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IRB Approved at the
Protocol Level
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Inclusion/Exclusion Criteria

A study for subjects with **moderate-to-severe atopic dermatitis** (AD)

Protocol number: RD.06.SPR.118161
(Version 3.0, 03 October 2019)

Protocol number: RD.06.SPR.118169
(Version 3.0, 03 October 2019)

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Eligibility Criteria

Inclusion Criteria

To be eligible for study entry, subjects must satisfy all of the following inclusion criteria:

1. Male or female subjects aged ≥ 12 years at the screening visit.

Note: Enrollment of subjects aged 12 to 17 years will begin after an IDMC has assessed interim safety data from the phase 2 study (Protocol 116912) and provided recommendations to the sponsor, who will then determine the eligibility of this age group for enrollment in the study. The sponsor will send a written communication to the site confirming that the study is open for enrollment of adolescents. Adolescents must not be enrolled in the study until such communication is received.

2. Chronic AD for at least 2 years before the screening visit, and confirmed according to American Academy of Dermatology Consensus Criteria (see Appendix 1 in the protocol) at the time of the screening visit.

3. EASI score ≥ 16 at both the screening and baseline visits.

4. IGA score ≥ 3 (based on the IGA scale ranging from 0 to 4, in which 3 is moderate and 4 is severe) at both the screening and baseline visits.

5. AD involvement ≥ 10% of body surface area (BSA) at both the screening and baseline visits.

6. Peak (maximum) pruritus NRS score of at least 4.0 at the screening and baseline visit.

Screening PP NRS score will be determined by a single PP NRS assessment (score ranging from 0 to 10) for the 24-hour period immediately preceding the screening visit.

Baseline PP NRS score will be determined based on the average of daily PP NRS scores (score ranging from 0 to 10) during the 7 days immediately preceding baseline (rounding is not permitted). A minimum of 4 daily scores out of the 7 days immediately preceding baseline is required for this calculation.

Inclusion Criteria continued

7. Documented recent history (within 6 months before the screening visit) of inadequate response to topical medications (TCS with or without TCI). All subjects must demonstrate inadequate response to TCS. All subjects who have used TCI within 6 months of the screening visit, or for whom TCI is selected as background therapy for sensitive areas, must also demonstrate inadequate response to TCI. Acceptable documentation includes patient records with information on TCS (with or without TCI) prescription and treatment outcome, or written documentation of the conversation with the subject's treating physician, if different than the investigator. If documentation is inadequate, subjects may be re-screened after such documentation is obtained.

Inadequate response to TCS treatments (with or without TCI) is defined as:

7a. Failure to achieve or maintain remission or low disease activity (equivalent to IGA ≤ 2) despite treatment with a daily regimen of a medium-, high-, or very high-potency TCS (Class I-III according to the US classification) (with or without TCI), applied for at least 4 weeks or for the maximum duration per prescribing information;

or

7b. Requirement of a long-term treatment (> 4 weeks) with a high- or very high-potency TCS (Class I-II according to the US classification) (with or without TCI) to achieve or maintain remission or low disease activity (equivalent to IGA ≤ 2);

or

7c. If documentation of inadequate response to topical treatments is not available, subjects with a documented recent course of systemic treatment or phototherapy for AD (within 6 months before the visit) will also be considered as inadequate responders to topical treatments.

8. Agree to apply a moisturizer throughout the study from the screening visit; agree to apply authorized topical therapy from the screening visit and throughout the study as determined appropriate by the investigator.

9. Female subjects of childbearing potential must agree either to be strictly abstinent throughout the study and for 12 weeks after the last study drug injection, or to use an effective and approved method of contraception throughout the study and for 12 weeks after the last study drug injection. This criterion also applies to a prepubertal female subject who begins menses during the study.

Inclusion Criteria continued

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

- Progestogen-only oral hormonal contraception
- Male or female condom
- Cap, diaphragm, or sponge with spermicide
- Combination of male or female condom with cap, diaphragm, or sponge with spermicide
- Combined (estrogen- and progestogen-containing) oral, intravaginal, or transdermal hormonal contraception
- Injectable or implanted hormonal contraception
- Intrauterine devices
- Bilateral tubal ligation or tube insert (such as the Essure system) at least 3 months before the study
- Vasectomy of partner at least 3 months before the study

10. Female subjects of non-childbearing potential must meet one of the following criteria:

- Absence of menstrual bleeding for 1 year prior to screening without any other medical reason
- Documented hysterectomy or bilateral oophorectomy at least 3 months before screening

11. Subject (and guardian, when applicable) willing and able to comply with all of the time commitments and procedural requirements of the clinical study protocol, including daily diary recordings by the subject using an electronic handheld device provided for this study.

12. Understand and sign an informed consent form (and assent form, when applicable) before any investigational procedure(s) are performed.

Eligibility Criteria

Exclusion Criteria

Subjects will be excluded from the study if 1 or more of the following criteria are applicable:

1. Body weight < 30 kg.

2. Subjects meeting 1 or more of the following criteria at screening or baseline:

2a. Had an exacerbation of asthma requiring hospitalization in the preceding 12 months.

2b. Reporting asthma that has not been well-controlled (ie, symptoms occurring on > 2 days per week, nighttime awakenings > 1-3 times per week, or some interference with normal activities) during the preceding 3 months.

2c. Asthma Control Test ≤ 19 (only for subjects with a history of asthma).

2d. Peak expiratory flow < 80% of the predicted value.

3. Subjects with a current medical history of chronic obstructive pulmonary disease and/or chronic bronchitis.

4. Cutaneous infection within 1 week before the screening visit or any infection requiring treatment with oral or parenteral antibiotics, antivirals, antiparasitics or antifungals within 1 week before the screening visit. Subjects may be rescreened once the infection has resolved.

5. Requiring rescue therapy for AD during the run-in period or expected to require rescue therapy within 2 weeks following the baseline visit.

6. Positive serology results (hepatitis B surface antigen [HBsAg] or hepatitis B core antibody [HBcAb], hepatitis C antibody, or human immunodeficiency virus antibody) at the screening visit.

Note: Subjects with a positive HBcAb and a negative HBsAg can be included in this clinical study if hepatitis B surface antibody is positive (considered immune after a natural infection).

Exclusion Criteria continued

7. Having received any of the following treatments in Table 6 within the specified timeframe before the baseline visit:

Table 6: Prior Treatments

Treatment(s)	Timeframe
Coal tar products	2 weeks
Topical PDE-4 inhibitor	2 weeks
TCIs used in non-permitted areas (eg, trunk, extremities)	2 weeks
Non-authorized TCS	2 weeks
Topical medications, including authorized TCS/TCI, with occlusive dressings (eg, wet wraps)	2 weeks
Systemic corticosteroids (corticosteroid inhalers are permitted)	4 weeks
Phototherapy or tanning beds	4 weeks
Immunosuppressive or immunomodulatory drugs (eg, cyclosporine A, oral tacrolimus, cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil)	4 weeks or 5 half-lives (whichever is longer)
Biologics and their biosimilars (eg, dupilumab, etanercept, adalimumab, infliximab, omalizumab, etc)	8 weeks or 5 half-lives (whichever is longer)
Live attenuated vaccine	12 weeks
Investigational topical or systemic medication (eg, topical or oral JAK inhibitors)	16 weeks
Drugs with a sedative effect such as benzodiazepines, imidazopyridines, barbiturates, or sedative anti-depressants (eg, amitryptiline) (Stable treatment with antihistamines with sedative effect or SSRIs is allowed.)	1 week
Gabapentinoids (eg, gabapentin, pregabalin)	4 weeks
Cannabinoids	2 weeks
Alternative medicine for AD (eg, traditional Chinese medicine)	2 weeks

Abbreviation(s): AD=atopic dermatitis; JAK=Janus kinase; PDE-4=phosphodiesterase-4; SSRI=selective serotonin reuptake inhibitor; TCI=topical calcineurin inhibitor; TCS=topical corticosteroid.
Note: These treatments should not be discontinued for reasons related to this clinical study.

Exclusion Criteria continued

8. Previous treatment with nemolizumab.
9. Subjects who failed to respond clinically to previous treatment with a biologic (eg, dupilumab) or an oral Janus kinase inhibitor.
10. Pregnant women (positive serum pregnancy test result at the screening visit or positive urine pregnancy test at the baseline visit), breastfeeding women, or women planning a pregnancy during the clinical study.
11. History of lymphoproliferative disease or history of malignancy of any organ system within the last 5 years, except for (1) basal cell carcinoma, squamous cell carcinoma in situ (Bowen's disease), or carcinomas in situ of the cervix that have been treated and have no evidence of recurrence in the last 52 weeks before the baseline visit, or (2) actinic keratoses that have been treated and have no evidence of recurrence in the last 12 weeks.
12. History of hypersensitivity (including anaphylaxis) to an immunoglobulin product (plasma-derived or recombinant, eg, monoclonal antibody) or to any of the study drug excipients.
13. History of intolerance to TCS or for whom TCS is not advisable (eg, hypersensitivity, significant skin atrophy).
14. Known active or latent tuberculosis infection.
15. Known or suspected immunosuppression or unusually frequent, recurrent, severe, or prolonged infections as per investigator judgment.
16. History of or current confounding skin condition (eg, Netherton syndrome, psoriasis, cutaneous Tcell lymphoma [mycosis fungoides or Sezary syndrome], contact dermatitis, chronic actinic dermatitis, dermatitis herpetiformis).
17. Any medical or psychological condition or any clinically relevant laboratory abnormalities, such as but not limited to elevated ALT or AST ($> 3 \times$ upper limit of normal [ULN]) in combination with elevated bilirubin ($> 2 \times$ ULN), at the screening visit that may put the subject at significant risk according to the investigator's judgment, if he/she participates in the clinical study, or may interfere with study assessments (eg, poor venous access or needle-phobia).

Exclusion Criteria continued

18. Planned or expected major surgical procedure during the clinical study.

19. Subjects unwilling to refrain from using prohibited medications during the clinical study (see Section 8.4.9.2 in protocol).

20. Currently participating or participated in any other study of a drug or device, within the past 3 months before the screening visit, or is in an exclusion period (if verifiable) from a previous study.

21. History of alcohol or substance abuse within 2 years of the screening visit.

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