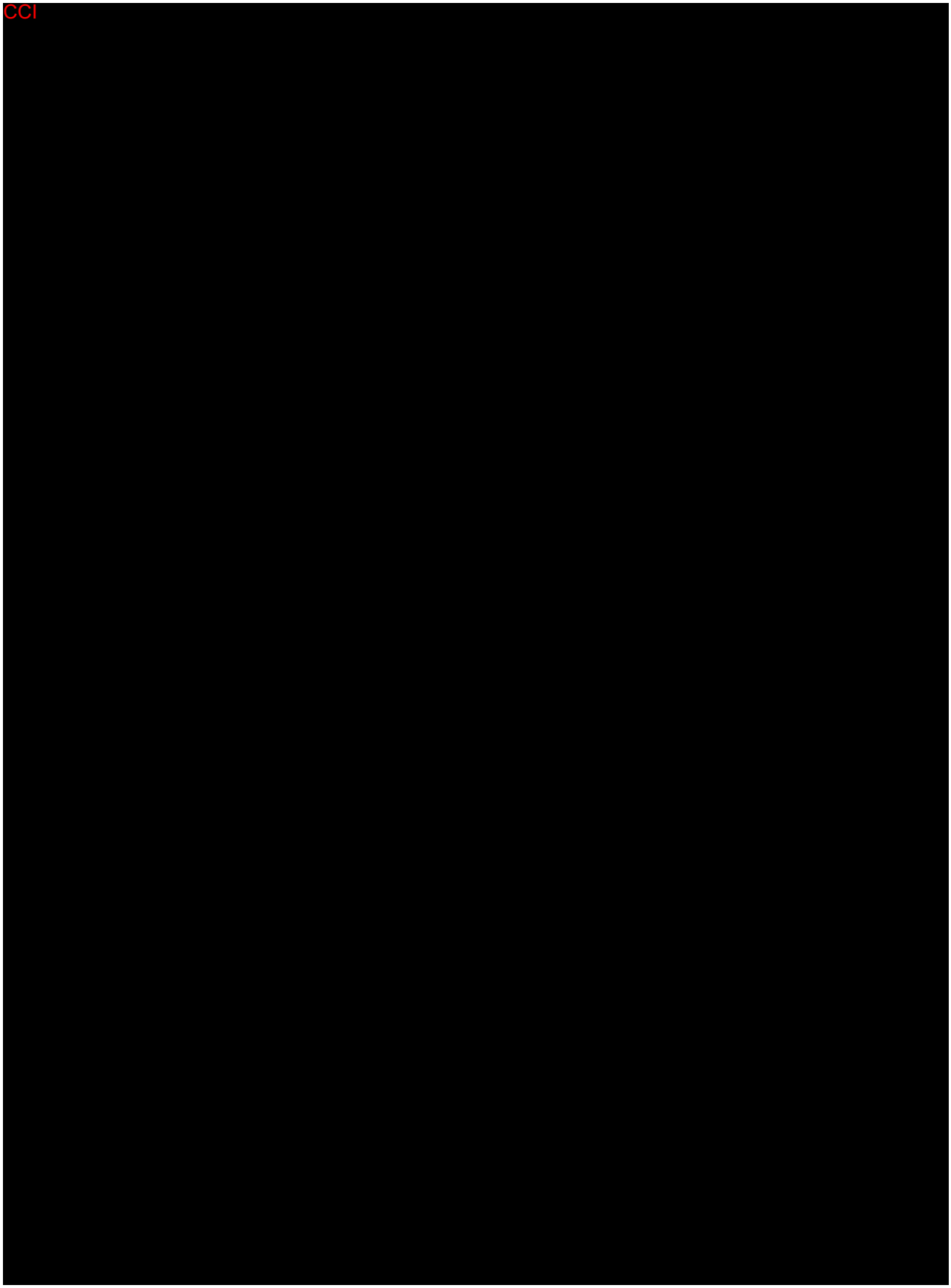

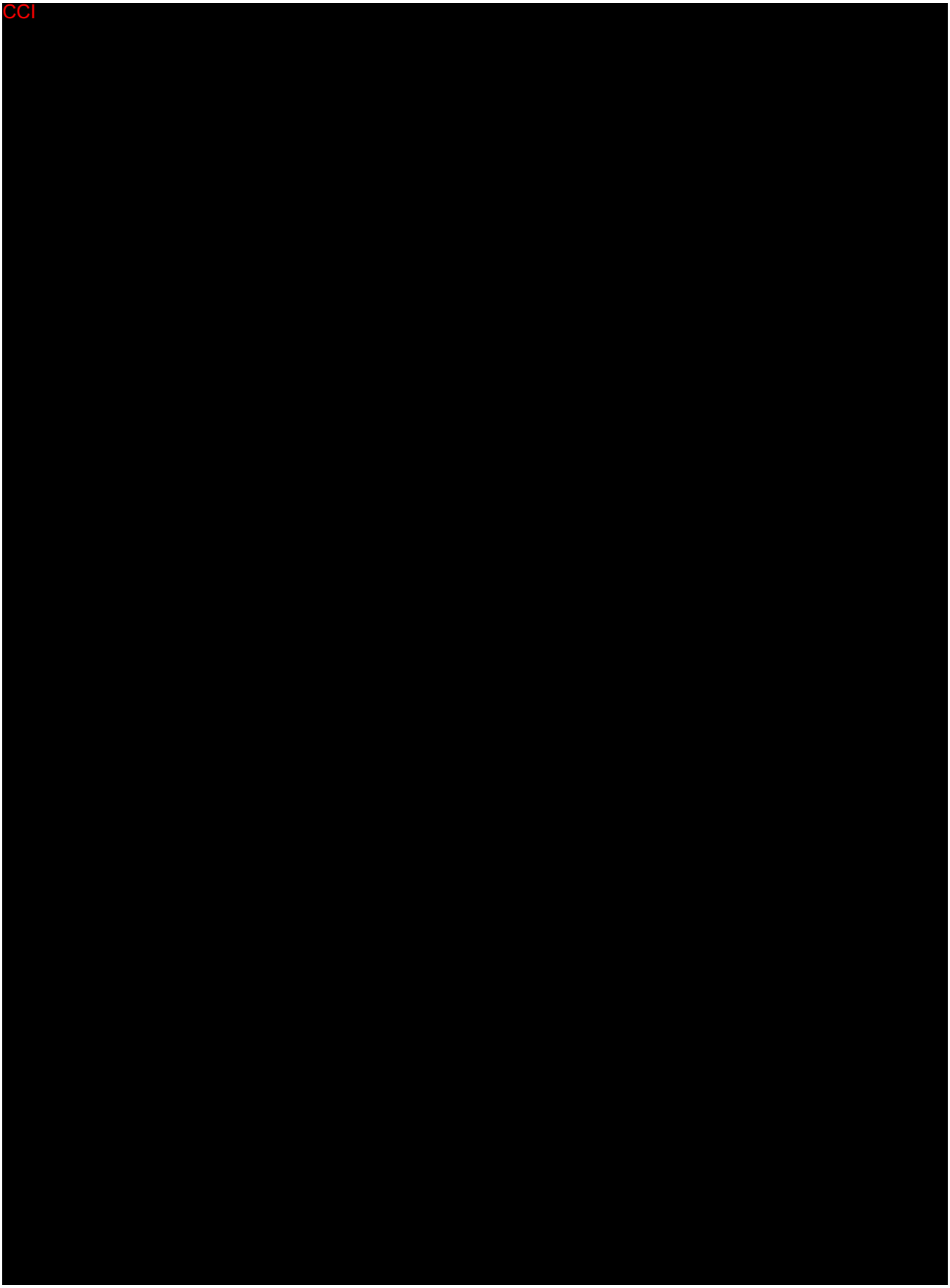
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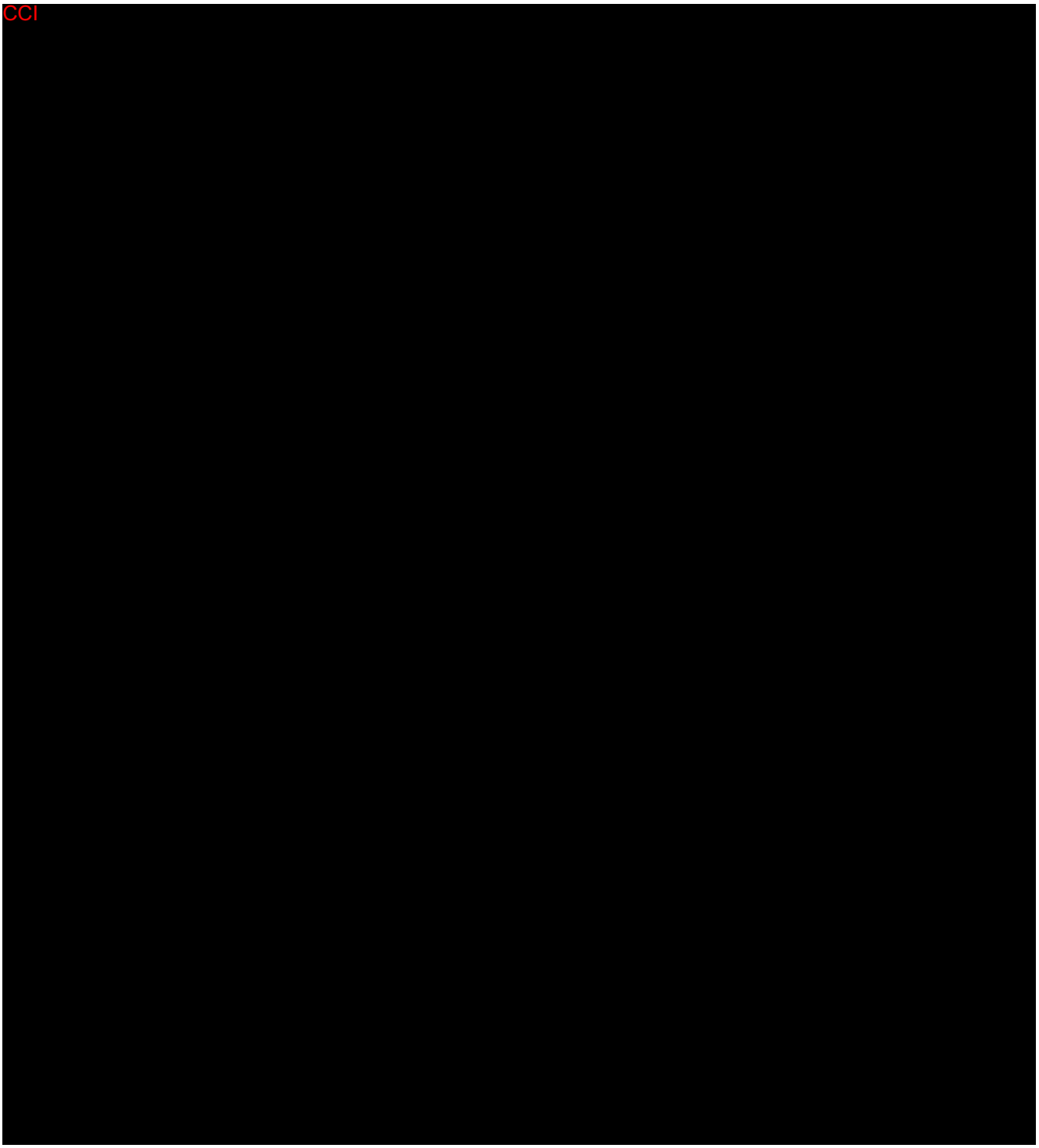
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## 19.6 Appendix F: List of Tables, Figures and Listings

| TLF | Title | Analysis Set |
|---|---|---|
| Table 14.1.1.1 | Summary of Subjects' Disposition | Screened Set |
| Table 14.1.1.2 | Summary of Screen Failure/Not Assigned Subjects | Screened Set |
| Table 14.1.1.3 | Summary of Inclusion/Exclusion Criteria Not Met | Screened Set |
| Table 14.1.1.4 | Summary of Analysis Sets | ITT Set |
| Table 14.1.1.5 | Summary of Subjects Accounting by Clinical Visit | ITT Set |
| Table 14.1.1.6 | Summary of Subjects Accounting by Analysis Visit | ITT Set |
| Table 14.1.2.1.1 | Summary of Demographics and Baseline Characteristics | ITT Set |
| Table 14.1.2.1.2 | Summary of Demographics and Baseline Characteristics | Safety Set |
| CCI [redacted] | [redacted] | [redacted] |
| Table 14.1.2.2.1 | Summary of Baseline Disease Characteristics | ITT Set |
| Table 14.1.2.2.2 | Summary of Baseline Disease Characteristics | Safety Set |
| CCI [redacted] | [redacted] | [redacted] |
| Table 14.1.2.3 | Summary of Childbearing Potential Status, Methods of Contraception and Reproductive Status | ITT Set (Women only) |
| Table 14.1.3.1 | Summary of Major Protocol Deviations | ITT Set |
| Table 14.1.3.2 | Summary of Major Protocol Deviations Leading to the Exclusion from PP Set | ITT Set |
| Table 14.1.4.1 | Summary of Extent of Exposure and Compliance | Safety Set |
| Table 14.1.5.1 | Summary of Medical History | ITT Set |
| Table 14.1.6.1 | Summary of Prior Medications | ITT Set |
| Table 14.1.6.2 | Summary of Concomitant Medications | ITT Set |
| Table 14.1.7.1 | Summary of Prior Medical and Surgical Procedures | ITT Set |
| Table 14.1.7.2 | Summary of Concomitant Medical and Surgical Procedures | ITT Set |
| Table 14.1.8.1 | Summary of Rescue Medications | ITT Set |
| Table 14.1.8.2 | Summary of Rescue Medical and Surgical Procedures | ITT Set |
| Table 14.1.8.3 | Kaplan-Meier Analysis of Time to First Rescue Therapy | ITT Set |
| Figure 14.1.8.4 | Kaplan-Meier Plots of Time to First Rescue Therapy | ITT Set |
| Table 14.2.1.1 | Summary of Proportion of Subjects with Improvement of WI NRS >= 4 from Baseline - Observed Case | ITT Set |
| Table 14.2.1.2.1 | Subgroup Summary by Age of Proportion of Subjects with Improvement of WI NRS >= 4 from Baseline - Observed Case | ITT Set |
| Table 14.2.1.2.2 | Subgroup Summary by Sex of Proportion of Subjects with Improvement of WI NRS >= 4 from Baseline - Observed Case | ITT Set |
| Table 14.2.1.2.3 | Subgroup Summary by Race of Proportion of Subjects with Improvement of WI NRS >= 4 from Baseline - Observed Case | ITT Set |
| Table 14.2.1.2.4 | Subgroup Summary by Region of Proportion of Subjects with Improvement of WI NRS >= 4 from Baseline - Observed Case | ITT Set |
| Table 14.2.1.2.5 | Subgroup Summary by Severity of Pruritus of Proportion of Subjects with Improvement of WI NRS >= 4 from Baseline - Observed Case | ITT Set |
| Table 14.2.1.2.6 | Subgroup Summary by Duration of Pruritus of Proportion of Subjects with Improvement of WI NRS >= 4 from Baseline - Observed Case | ITT Set |
| Table 14.2.1.2.7 | Subgroup Summary by Duration of Hemodialysis of Proportion of Subjects with Improvement of WI NRS >= 4 from Baseline - Observed Case | ITT Set |
| Table 14.2.1.2.8 | Subgroup Summary by Systemic Anti-Pruritus Treatment of Proportion of Subjects with Improvement of WI NRS >= 4 from Baseline - Observed Case | ITT Set |
| Table 14.2.1.3.1 | Primary Analysis (Estimand 1) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at | ITT Set |

| TLF | Title | Analysis Set |
|---|---|---|
| | Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | |
| Figure 14.2.1.3.2 | Primary Analysis (Estimand 1) - Bar Chart of Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.1.4.1 | Sensitivity Analysis 1 (Estimand 1) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI using Copy Reference under MNAR | ITT Set |
| Table 14.2.1.4.2 | Sensitivity Analysis 2 (Estimand 1) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - Non-responder Imputation | ITT Set |
| Table 14.2.1.4.3 | Sensitivity Analysis 3 (Estimand 1) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - Tipping Point Analysis based on Delta-adjustment MI under MNAR | ITT Set |
| Figure 14.2.1.4.4 | Sensitivity Analysis 3 (Estimand 1) - Heatmap Display of Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - Tipping Point Analysis based on Delta-adjustment MI under MNAR | ITT Set |
| Table 14.2.1.4.5 | Sensitivity Analysis 4 (Estimand 1) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR (Using Weekly Averages of WI NRS Obtained by Averaging at least 3 Daily Scores over a 7-day Period) | ITT Set |
| Table 14.2.1.4.6 | Sensitivity Analysis 5 (Estimand 1) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR (Using Weekly Averages of WI NRS Obtained by Averaging at least 2 Daily Scores over a 7-day Period) | ITT Set |
| Table 14.2.1.4.7 | Sensitivity Analysis 6 (Estimand 1) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR (Using Weekly Averages of WI NRS Obtained by Averaging at least 1 Daily Score over a 7-day Period) | ITT Set |
| Table 14.2.1.4.8 | Supplementary Analysis 1 (Estimand 1) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and | mITT Set |

| TLF | Title | Analysis Set |
|---|---|---|
| | without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | |
| Table 14.2.1.4.9 | Supplementary Analysis 2 (Estimand 1) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug | PP Set |
| Table 14.2.1.4.10 | Supplementary Analysis 3 (Treatment Policy Adaptation of Estimand 1) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 12 Irrespective of Use of Rescue Therapies and Treatment Discontinuation - Observed Case | ITT Set |
| Table 14.2.1.4.11 | COVID-19 Impact (Estimand 1) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set excluding Subjects with COVID-19 disruptions |
| Table 14.2.1.5.1 | Subgroup Analysis by Age (Estimand 1) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.1.5.2 | Subgroup Analysis by Sex (Estimand 1) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.1.5.3 | Subgroup Analysis by Race (Estimand 1) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.1.5.4 | Subgroup Analysis by Region (Estimand 1) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.1.5.5 | Subgroup Analysis by Severity of Pruritus (Estimand 1) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.1.5.6 | Subgroup Analysis by Duration of Pruritus (Estimand 1) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.1.5.7 | Subgroup Analysis by Duration of Hemodialysis (Estimand 1) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.1.5.8 | Subgroup Analysis by Systemic Anti-Pruritus Treatment (Estimand 1) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 12 without | ITT Set |

| TLF | Title | Analysis Set |
|---|---|---|
| | Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | |
| Figure 14.2.1.5.9 | Forest Plot (Estimand 1) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.2.1 | Summary of Proportion of Subjects with Improvement of WI NRS >= 3 from Baseline - Observed Case | ITT Set |
| Table 14.2.2.2.1 | Subgroup Summary by Age of Proportion of Subjects with Improvement of WI NRS >= 3 from Baseline - Observed Case | ITT Set |
| Table 14.2.2.2.2 | Subgroup Summary by Sex of Proportion of Subjects with Improvement of WI NRS >= 3 from Baseline - Observed Case | ITT Set |
| Table 14.2.2.2.3 | Subgroup Summary by Race of Proportion of Subjects with Improvement of WI NRS >= 3 from Baseline - Observed Case | ITT Set |
| Table 14.2.2.2.4 | Subgroup Summary by Region of Proportion of Subjects with Improvement of WI NRS >= 3 from Baseline - Observed Case | ITT Set |
| Table 14.2.2.2.5 | Subgroup Summary by Severity of Pruritus of Proportion of Subjects with Improvement of WI NRS >= 3 from Baseline - Observed Case | ITT Set |
| Table 14.2.2.2.6 | Subgroup Summary by Duration of Pruritus of Proportion of Subjects with Improvement of WI NRS >= 3 from Baseline - Observed Case | ITT Set |
| Table 14.2.2.2.7 | Subgroup Summary by Duration of Hemodialysis of Proportion of Subjects with Improvement of WI NRS >= 3 from Baseline - Observed Case | ITT Set |
| Table 14.2.2.2.8 | Subgroup Summary by Systemic Anti-Pruritus Treatment of Proportion of Subjects with Improvement of WI NRS >= 3 from Baseline - Observed Case | ITT Set |
| Table 14.2.2.3.1 | Main Analysis (Estimand 2) - Difference in Proportions of Subjects with Improvement of WI NRS >= 3 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Figure 14.2.2.3.2 | Main Analysis (Estimand 2) - Bar Chart of Proportions of Subjects with Improvement of WI NRS >= 3 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.2.4.1 | Sensitivity Analysis 1 (Estimand 2) - Difference in Proportions of Subjects with Improvement of WI NRS >= 3 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI using Copy Reference under MNAR | ITT Set |
| Table 14.2.2.4.2 | Sensitivity Analysis 2 (Estimand 2) - Difference in Proportions of Subjects with Improvement of WI NRS >= 3 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - Non-responder Imputation | ITT Set |
| Table 14.2.2.4.3 | COVID-19 Impact (Estimand 2) - Difference in Proportions of Subjects with Improvement of WI NRS >= 3 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set excluding Subjects with COVID-19 disruptions |

| TLF | Title | Analysis Set |
|---|---|---|
| Table 14.2.2.5.1 | Subgroup Analysis by Age (Estimand 2) - Difference in Proportions of Subjects with Improvement of WI NRS >= 3 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.2.5.2 | Subgroup Analysis by Sex (Estimand 2) - Difference in Proportions of Subjects with Improvement of WI NRS >= 3 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.2.5.3 | Subgroup Analysis by Race (Estimand 2) - Difference in Proportions of Subjects with Improvement of WI NRS >= 3 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.2.5.4 | Subgroup Analysis by Region (Estimand 2) - Difference in Proportions of Subjects with Improvement of WI NRS >= 3 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.2.5.5 | Subgroup Analysis by Severity of Pruritus (Estimand 2) - Difference in Proportions of Subjects with Improvement of WI NRS >= 3 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.2.5.6 | Subgroup Analysis by Duration of Pruritus (Estimand 2) - Difference in Proportions of Subjects with Improvement of WI NRS >= 3 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.2.5.7 | Subgroup Analysis by Duration of Hemodialysis (Estimand 2) - Difference in Proportions of Subjects with Improvement of WI NRS >= 3 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.2.5.8 | Subgroup Analysis by Systemic Anti-Pruritus Treatment (Estimand 2) - Difference in Proportions of Subjects with Improvement of WI NRS >= 3 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Figure 14.2.2.5.9 | Forest Plot (Estimand 2) Difference in Proportions of Subjects achieving an Improvement of WI NRS >= 3 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.3.1.1 | Main Analysis (Estimand 3) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Figure 14.2.3.1.2 | Main Analysis (Estimand 3) - Bar Chart of Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment | ITT Set |

| TLF | Title | Analysis Set |
|---|---|---|
| | Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | |
| Table 14.2.3.2.1 | Sensitivity Analysis 1 (Estimand 3) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI using Copy Reference under MNAR | ITT Set |
| Table 14.2.3.2.2 | Sensitivity Analysis 2 (Estimand 3) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - Non-responder Imputation | ITT Set |
| Table 14.2.3.2.3 | COVID-19 Impact (Estimand 3) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set excluding Subjects with COVID-19 disruptions |
| Table 14.2.3.3.1 | Subgroup Analysis by Age (Estimand 3) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.3.3.2 | Subgroup Analysis by Sex (Estimand 3) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.3.3.3 | Subgroup Analysis by Race (Estimand 3) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.3.3.4 | Subgroup Analysis by Region (Estimand 3) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.3.3.5 | Subgroup Analysis by Severity of Pruritus (Estimand 3) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.3.3.6 | Subgroup Analysis by Duration of Pruritus (Estimand 3) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.3.3.7 | Subgroup Analysis by Duration of Hemodialysis (Estimand 3) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.3.3.8 | Subgroup Analysis by Systemic Anti-Pruritus Treatment (Estimand 3) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 4 without | ITT Set |

| TLF | Title | Analysis Set |
|---|---|---|
| | Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | |
| Figure 14.2.3.3.9 | Forest Plot (Estimand 3) - Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.4.1 | Summary of Proportion of Subjects with Improvement of SD NRS >= 4 from Baseline - Observed Case | ITT Set |
| Table 14.2.4.2.1 | Subgroup Summary by Age of Proportion of Subjects with Improvement of SD NRS >= 4 from Baseline - Observed Case | ITT Set |
| Table 14.2.4.2.2 | Subgroup Summary by Sex of Proportion of Subjects with Improvement of SD NRS >= 4 from Baseline - Observed Case | ITT Set |
| Table 14.2.4.2.3 | Subgroup Summary by Race of Proportion of Subjects with Improvement of SD NRS >= 4 from Baseline - Observed Case | ITT Set |
| Table 14.2.4.2.4 | Subgroup Summary by Region of Proportion of Subjects with Improvement of SD NRS >= 4 from Baseline - Observed Case | ITT Set |
| Table 14.2.4.2.5 | Subgroup Summary by Severity of Pruritus of Proportion of Subjects with Improvement of SD NRS >= 4 from Baseline - Observed Case | ITT Set |
| Table 14.2.4.2.6 | Subgroup Summary by Duration of Pruritus of Proportion of Subjects with Improvement of SD NRS >= 4 from Baseline - Observed Case | ITT Set |
| Table 14.2.4.2.7 | Subgroup Summary by Duration of Hemodialysis of Proportion of Subjects with Improvement of SD NRS >= 4 from Baseline - Observed Case | ITT Set |
| Table 14.2.4.2.8 | Subgroup Summary by Systemic Anti-Pruritus Treatment of Proportion of Subjects with Improvement of SD NRS >= 4 from Baseline - Observed Case | ITT Set |
| Table 14.2.4.3.1 | Main Analysis (Estimand 4) - Difference in Proportions of Subjects with Improvement of SD NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Figure 14.2.4.3.2 | Main Analysis (Estimand 4) - Bar Chart of Proportions of Subjects with Improvement of SD NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.4.4.1 | Sensitivity Analysis 1 (Estimand 4) - Difference in Proportions of Subjects with Improvement of SD NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI using Copy Reference under MNAR | ITT Set |
| Table 14.2.4.4.2 | Sensitivity Analysis 2 (Estimand 4) - Difference in Proportions of Subjects with Improvement of SD NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - Non-responder Imputation | ITT Set |
| Table 14.2.4.4.3 | COVID-19 Impact (Estimand 4) - Difference in Proportions of Subjects with Improvement of SD NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set excluding Subjects with COVID-19 disruptions |

| TLF | Title | Analysis Set |
|---|---|---|
| Table 14.2.4.5.1 | Subgroup Analysis by Age (Estimand 4) - Difference in Proportions of Subjects with Improvement of SD NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.4.5.2 | Subgroup Analysis by Sex (Estimand 4) - Difference in Proportions of Subjects with Improvement of SD NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.4.5.3 | Subgroup Analysis by Race (Estimand 4) - Difference in Proportions of Subjects with Improvement of SD NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.4.5.4 | Subgroup Analysis by Region (Estimand 4) - Difference in Proportions of Subjects with Improvement of SD NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.4.5.5 | Subgroup Analysis by Severity of Pruritus (Estimand 4) - Difference in Proportions of Subjects with Improvement of SD NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.4.5.6 | Subgroup Analysis by Duration of Pruritus (Estimand 4) - Difference in Proportions of Subjects with Improvement of SD NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.4.5.7 | Subgroup Analysis by Duration of Hemodialysis (Estimand 4) - Difference in Proportions of Subjects with Improvement of SD NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.4.5.8 | Subgroup Analysis by Systemic Anti-Pruritus Treatment (Estimand 4) - Difference in Proportions of Subjects with Improvement of SD NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Figure 14.2.4.5.9 | Forest Plot (Estimand 4) - Difference in Proportions of Subjects with Improvement of SD NRS >= 4 from Baseline at Week 12 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.5.1.1 | Main Analysis (Estimand 5) - Difference in Proportions of Subjects with Improvement of WI NRS >= 3 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Figure 14.2.5.1.2 | Main Analysis (Estimand 5) - Bar Chart of Proportions of Subjects with Improvement of WI NRS >= 3 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment | ITT Set |

| TLF | Title | Analysis Set |
|---|---|---|
| | Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | |
| Table 14.2.5.2.1 | Sensitivity Analysis 1 (Estimand 5) - Difference in Proportions of Subjects with Improvement of WI NRS >= 3 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI using Copy Reference under MNAR | ITT Set |
| Table 14.2.5.2.2 | Sensitivity Analysis 2 (Estimand 5)- Difference in Proportions of Subjects with Improvement of WI NRS >= 3 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - Non-responder Imputation | ITT Set |
| Table 14.2.5.2.3 | COVID-19 Impact (Estimand 5) - Difference in Proportions of Subjects with Improvement of WI NRS >= 3 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set excluding Subjects with COVID-19 disruptions |
| Table 14.2.5.3.1 | Subgroup Analysis by Age (Estimand 5) - Difference in Proportions of Subjects with Improvement of WI NRS >= 3 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.5.3.2 | Subgroup Analysis by Sex (Estimand 5) - Difference in Proportions of Subjects with Improvement of WI NRS >= 3 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.5.3.3 | Subgroup Analysis by Race (Estimand 5) - Difference in Proportions of Subjects with Improvement of WI NRS >= 3 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.5.3.4 | Subgroup Analysis by Region (Estimand 5) - Difference in Proportions of Subjects with Improvement of WI NRS >= 3 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.5.3.5 | Subgroup Analysis by Severity of Pruritus (Estimand 5) - Difference in Proportions of Subjects with Improvement of WI NRS >= 3 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.5.3.6 | Subgroup Analysis by Duration of Pruritus (Estimand 5) - Difference in Proportions of Subjects with Improvement of WI NRS >= 3 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.5.3.7 | Subgroup Analysis by Duration of Hemodialysis (Estimand 5) - Difference in Proportions of Subjects with Improvement of WI NRS >= 3 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.5.3.8 | Subgroup Analysis by Systemic Anti-Pruritus Treatment (Estimand 5) - Difference in Proportions of Subjects with Improvement of WI NRS >= 3 from Baseline at Week 4 without | ITT Set |

| TLF | Title | Analysis Set |
|---|---|---|
| | Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | |
| Figure 14.2.5.3.9 | Forest Plot (Estimand 5) - Difference in Proportions of Subjects achieving an Improvement of WI NRS >= 3 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.6.1.1 | Main Analysis (Estimand 6) - Difference in Proportions of Subjects with Improvement of SD NRS >= 4 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Figure 14.2.6.1.2 | Main Analysis (Estimand 6) - Bar Chart of Proportions of Subjects with Improvement of SD NRS >= 4 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.6.2.1 | Sensitivity Analysis 1 (Estimand 6) - Difference in Proportions of Subjects with Improvement of SD NRS >= 4 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI using Copy Reference under MNAR | ITT Set |
| Table 14.2.6.2.2 | Sensitivity Analysis 2 (Estimand 6)- Difference in Proportions of Subjects with Improvement of SD NRS >= 4 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - Non-responder Imputation | ITT Set |
| Table 14.2.6.2.3 | COVID-19 Impact (Estimand 6) - Difference in Proportions of Subjects with Improvement of SD NRS >= 4 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set excluding Subjects with COVID-19 disruptions |
| Table 14.2.6.3.1 | Subgroup Analysis by Age (Estimand 6) - Difference in Proportions of Subjects with Improvement of SD NRS >= 4 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.6.3.2 | Subgroup Analysis by Sex (Estimand 6) - Difference in Proportions of Subjects with Improvement of SD NRS >= 4 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.6.3.3 | Subgroup Analysis by Race (Estimand 6) - Difference in Proportions of Subjects with Improvement of SD NRS >= 4 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.6.3.4 | Subgroup Analysis by Region (Estimand 6) - Difference in Proportions of Subjects with Improvement of SD NRS >= 4 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.6.3.5 | Subgroup Analysis by Severity of Pruritus (Estimand 6) - Difference in Proportions of Subjects with Improvement of SD | ITT Set |

| TLF | Title | Analysis Set |
|---|---|---|
| | NRS >= 4 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | |
| Table 14.2.6.3.6 | Subgroup Analysis by Duration of Pruritus (Estimand 6) - Difference in Proportions of Subjects with Improvement of SD NRS >= 4 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.6.3.7 | Subgroup Analysis by Duration of Hemodialysis (Estimand 6) - Difference in Proportions of Subjects with Improvement of SD NRS >= 4 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Table 14.2.6.3.8 | Subgroup Analysis by Systemic Anti-Pruritus Treatment (Estimand 6) - Difference in Proportions of Subjects with Improvement of SD NRS >= 4 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| Figure 14.2.6.3.9 | Forest Plot (Estimand 6) - Difference in Proportions of Subjects achieving an Improvement of SD NRS >= 4 from Baseline at Week 4 without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - MI under MAR | ITT Set |
| CCI [redacted] | [redacted] | [redacted] |
| CCI [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| Table 14.2.12.1 | Summary of Weekly Average of WI NRS - Observed Case | ITT Set |
| Table 14.2.12.2 | ANCOVA of Percent Change from Baseline in Weekly Average of WI NRS at Week 12 - MI under MAR | ITT Set |
| Table 14.2.12.3 | ANCOVA of Percent Change from Baseline in Weekly Average of WI NRS at Week 4 - MI under MAR | ITT Set |
| CCI [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| Table 14.2.14.1 | Kaplan-Meier Analysis of Time to Onset of Effect on Pruritus from Baseline | ITT Set |
| Figure 14.2.14.2 | Kaplan-Meier Plots of Time to Onset of Effect on Pruritus from Baseline | ITT Set |
| Table 14.2.14.3 | Competing-Risks Analysis of Time to Onset of Effect on Pruritus from Baseline | ITT Set |

| TLF | Title | Analysis Set |
|---|---|---|
| Figure 14.2.14.4 | Competing-Risks Cumulative Incidence Function Plots of Time to Onset of Effect on Pruritus from Baseline | ITT Set |
| Table 14.2.15.1 | Difference in Proportions of Subjects with Improvement of WI NRS >= 4 from Baseline at Week 1 without Use of Rescue Therapies - MI under MAR | ITT Set |
| Table 14.2.16.1 | Summary of Investigator's Global Assessment of CKD-aP Skin Status - Observed Case | ITT Set |
| Table 14.2.16.2 | Summary of Proportion of Subjects Achieving IGA Success - Observed Case | ITT Set |
| Table 14.2.16.3 | Difference in Proportions of Subjects achieving IGA Success without Use of Rescue Therapies and without Treatment Discontinuation due to Lack of Efficacy or AE/Death related to the Study Drug - Non-responder imputation | ITT Set |
| Table 14.3.1.1 | Overall Summary of Treatment-Emergent Adverse Events | Safety Set |
| Table 14.3.1.2 | Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term | Safety Set |
| Table 14.3.1.3 | Summary of Treatment-Emergent Adverse Events by Greatest Severity, System Organ Class and Preferred Term | Safety Set |
| Table 14.3.1.4 | Summary of Treatment-Emergent Adverse Events Related to Study Drug by System Organ Class and Preferred Term | Safety Set |
| Table 14.3.1.5 | Summary of Treatment-Emergent Adverse Events Related to Study Procedures by System Organ Class and Preferred Term | Safety Set |
| Table 14.3.1.6 | Summary of Treatment-Emergent Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term | Safety Set |
| Table 14.3.1.7 | Summary of Treatment-Emergent Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term | Safety Set |
| Table 14.3.1.8 | Summary of Treatment-Emergent Adverse Events of Special Interest by System Organ Class and Preferred Term | Safety Set |
| Table 14.3.1.9 | Summary of Treatment-Emergent Adverse Events of Special Interest by Greatest Severity, by System Organ Class and Preferred Term | Safety Set |
| Table 14.3.1.10 | Summary of Treatment-Emergent Adverse Events due to COVID-19 by System Organ Class and Preferred Term | Safety Set |
| Table 14.3.1.11 | Summary of Asthma-Related Treatment-Emergent Adverse Events Adjudicated by IAC by System Organ Class and Preferred Term | Safety Set |
| Table 14.3.1.12 | Summary of Asthma-Related Treatment-Emergent Adverse Events Related to Study Drug Adjudicated by IAC by System Organ Class and Preferred Term | Safety Set |
| Table 14.3.1.13 | Summary of Asthma-Related Treatment-Emergent Adverse Events Reported by Investigator with Adjudication Outcome by IAC by System Organ Class and Preferred Term | Safety Set |
| Table 14.3.1.14 | Summary of Asthma-Related Treatment-Emergent Adverse Events Related to Study Drug Reported by Investigator with Adjudication Outcome by IAC by System Organ Class and Preferred Term | Safety Set |
| Table 14.3.1.15 | Summary of Asthma-Related Treatment-Emergent Adverse Events Adjudicated by IAC, by Greatest Severity, System Organ Class and Preferred Term | Safety Set |
| Table 14.3.1.16 | Summary of Asthma-Related Treatment-Emergent Adverse Events Related to Study Drug Adjudicated by IAC, by Greatest Severity, System Organ Class and Preferred Term | Safety Set |

| TLF | Title | Analysis Set |
|---|---|---|
| Table 14.3.1.17 | Summary of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term | Safety Set |
| Table 14.3.1.18 | Summary of Non-Fatal Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term | Safety Set |
| Table 14.3.1.19 | Summary of Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term | Safety Set |
| Table 14.3.1.20 | Summary of Serious Treatment-Emergent Adverse Events Related to Study Drug by System Organ Class and Preferred Term | Safety Set |
| Table 14.3.1.21 | Summary of Serious Treatment-Emergent Adverse Events Related to Study Procedures by System Organ Class and Preferred Term | Safety Set |
| Table 14.3.1.22 | Summary of Serious Treatment-Emergent Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term | Safety Set |
| Table 14.3.1.23 | Summary of Serious Treatment-Emergent Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term | Safety Set |
| Listing 14.3.2.1 | Treatment-Emergent Adverse Events Leading to Death | Safety Set |
| Listing 14.3.2.2 | Serious Treatment-Emergent Adverse Events | Safety Set |
| Listing 14.3.2.3 | Non-Fatal Serious Treatment-Emergent Adverse Events | Safety Set |
| Listing 14.3.2.4 | Severe Treatment-Emergent Adverse Events | Safety Set |
| Listing 14.3.2.5 | Treatment-Emergent Adverse Events of Special Interest | Safety Set |
| Listing 14.3.2.6 | Treatment-Emergent Adverse Events Leading to Treatment Discontinuation | Safety Set |
| Listing 14.3.2.7 | Treatment-Emergent Adverse Events Leading to Study Discontinuation | Safety Set |
| Listing 14.3.2.8 | Treatment-Emergent Adverse Events due to COVID-19 | Safety Set |
| Table 14.3.4.1.1 | Summary of Observed Value and Change from Baseline of Hematology Laboratory Tests | Safety Set |
| Table 14.3.4.1.2 | Shift Tables based on Normal Ranges of Hematology Laboratory Tests | Safety Set |
| Table 14.3.4.1.3 | Shift Tables based on Normality and Clinical Significance of Hematology Laboratory Tests | Safety Set |
| Table 14.3.4.1.4 | Summary of Subjects who Met Potentially Clinically Significant Value Criteria for Hematology Laboratory Tests | Safety Set |
| Listing 14.3.4.1.5 | Abnormal Hematology Values | Safety Set |
| Listing 14.3.4.1.6 | Potentially Clinically Significant Hematology Values | Safety Set |
| Table 14.3.4.2.1 | Summary of Observed Value and Change from Baseline of Serum Chemistry Laboratory Tests | Safety Set |
| Table 14.3.4.2.1.1 | Summary of Observed Value and Change from Baseline of Aspartate Aminotransferase, Alanine Aminotransferase, Alkaline Phosphatase, Bilirubin and Creatine Kinase by Sex | Safety Set |
| Table 14.3.4.2.2 | Shift Tables based on Normal Ranges of Serum Chemistry Laboratory Tests | Safety Set |
| Table 14.3.4.2.3 | Shift Tables based on Normality and Clinical Significance of Serum Chemistry Laboratory Tests | Safety Set |
| Table 14.3.4.2.4 | Summary of Subjects who Met Potentially Clinically Significant Value Criteria for Serum Chemistry Laboratory Tests | Safety Set |
| Figure 14.3.4.2.5 | Distribution of Aspartate Aminotransferase by Visit and Maximum Post Baseline Values | Safety Set |
| Figure 14.3.4.2.6 | Distribution of Alanine Aminotransferase by Visit and Maximum Post Baseline Values | Safety Set |
| Figure 14.3.4.2.7 | Distribution of Alkaline Phosphatase by Visit and Maximum Post Baseline Values | Safety Set |

| TLF | Title | Analysis Set |
|---|---|---|
| Figure 14.3.4.2.8 | Distribution of Bilirubin by Visit and Maximum Post Baseline Values | Safety Set |
| Figure 14.3.4.2.9 | Distribution of Creatine Kinase by Visit with Maximum Post Baseline Values | Safety Set |
| Figure 14.3.4.2.10 | Individual Plot of Aspartate Aminotransferase - Subjects with Post Baseline Abnormal Values by Visit | Safety Set |
| Figure 14.3.4.2.11 | Individual Plot of Alanine Aminotransferase - Subjects with Post Baseline Abnormal Values by Visit | Safety Set |
| Figure 14.3.4.2.12 | Individual Plot of Alkaline Phosphatase - Subjects with Post Baseline Abnormal Values by Visit | Safety Set |
| Figure 14.3.4.2.13 | Individual Plot of Bilirubin - Subjects with Post Baseline Abnormal Values by Visit | Safety Set |
| Figure 14.3.4.2.14 | Individual Plot of Creatine Kinase - Subjects with Post Baseline Abnormal Values by Visit | Safety Set |
| Figure 14.3.4.2.15 | Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) | Safety Set |
| Listing 14.3.4.2.16 | Abnormal Serum Chemistry Values | Safety Set |
| Listing 14.3.4.2.17 | Potentially Clinically Significant Serum Chemistry Values | Safety Set |
| Table 14.3.4.3.1 | Summary of Observed Value and Change from Baseline of Quantitative Urinalysis Laboratory Tests | Safety Set |
| Table 14.3.4.3.2 | Summary of Categorical Urinalysis Laboratory Tests | Safety Set |
| Table 14.3.4.3.3 | Shift Tables based on Normal Ranges of Quantitative Urinalysis Laboratory Tests | Safety Set |
| Table 14.3.4.3.4 | Shift Tables based on Normality and Clinical Significance of Urinalysis Laboratory Tests | Safety Set |
| Listing 14.3.4.3.5 | Abnormal Urinalysis Values | Safety Set |
| Table 14.3.4.4 | Summary of Anti-drug Antibody Results | Safety Set |
| CCI [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| Table 14.3.4.6.1 | Summary of Observed Value and Change from Baseline of Vital Signs | Safety Set |
| Table 14.3.4.6.2 | Summary of Results of Vital Signs Evaluation | Safety Set |
| Table 14.3.4.6.3 | Shift Tables of Results of Vital Signs Evaluation | Safety Set |
| Table 14.3.4.6.4 | Summary of Subjects who Met Potentially Clinically Significant Value Criteria for Vital Signs | Safety Set |
| Table 14.3.4.7 | Summary of Physical Examination | Safety Set |
| Table 14.3.4.8.1 | Summary of Observed Value and Change from Baseline of ECG Parameters | Safety Set |
| Table 14.3.4.8.2 | Summary of ECG Interpretation Results | Safety Set |
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| Table 14.3.4.9.1 | Summary of Observed Value and Change from Baseline of Asthma Control Test | Safety Set |
| Table 14.3.4.9.2 | Summary of Proportion of Subjects with Asthma Control Test Score <=19 | Safety Set |
| Figure 14.3.4.9.3 | Individual Plot of Asthma Control Test (ACT) - Subjects with Post Baseline Abnormal Values by Visit | Safety Set |
| Table 14.3.4.10.1 | Summary of Observed Value and Change from Baseline of Percentage of Predicted PEF | Safety Set |
| Table 14.3.4.10.2 | Summary of Classified Percent Change from Baseline of Peak Expiratory Flow Test | Safety Set |
| Figure 14.3.4.10.3 | Individual Plot of Peak Expiratory Flow (PEF) - Subjects with Post Baseline Abnormal Values by Visit | Safety Set |

| TLF | Title | Analysis Set |
|---|---|---|
| Listing 16.2.1.1 | Subjects' Disposition | Screened Set |
| Listing 16.2.1.2 | Screen Failure/Not Assigned Subjects | Screened Set |
| Listing 16.2.1.3 | Treatment Discontinuation | ITT Set |
| Listing 16.2.1.4 | Study Discontinuation | ITT Set |
| Listing 16.2.1.5 | COVID-19 Related Study Disruptions | Screened Set |
| Listing 16.2.2.1 | Protocol Deviations | ITT Set |
| Listing 16.2.3.1 | Inclusion/Exclusion Criteria Not Met | Screened Set |
| Listing 16.2.3.2 | Subjects in Analysis Sets | Screened Set |
| Listing 16.2.4.1 | Demographics and Baseline Characteristics | Screened Set |
| Listing 16.2.4.2 | Baseline Disease Characteristics | ITT Set |
| Listing 16.2.4.3 | Childbearing Potential Status, Methods of Contraception and Reproductive Status | Screened Set (Women only) |
| Listing 16.2.4.4 | Medical History | ITT Set |
| Listing 16.2.4.5 | Prior and Concomitant Medications | ITT Set |
| Listing 16.2.4.6 | Prior and Concomitant Medical and Surgical Procedures | ITT Set |
| Listing 16.2.4.7 | Rescue Medications | ITT Set |
| Listing 16.2.4.8 | Rescue Medical and Surgical Procedures | ITT Set |
| Listing 16.2.4.9 | Analysis Centers | ITT Set |
| Listing 16.2.4.10 | Subject Scheduled Visits | ITT Set |
| Listing 16.2.4.11 | Subject Unscheduled Visits | ITT Set |
| Listing 16.2.5.1 | Study Drug Administration | Safety Set |
| Listing 16.2.5.2 | Extent of Exposure and Compliance | Safety Set |
| Listing 16.2.5.3 | Anti-drug Antibody Assessments | Safety Set |
| Listing 16.2.5.4 | Individual Observed Serum Nemolizumab Concentrations (Ctrough) versus Time | Safety Set |
| Figure 16.2.5.5 | Individual Observed Serum Nemolizumab Concentrations (Ctrough) versus Time | Safety Set |
| CCI [redacted] | [redacted] | [redacted] |
| Listing 16.2.6.1 | Worst Itch Numeric Rating Scale | ITT Set |
| CCI [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| Listing 16.2.7.1 | Treatment-Emergent Adverse Events | Safety Set |
| Listing 16.2.7.2 | Pre-treatment Adverse Events | Safety Set |
| Listing 16.2.8.1 | Hematology | Safety Set |
| Listing 16.2.8.2 | Serum Chemistry | Safety Set |
| Listing 16.2.8.3 | Urinalysis | Safety Set |
| Listing 16.2.8.4 | Virology at Screening | Safety Set |
| Listing 16.2.8.5 | Tuberculosis Testing at Screening | Safety Set |
| Listing 16.2.8.6 | Pregnancy Test | Safety Set |
| Listing 16.2.8.7 | Vital Signs | Safety Set |
| Listing 16.2.8.8 | Physical Examination | Safety Set |
| Listing 16.2.8.9 | 12-Lead ECG | Safety Set |
| Listing 16.2.8.10 | Asthma Control Test | Safety Set |
| Listing 16.2.8.11 | Respiratory Assessment | Safety Set |
| Listing 16.2.8.12 | Peak Expiratory Flow Test | Safety Set |
| Listing 16.2.8.13 | Known Asthma Triggers | Safety Set |

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Parties agreed to: Matteo Rossini