Real-world effectiveness and safety of nemolizumab in moderate-to-severe atopic dermatitis: A phase IV, prospective, non-interventional study design from RE-UNITE-AD (NCT06988605)

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OBJECTIVE

- RE-UNITE-AD (NCT06988605) is a prospective, multicenter, non-interventional study (NIS) that aims to enroll approximately 1000 adults/adolescents (across 200 sites in Europe and North America) with moderate-to-severe AD newly initiated on nemolizumab per physician discretion, to complement pivotal trial data. Here we describe the study's design and rationale.

CONCLUSION

- This NIS represents real-world clinical practice and is expected to complement the existing evidence from pivotal trials on the clinical effectiveness and safety of nemolizumab in patients (≥12 years old) with moderate-to-severe AD.

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References:

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INTRODUCTION

- Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by intense itch and eczematous lesions.[1]
- Nemolizumab, an interleukin-31 receptor antagonist, is approved for the treatment of moderate-to-severe AD in ≥12-year-old patients in several countries at an initial dose of 60 mg (two 30 mg injections), followed by 30 mg given every 4 weeks.
- Nemolizumab with background topical therapy has shown efficacy and safety in adults and adolescents with moderate-to-severe AD in two phase 3 AD trials, ARCADIA 1 and ARCADIA 2.[2]
- Controlled trials, however, may not reflect real-world practice, necessitating a study that may better reflect real-world settings beyond the limitations of controlled trials.

METHODS

STUDY OBJECTIVES

Primary objective

- To evaluate real-world effectiveness of nemolizumab in AD as measured by physician assessment (Investigator's Global Assessment [IGA]) and by patient-reported outcomes (PROs; Peak Pruritus Numerical Rating Scale [PP-NRS]) in clinical practice at month 6.

Secondary objective

- To evaluate real-world effectiveness of nemolizumab in AD as measured by physician assessment (Eczema Area and Severity Index [EASI], SCORing Atopic Dermatitis [SCORAD], and IGA) and by PROs (PP-NRS, Average Pruritus Numerical Rating Scale [AP-NRS], Sleep Disturbance Numerical Rating Scale [SD-NRS], and Pain Numerical Rating Scale [Pain NRS]) in clinical practice up to month 12.

Exploratory objectives

- To evaluate real-world effectiveness of nemolizumab in AD as measured by PROs pertaining to itch, well-being, quality of life, and 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.

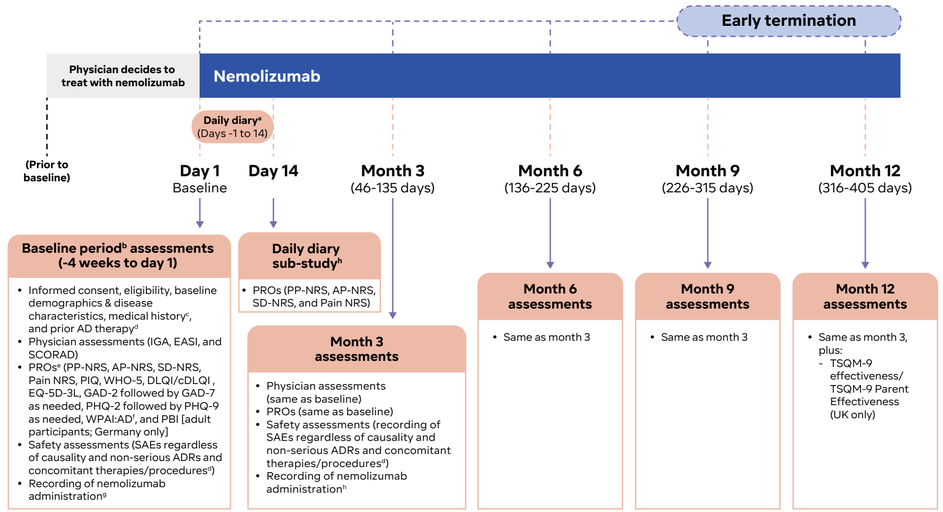
Safety objective

- To evaluate the safety of nemolizumab (incidence of serious adverse events [SAEs] regardless of causality and non-serious adverse drug reactions [ADRs]).

STUDY DESIGN

- 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.

Figure 1. Study design of RE-UNITE-AD: Prospective, multicenter, non-interventional study



AD, atopic dermatitis; ADR, adverse drug reactions; AP-NRS, Average Pruritus Numerical Rating Scale; cDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D-3L, EuroQol 5 Dimensions 3 Levels; ET, early termination; GAD-2/-7, Generalized Anxiety Disorder 2-item/7-item; IGA, Investigator's Global Assessment; NRS, Numerical Rating Scale; PBI, Patient Benefit Index; PHQ-2/-9, Patient Health Questionnaire-2/-9; PIQ, PROMIS® Itch Questionnaires; PP-NRS, Peak Pruritus Numerical Rating Scale; PRO, patient-reported outcome; SAE, serious adverse events; SD-NRS, Sleep Disturbance Numerical Rating Scale; SCORAD, Scoring Atopic Dermatitis; TSQM-9, Treatment Satisfaction Questionnaire for Medication-9; WHO-5, World Health Organization-Five Well-Being Index, WPAI, Work Productivity Absenteeism Index

Visit windows are calculated as days after day 1 (first dose of nemolizumab).[a]Sub-study in Germany and the United Kingdom at selected sites: PP-NRS, AP-NRS, SD-NRS, and Pain NRS will be collected on a daily basis remotely from day 1 to day 14 without in-person visits. Day 1 refers to the 24 hours prior to the first dose of nemolizumab. [b]If more than 4 weeks have elapsed from the date of the nemolizumab prescription to the date of the first injection, the investigator may choose to update the baseline information. [c]General medical history: All significant ongoing medical conditions prior to study entry, regardless of date should be documented at baseline. Medical history of AD: AD history data to be documented at baseline (date of the first symptoms; date of diagnosis; and AD-related comorbidities such as but not limited to other atopy conditions i.e., asthma, allergic rhinitis). [d]Prior and concomitant therapy: All prior procedures/ medications received for AD (including any change in treatment during the study), and for treatment of SAEs regardless of causality and non-serious ADRs must be included; the reasons for discontinuation of prior procedures/ medications for AD should also be documented. [e]Questionnaire should be completed before nemolizumab administration to ensure true baseline values. [f]WPAI in adolescents should consider school absenteeism. [g]Nemolizumab dosing should be in accordance with the country-specific package label. Administrations and frequency of dosing that occur in between visits should also be captured. [h]A sub-study in Germany and the United Kingdom at selected sites (no clinic visits required): PP-NRS, AP-NRS, SD-NRS, and Pain NRS to be completed by participants remotely every day from day 1 to day 14. Day 1 refers to the 24 h prior to the first dose of nemolizumab.

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

- Nemolizumab-treated patients with moderate-to-severe AD aged ≥12 years with
  - Baseline PP-NRS score ≥7 (if previously untreated with a biologic/Janus kinase [JAK] inhibitor) or
  - Baseline PP-NRS score ≥4 (if switching from a biologic/JAK inhibitor; with a minimum 3-month washout period).[a]

Exclusion criteria

- Patients with contraindications to or prior exposure to nemolizumab
- Patients who have received any investigational drug within 3 months prior to baseline.

[a]Approximately 300 participants with previous exposure to biologics or JAK inhibitors to treat AD will be allowed to enroll in the study. When recruitment reaches this number, a communication will be sent to the study sites and the study will halt enrollment of participants with previous exposure to biologics or JAK inhibitors to treat AD. Deviations from this cap may occur to accommodate practical recruitment challenges. In such cases, the study team will document the reasons for it.

PROTECTION OF PARTICIPANTS

- The study follows all applicable NIS regulations and 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, and 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 pooled data from two pivotal phase 3 AD trials, ARCADIA 1 and ARCADIA 2.
- A sample size of approximately 1000 patients ensures precise estimates with narrow 95% confidence intervals (CI) for key outcomes at month 6.

Analysis populations

- The primary analysis population is **All Subjects Treated set (AST)**, defined as all participants who provided informed consent and received ≥1 dose of nemolizumab.
- Analyses will also be performed in the **Full Analysis Set (FAS)**, which includes participants who provided informed consent, met the selection criteria, received ≥1 dose of nemolizumab, and had both a baseline assessment and ≥1 post-baseline assessment of IGA and PP-NRS.

Analysis of primary, secondary and exploratory variables

- **Primary effectiveness variables**:
  - IGA responder proportions will be analyzed in AST and FAS using a generalized linear mixed model (GLMM) for repeated measures including potential confounders as fixed effects. Proportion of responders and 95% CI will be presented at month 6 visit.
  - Change from baseline in PP-NRS will be analyzed in AST and FAS using a mixed model for repeated measures (MMRM) including potential confounders as fixed effects. Estimate of treatment time effect and 95% CI will be presented at month 6 visit.
- **Dichotomous variables:** GLMM for repeated measures including potential confounders as fixed effects will be used for analysis in AST and FAS. Proportion of responders and 95% CI will be presented by visit.
- **Continuous variables:** MMRM including potential confounders as fixed effects will be used for analysis in 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 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 AST and FAS. Estimate of treatment time effect and 95% CI will be presented by visit.

Safety analysis (adverse event reporting)

- Serious adverse events (any causality) and non-serious 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 SAE 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 SAEs within 24 h in the electronic case report form; complete the electronic SAE form and ensure all related data (demographics, medical history, and 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 upon site documentation.
- Site training and monitoring will minimize missing data and improve source documentation practices.
- Electronic data capture system will use automated checks to prevent missing or incorrect entries.
- Statistical Analysis Plan will define statistical methods for handling missing data.

Subgroup analysis

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

Interim analyses

- Two interim analyses are planned to assess the safety and effectiveness of nemolizumab in treating moderate-to-severe AD:
  - 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% 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, and regression models.