The RE-UNITE-PN study design – a prospective, non-interventional, Phase 4 study of nemolizumab for the treatment of prurigo nodularis

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OBJECTIVE

- RE-UNITE-PN (NCT06988618) is a prospective, multicenter, non-interventional study (NIS) that aims to enroll ~600 adults (across 150 sites in Europe and North America) newly initiated on nemolizumab for the treatment of PN per physician discretion, providing real-world evidence to complement pivotal trial data. Here we describe the study's design and rationale

CONCLUSION

- This non-interventional study, with large sample size and real-world design, is expected to address data gaps from pivotal clinical trials and complement existing evidence on the effectiveness and safety data of nemolizumab in PN. By enrolling adults with PN based on routine clinical decisions made independently by treating physicians, the study will reflect everyday clinical practice and provide valuable insights into the real-world effectiveness and PROs associated with nemolizumab

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INTRODUCTION

- Prurigo nodularis (PN) is a chronic neuroimmune skin disease, characterized by debilitating itch and multiple pruriginous lesions[1,2]
- Nemolizumab, an IL-31 receptor alpha antagonist, has shown efficacy and safety in the phase 3 OLYMPIA trials[3,4] and is approved for the treatment of PN in adults in several countries[5,6]
- Controlled trials, however, may not precisely mirror clinical practice, necessitating a study that better reflects real-world settings

METHODS

STUDY OBJECTIVES

Primary objective

- To evaluate real-world effectiveness of nemolizumab in PN as measured by physician assessment (IGA-CPG stage) and by PRO (PP-NRS) in clinical practice at month 6

Secondary objective

- To evaluate real-world effectiveness of nemolizumab in PN as measured by physician assessment (IGA-CPG stage, PAS), and PROs (PP-NRS, SD-NRS) in clinical practice up to month 12

Exploratory objectives

- To evaluate real-world effectiveness of nemolizumab in PN as measured by PROs pertaining to itch, well-being, quality of life, health and treatment satisfaction up to month 12
- To describe baseline demographics and disease characteristics of patients initiated on nemolizumab
- To characterize patterns of nemolizumab use

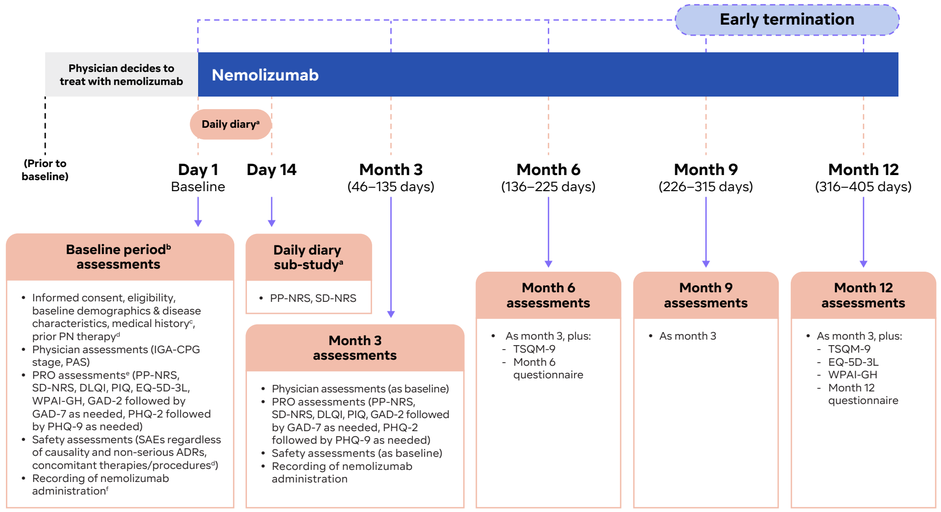
Safety objective

- To evaluate the safety of nemolizumab (incidence of SAEs regardless of causality and non-serious ADRs)

ADR, adverse drug reaction; IGA-CPG, investigator's global assessment-chronic prurigo; PAS, prurigo activity and severity score; PN, prurigo nodularis; PP-NRS, peak pruritus numerical rating scale; PRO, patient-reported outcome; SAE, serious adverse events; SD-NRS, sleep disturbance numerical rating scale

STUDY DESIGN

Figure 1. Study design of RE-UNITE-PN: a prospective, multicenter, non-interventional study



[a]Sub-study in Germany and the UK at selected sites (no clinic visits required); PP-NRS and SD-NRS to be completed by participants remotely every day from day -1 to day 14. Day -1 refers to the 24 hours prior to the first dose of nemolizumab. [b]If more than 4 weeks has elapsed from date of the nemolizumab prescription to date of first injection, the investigator may choose to update the baseline information. [c]General Medical History: All significant ongoing medical conditions will be documented at baseline, including concurrent atopic dermatitis. All significant medical conditions prior to study entry, regardless of date, will be documented. Medical History of Prurigo Nodularis: PN history data to be documented at baseline including date of first symptoms, date of diagnosis, PN-related comorbidities (such as but not limited to atopy, renal disease, diabetes, and any previous known neuropathic disease). [d]Prior and Concomitant Therapy: All prior procedures/ medications received for PN and significant medical history; all current procedures/ medications for PN (including any change in treatment during the study) and for treatment of SAEs regardless of causality and non-serious ADRs; the reasons for discontinuation of prior procedures/ medications for PN should also be documented. [e]Questionnaires should be completed before nemolizumab administration to ensure true baseline values. [f]Nemolizumab dosing should be in accordance with the country-specific package label. Administrations and frequency of dosing that occurs between visits should also be captured.
DLQI, dermatology life quality index; EQ-5D-3L, European quality of life 5-dimensions (3 levels); GAD, generalized anxiety disorder; IGA-CPG, investigator global assessment of chronic prurigo; NRS, numerical rating scale; PAS, prurigo activity and severity score; PHQ, patient health questionnaire; PN, prurigo nodularis; PP, peak pruritus; SD, sleep disturbance; TSQM, treatment satisfaction questionnaire for medication; WPAI-GH, work productivity absenteeism index - general health.

- Approximately 600 participants are planned to be enrolled in ~150 sites in Europe and North America
- The decision to treat with nemolizumab will be made by physicians before enrollment
- No additional visits, procedures, or laboratory tests beyond routine clinical care will be required and visit schedules will follow routine medical practice

METHODS CONT.

STUDY POPULATION

- The decision to treat with nemolizumab will be made by physicians independently of this non-interventional study and before obtaining informed consent

Inclusion criteria

- Aged ≥18 years with moderate-to-severe PN
- All patients newly initiated on nemolizumab treatment as per local label
  - Decision to initiate nemolizumab treatment made to the patient's medical need and the standard of best medical practice prior to study inclusion
- Signed written ICF prior to the start of observational study documentation

Exclusion criteria[a]

- Contraindication to nemolizumab according to the local label
- Treatment with an agent under clinical development/ investigation 3 months prior to baseline
- Previous nemolizumab use
- Patients who are mentally, physically, or linguistically unable to understand the content of the ICF and/or to complete the study questionnaires

[a]An enrollment cap may be applied based on the number of dupilumab-experienced participants.
ICF, informed consent form; PN, prurigo nodularis.

PROTECTION OF PARTICIPANTS

- The study follows all applicable NIS regulations, ethical principles (Declaration of Helsinki), and does not involve procedures beyond routine medical practice; therefore, participation poses no additional risk or immediate medical benefit
- Patients will be informed about data collection, privacy rights, and must provide written informed consent after having time to review information and ask questions; copies of consent and documentation will be maintained
- Participants can withdraw consent at any time without providing reasons and without any impact on their ongoing medical treatment

DATA ANALYSIS AND STATISTICAL METHODS

Sample size

- As a non-interventional study, no formal hypothesis or power calculation is set
- Assumptions for the sample size are based on data from the pivotal phase 3 PN trial, OLYMPIA 1
- A sample size of ~600 patients ensures precise estimates with narrow 95% confidence intervals (CIs) for key outcomes at month 6

Analysis populations

- The primary analysis population is the **All Subjects Treated set (AST)**, defined as all participants who provide informed consent and receive ≥1 dose of nemolizumab
- Analyses will also be performed in the **Full Analysis Set (FAS)**, defined as all participants who provide informed consent, meet the selection criteria, receive ≥1 dose of nemolizumab, and have a baseline assessment and ≥1 post-baseline assessment of IGA-CPG and PP-NRS

Analysis of primary, secondary and exploratory variables

- The primary effectiveness endpoints are:
  - The proportion of patients with IGA-CPG of 0 (clear) or 1 (almost clear) at month 6
  - Change and percent change from baseline in PP-NRS at month 6
- **Dichotomous variables:** Generalized Linear Mixed Model (GLMM) for Repeated Measures including potential confounders as fixed effects will be used for analysis in the AST and FAS. Proportion of responder and 95% CI will be presented by visit
- **Continuous variables:** Mixed Model for Repeated Measures (MMRM) including potential confounders as fixed effects will be used for analysis in the AST and FAS. Estimate of Treatment Time Effect and 95% CI will be presented by visit
- **Ordinal Categorical variables:**
  - **With up to 11 categories:** GLMM for Repeated Measures including potential confounders as fixed effects will be used for analysis in the AST and FAS. Estimate of Treatment Time Effect and 95% CI will be presented by visit
  - **With more than 11 categories:** MMRM including potential confounders as fixed effects will be used for analysis in the AST and FAS. Estimate of Treatment Time Effect and 95% CI will be presented by visit

Safety analysis (adverse event reporting)

- Serious adverse events (AEs; any causality) and non-serious adverse drug reactions (ADRs) will be summarized in the AST using frequency tables, by System Organ Class and Preferred Term based on the Medical Dictionary for Regulatory Activities (version 27.1 or later).
- For any serious AE that occurs during this NIS—regardless of its relationship to treatment or whether it was expected—the investigator is required to take the following actions:
  - Prioritize participant safety by taking prompt and appropriate medical action when necessary
  - Classify and report serious events within 24 hours in the electronic case report form; complete the electronic serious AE form and ensure all related data (demographics, medical history, therapies) are updated
  - Monitor and document the event until resolution or stable outcome, including all follow-up information and maintaining relevant medical records
  - Ensure timely updates to the Sponsor for regulatory compliance; the Sponsor will notify authorities, institutional review boards/ independent ethics committees, and investigators as per country-specific requirements

Quality of life

- Quality of life questionnaires will be summarized by visit in the AST using descriptive statistics or frequency tables as applicable

Handling of missing data

- Data quality depends on site documentation
- Site training and monitoring will minimize missing data and improve source documentation practices
- An electronic data capture system will use automated checks to prevent missing or incorrect entries
- The statistical analysis plan will define statistical methods for handling missing data

Subgroup analyses

- Primary and secondary effectiveness variables will be summarized by visit (in the AST and FAS) in the following subgroups:
  - Age group
  - Gender
  - Race group
  - Fitzpatrick skin type
  - Geographic region
  - Baseline disease severity
  - Previous treatment
  - Concurrent atopic dermatitis (AD), by severity
  - Comorbidities

Interim analyses

- Two interim analyses (descriptive only) are planned:
  - Interim analysis 1 will be conducted when approximately 40% of patients are enrolled
  - Interim analysis 2 will be conducted when all patients are enrolled or approximately 40% of patients have completed the month 6 visit

Study limitations

- As with all real-world studies, confounding may occur if treatment or exposure effects are influenced by other factors (effect modifiers). To minimize confounding, all relevant variables that could impact treatment outcomes will be collected. Effect modifiers will be handled via stratification, subgroup analyses, or regression models

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