IMSIDOLIMAB

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Imsidolimab (ANB019) in the Treatment of Adult Subjects with Generalized Pustular Psoriasis

Protocol Number: ANB019-301

Phase: III

Investigational New Drug (IND) Number: 136145

European Clinical Trials Database (EudraCT) Number: 2021-001447-27

NCT Number: NCT05352893

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Clinical Study Protocol

09 December 2022

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Imsidolimab (ANB019) in the Treatment of Adult Subjects with Generalized Pustular Psoriasis

Short Title: Efficacy and Safety of Imsidolimab in Subjects with Generalized Pustular Psoriasis

Study Description: This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of imsidolimab compared with placebo in adult subjects with generalized pustular psoriasis (GPP). This study will also characterize the pharmacokinetic (PK) profile of imsidolimab and explore the immunogenicity of imsidolimab in subjects with GPP.

Written informed consent will be obtained from each subject prior to initiating any study-related procedures. Subjects will also provide consent for skin biopsies and blood sample collection for genetic testing if they wish to participate in these tests.

To be eligible for the study, subjects will need to have a confirmed diagnosis of GPP (as described in Section 5.1) at the initial Screening and Day 1. Subject can enter the initial Screening regardless of their current GPP severity. However, subjects must be experiencing a GPP flare of moderate to severe intensity (as defined by a body surface area [BSA] affected with pustules [excluding palms and soles] of at least 5%, a Generalized Pustular Psoriasis Physician's Global Assessment [GPPPGA] score of at least 3 [moderate severity], and a Pustulation Rating Scale [PRS] score of at least 3 [moderate severity]) on Day 1 (refer to Section 5.1, Inclusion Criterion 3). Randomization will be stratified based on GPP severity on Day 1, as evaluated by GPPPGA score (3 [moderate] vs 4 [severe]).

The duration of Screening and the number and timing of screening visits may vary depending on the clinical course of each subject during the screening period, but screening visits should occur at least once every 6 months. Subjects who enter the study in a nonflaring state and/or have a GPP severity that does not meet the requirements of Inclusion Criterion 3 (refer to Section 5.1) will typically complete a Part 1a screening visit only, then have their clinical status and GPP severity monitored and reassessed periodically at Unscheduled Flare Assessment visits and/or Screening Part 1b visits during the screening period. Refer to Section 5.4 for additional details on monitoring for flares. Once a subject is in flare during the screening period, all Screening Part 2 visit assessments must be performed within 30 days prior to Day 1 (refer to Section 1.3).

Subjects who enter the study with a GPP severity that meets the requirements of

Inclusion Criterion 3 (refer to Section 5.1), may complete both Part 1a and Part 2 of Screening as rapidly as possible, including combining Screening Part 1a and Part 2 activities into a single visit (Part 1b is not necessary in this case).

Subjects who are experiencing a flare of GPP during Screening that does not meet the severity criteria (refer to Section 5.1, Inclusion Criterion 3) at a Part 1a, Part 1b, or Unscheduled Flare Assessment visit may complete Part 2 assessments at that time if the investigator is of the opinion that they are very likely to meet the severity criteria within a 30-day window based on their individual prior clinical GPP activity history and typical recurrent flare profile.

If more than 30 days have elapsed since the Screening Part 2 assessments were performed or if a subject completes all Screening Part 2 assessments but cannot be randomized within a 30-day window due solely to not meeting Inclusion Criterion 3 (refer to Section 5.1), the subject may remain in Screening, but upon subsequent flare, all Screening Part 2 assessments must be repeated at Unscheduled Visit(s) within a 30-day window prior to randomization on Day 1. All Unscheduled Part 2 visits and randomization must occur within the 18-month Screening period.

Once all screening activities have been completed, and if all inclusion criteria and no exclusion criteria are met, subjects will be randomized and administered treatment on Day 1. On Day 1, eligible subjects will be randomized in a 1:1:1 ratio to receive a single intravenous (IV) dose of imsidolimab 750 mg, imsidolimab 300 mg, or placebo. Following the end of IV administration on Day 1, subjects will leave the study site after completing the 2-hour postinfusion observation period. The primary endpoint will be evaluated on Day 29 (Week 4).

At the Day 29 (Week 4) visit, after completing the 4-week treatment period, subjects will be offered the opportunity to exit the study and rollover into the long-term extension study ANB019-302 or complete the safety follow-up period and then exit the study. In addition, starting on Day 8 (Week 1), subjects who have worsened or not improved (as specified in Section 6.5.3) will be offered the opportunity to exit the study and rollover into the long-term extension study ANB019-302 where they will receive rescue medication. Subjects not consenting to participate in the long-term extension study ANB019-302 will only be asked to return for a final safety follow-up visit (Day 85 [Week 12] / early termination [ET] visit) 12 weeks after they received their IV study treatment dose.

Once all screening activities have been completed, and if all inclusion criteria and no exclusion criteria are met, subjects may be randomized on Day 1. Subjects will come to the study site on up to 7 occasions to assess disease activity, PK, and safety: Day 1, Day 3, Day 8 (Week 1), Day 15 (Week 2), Day 29 (Week 4), Day 57 (Week 8), and Day 85 (Week 12) / ET visits. Following the Day 1 visit, unscheduled visit(s) may be utilized to determine if subjects require rescue medication. On Day 1, following the end of the

IV administration, subjects will leave the study site after completing the 2-hour postinfusion observation period. All procedures will be conducted in accordance with the Schedule of Activities (SoA) in Section 1.3. Of note, the primary endpoint will be evaluated on Day 29 (Week 4).

Disease activity will be evaluated for all subjects using the GPPPGA, PRS, modified Japanese Dermatology Association (mJDA) severity index, Clinical Global Impression (CGI), Generalized Pustular Psoriasis Area and Severity Index (GPPASI), total BSA affected with GPP, BSA affected with pustules (excluding palms and soles), Clinician Global Impression of Change (CGI-C), pain Numeric Rating Scale (NRS), Dermatology Life Quality Index (DLQI), Euro Quality of Life 5 Dimensions 5 Levels (EQ-5D-5L), Patient Global Impression of Severity (PGI-S), Patient Global Impression of Bother (PGI-B), Patient Global Impression of Change (PGI-C), Subject Satisfaction Questionnaire (SSQ), Subject Satisfaction Rating Scale (SSRS), and Psoriasis Area Severity Index (PASI) (if plaque psoriasis is present on Day 1).

Safety assessments will include adverse event (AE)/serious adverse event (SAE) monitoring, vital signs, physical examination, electrocardiograms (ECGs), and clinical laboratory tests (hematology, biochemistry, and urinalysis).

Blood samples to determine PK and immunogenicity (presence of anti-drug antibodies [ADA] to imsidolimab) will be collected on Day 1 before the administration of the study treatment and at other time points as specified in the SoA (Section 1.3). Optional blood samples for genetic testing will be collected on Day 1 before the administration of the study treatment (for analysis of deoxynucleic acid [DNA] and messenger ribonucleic acid [mRNA] expression), and at other time points as specified in the SoA, if applicable. Tape strips and optional skin biopsies for biomarker analysis will be collected at the time points specified in the SoA. All subjects randomized in the study will be asked to participate in the blood sample collection for genetic testing and skin biopsies; however, the subject's participation is optional. In addition, standardized photographs will be taken of flaring subjects to document the GPP severity at the time points specified in the SoA.

Objectives:

Primary Objective:

- To evaluate the efficacy of imsidolimab compared with placebo in subjects with GPP flare

Secondary Objective:

- To assess the safety of imsidolimab in subjects with GPP flare

Exploratory Objectives:

- To explore the effect of imsidolimab on biomarkers
- To explore GPP-associated mutations and additional pharmacogenomic analysis

- To evaluate the PK of imsidolimab in subjects with GPP flare
- To evaluate the immunogenicity of imsidolimab
- To evaluate the effect of imsidolimab on plaque psoriasis, for subjects with concurrent plaque psoriasis at Baseline

Endpoints: Primary Efficacy Endpoint:

- Proportion of subjects achieving a GPPPGA score of 0 (clear) or 1 (almost clear) at Week 4

Key Secondary Efficacy Endpoint:

- Proportion of subjects achieving a PRS score of 0 (clear) or 1 (almost clear) at Week 1

Additional Secondary Efficacy Endpoints:

- Proportion of subjects achieving at least a 2-grade decrease from Baseline in GPPPGA score at Week 4
- Proportion of subjects achieving clinical response on the CGI scale at Week 4. Clinical response is defined as "Very much improved," "Much improved," and "Minimally improved" on the CGI scale according to the mJDA severity index total score
- Change from Baseline in BSA affected with erythema with pustules as assessed by the mJDA severity index at Week 1
- Percent change from Baseline in BSA affected with erythema with pustules as assessed by the mJDA severity index at Week 1
- Change from Baseline in BSA affected with erythema with pustules as assessed by the mJDA severity index at Week 4
- Percent change from Baseline in BSA affected with erythema with pustules as assessed by the mJDA severity index at Week 4
- Change from Baseline in BSA affected with total erythema as assessed by the mJDA severity index at Week 4
- Percent change from Baseline in BSA affected with total erythema as assessed by the mJDA severity index at Week 4
- Change from Baseline in BSA affected with edema as assessed by the mJDA severity index at Week 4
- Percent change from Baseline in BSA affected with edema as assessed by the mJDA severity index at Week 4
- Proportion of subjects achieving an improvement of 50% from Baseline in GPPASI (GPPASI 50) at Week 4
- Proportion of subjects achieving an improvement of 75% from Baseline in GPPASI (GPPASI 75) at Week 4
- Change from Baseline in DLQI at Week 4
- Change from Baseline in EQ-5D-5L at Week 4
- Proportion of subjects with at least a 3-point decrease from Baseline in pain NRS at Week 4 for subjects with a Baseline pain NRS of at least 3

Safety Endpoint:

- Incidence of AEs, SAEs, and AEs leading to withdrawals, as well as changes in vital signs, clinical laboratory parameters (hematology, biochemistry, and urinalysis), and 12-lead ECGs

Exploratory Efficacy Endpoints:

- Proportion of subjects achieving a GPPPGA score of 0 (clear) or 1 (almost clear) at visits other than Week 4
- Proportion of subjects with at least a 2-point decrease from Baseline in GPPPGA score at visits other than Week 4
- Change from Baseline in GPPPGA at each visit
- Proportion of subjects achieving a PRS score of 0 (clear) or 1 (almost clear) at visits other than Week 1
- Proportion of subjects with at least a 2-point decrease from Baseline in PRS score at each visit
- Change from Baseline in PRS at each visit
- Proportion of subjects in each response category for the CGI-C at each visit
- Change from Baseline in mJDA severity index total score (sum of skin lesion total score and systemic manifestation and laboratory findings total score) at each visit
- Change from Baseline in skin lesion total score (sum of erythema with pustules, total erythema, and edema scores) of the mJDA severity index at each visit
- Change from Baseline in individual scores of erythema with pustules, erythema total, and edema of the mJDA severity index at each visit
- Change from Baseline in BSA affected with erythema with pustules as assessed by the mJDA severity index at visits other than Week 1 and Week 4
- Percent change from Baseline in BSA affected with erythema with pustules as assessed by the mJDA severity index at visits other than Week 1 and Week 4
- Change from Baseline in BSA affected with total erythema as assessed by the mJDA severity index at visits other than Week 4
- Percent change from Baseline in BSA affected with total erythema as assessed by the mJDA severity index at visits other than Week 4
- Change from Baseline in BSA affected with edema as assessed by the mJDA severity index at visits other than Week 4
- Percent change from Baseline in BSA affected with edema as assessed by the mJDA severity index at visits other than Week 4
- Change from Baseline in total score of systemic manifestations and laboratory findings (sum of fever, white blood cell [WBC] count, C-reactive protein [CRP], serum albumin scores) of the mJDA severity index at each visit
- Change from Baseline in individual scores of systemic manifestations and laboratory findings (fever, WBC count, CRP, serum albumin) of the mJDA

severity index at each visit
- Proportion of subjects that achieve normalization of mJDA systemic manifestations and laboratory findings (fever, WBC count, CRP, serum albumin)
- Change from Baseline in absolute values of systemic manifestations and laboratory findings as assessed by the mJDA severity index at each visit
- Percent change from Baseline in absolute values of systemic manifestations and laboratory findings as assessed by the mJDA severity index at each visit
- Proportion of subjects achieving clinical response on the CGI scale according to the mJDA severity index at visits other than Week 4
- Proportion of subjects achieving GPPASI 50 at visits other than Week 4
- Proportion of subjects achieving GPPASI 75 at visits other than Week 4
- Change from Baseline in GPPASI at each visit
- Percent change from Baseline in GPPASI at each visit
- Change from Baseline in total BSA affected with GPP at each visit
- Percent change from Baseline in total BSA affected with GPP at each visit
- Change from Baseline in BSA (excluding palms and soles) affected with pustules at each visit
- Percent change from Baseline in BSA (excluding palms and soles) affected with pustules at each visit
- Change from Baseline in DLQI at visits other than Week 4
- Change from Baseline in EQ-5D-5L at visits other than Week 4
- Change from Baseline in pain NRS at each visit
- Percent change from Baseline in pain NRS at each visit
- Proportion of subjects with at least a 3-point decrease from Baseline in pain NRS at visits other than Week 4 for subjects with a Baseline pain NRS of at least 3
- Proportion of subjects with at least 4-point decrease from Baseline in pain NRS at each visit for subjects with a Baseline pain NRS of at least 4
- Proportion of subjects in each response category for each question for the PGI-S at each visit
- Proportion of subjects in each response category for the PGI-B at each visit
- Proportion of subjects in each response category for the PGI-C at each visit
- Proportion of subjects achieving a “None” or “Mild” for each question in the PGI-S at each visit
- Proportion of subjects achieving “A little bothered” or “Not bothered at all” for the PGI-B at each visit
- Proportion of subjects achieving “A little better,” “Better” or “Much better” for the PGI-C at each visit
- Proportion of subjects in each response category for the SSQ at each visit
- Proportion of subjects achieving “slightly satisfied”, “somewhat satisfied” or “extremely satisfied” for the SSQ at each visit
- Proportion of subjects in each response category for the SSRS at Week 1, Week 4, and Week 12

- Proportion of subjects achieving "slightly satisfied", "somewhat satisfied" or "extremely satisfied" for the SSRS at Week 1, Week 4, and Week 12
- Proportion of subjects requiring rescue medication

Other Exploratory Endpoints:

- Skin tape strip biomarkers analysis
- Optional skin biopsy biomarkers analysis
- Optional blood genetic testing: DNA and mRNA
- Serum concentration of imsidolimab following IV administration to evaluate PK
- Presence of ADA to imsidolimab
- Change from Baseline in PASI (for subjects with concurrent plaque psoriasis at Baseline) at each visit

Study Population: Approximately 45 male and female subjects, aged 18 to 80 years, will be randomized in this study. To be eligible for the study, subjects will need to have a confirmed diagnosis of GPP (as described in Section 5.1) at Screening and Day 1. Subjects can enter initial Screening regardless of their current GPP severity. However, subjects must be experiencing a GPP flare of moderate to severe intensity (as defined by a BSA affected with pustules [excluding palms and soles] of at least 5%, a GPPPGA score of at least 3 [moderate severity], and a PRS score of at least 3 [moderate severity]) on Day 1.

Phase: 3

Study Sites Enrolling Subjects: Up to 80 study sites located globally are expected to participate in this study.

Description of Study Treatments: Imsidolimab will be provided in a glass vial as a sterile, colorless to yellow, and clear to slightly opalescent solution for injection. The placebo contains no active ingredient and will be provided as a sterile, colorless to yellow, and clear to slightly opalescent solution for injection.

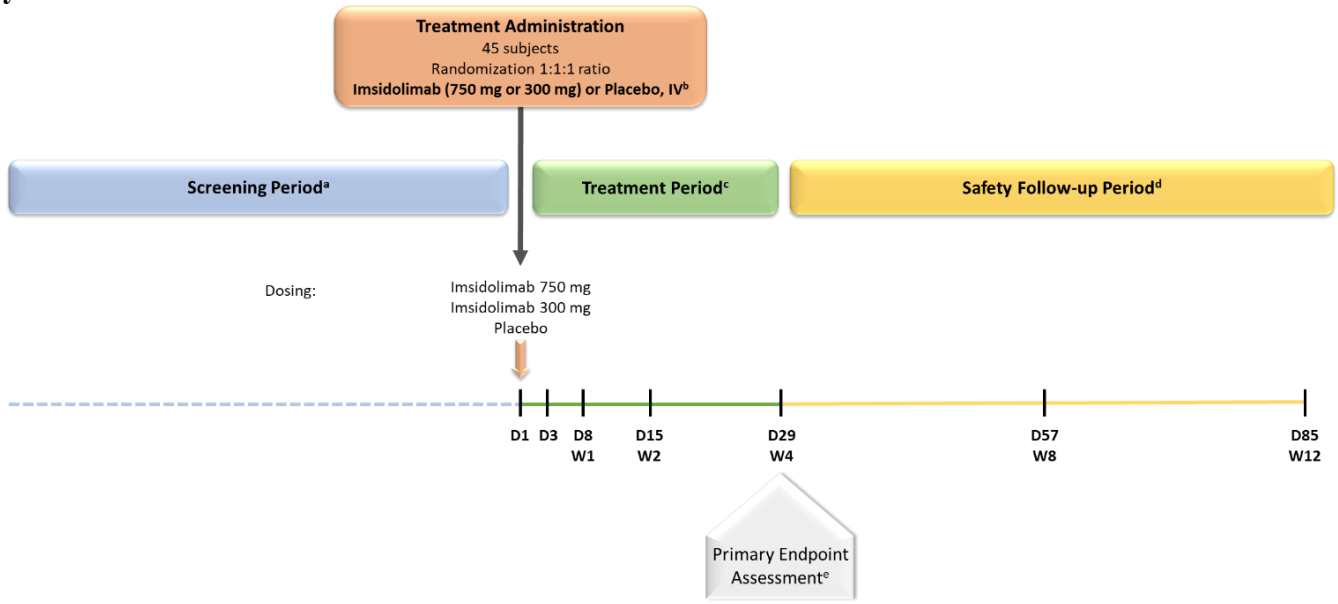
On Day 1, eligible subjects will be randomized in a 1:1:1 ratio to receive a single IV dose of imsidolimab 750 mg, imsidolimab 300 mg, or placebo, administered by infusion (1-hour duration) in polyvinyl chloride or polyolefin bags following dilution to a total volume of 100 mL with 0.9% sodium chloride.

Rescue Medication: The use of rescue medication should be delayed, if possible, for at least 1 week following administration of study treatment. Starting at Day 8 (Week 1), subjects who have demonstrated worsening or no improvement in their disease as evidenced by (1) worsening or no improvement in GPPPGA score and (2) worsening or no improvement in PRS score will be offered the opportunity to exit the study and rollover into the long-term extension study ANB019-302 where they will receive rescue medication.

	Subjects who receive rescue medication prior to the Day 8 (Week 1) visit assessments will not be eligible to rollover into the long-term extension study ANB019-302. They will be asked to return for a final safety follow-up visit (Day 85 (Week 12) / ET visit) 12 weeks after they received their IV study treatment dose.
Subject Duration:	The maximum study duration per subject included in this placebo-controlled study is up to approximately 21 months from Screening to last visit. The screening period may last up to 18 months. The screening period will be followed by a 4-week treatment period and 8-week safety follow-up period.

1.2 SCHEMA

Figure 1: Study Schema



Abbreviations: D, day; ET, early termination; IV, intravenous; W, week.

[a] The screening period may last up to 18 months, but the duration of Screening and the number and timing of screening visits may vary. Once a subject is in flare, all Screening Part 2 visit assessments must be performed within 30 days prior to Day 1 (refer to Section 1.3). If more than 30 days have elapsed since the Screening Part 2 assessments were performed or if a subject completes all Screening Part 2 assessments but cannot be randomized within a 30-day window due solely to not meeting Inclusion Criterion 3 (refer to Section 5.1), the subject may remain in Screening, but upon subsequent flare, all Screening Part 2 assessments must be repeated at Unscheduled Visit(s) within a 30-day window prior to randomization on Day 1. All Unscheduled Part 2 visits and randomization must occur within the 18-month Screening period.

[b] On Day 1, eligible subjects will be randomized in a 1:1:1 ratio to receive a single IV dose of imsidolimab 750 mg, imsidolimab 300 mg, or placebo.

[c] At the Day 29 (Week 4) visit, after completing the 4-week treatment period, subjects will be offered the opportunity to exit the study and rollover into the long-term extension study ANB019-302 or complete the safety follow-up period and then exit the study. In addition, starting on Day 8 (Week 1), subjects who have worsened or not improved will be offered the opportunity to exit the study and rollover into the long-term extension study ANB019-302 where they will receive rescue medication. Subjects not consenting to participate in the long-term extension study ANB019-302 will only be asked to return for a final safety follow-up visit (Day 85 [Week 12] / ET visit) 12 weeks after they received their IV study treatment dose. Subjects who receive rescue medication prior to the Day 8 (Week 1) visit assessments will not be eligible to rollover into the long-term extension study ANB019-302. They will be asked to return for a final safety follow-up visit (Day 85 [Week 12] / ET visit) 12 weeks after they received their IV study treatment dose.

[d] For subjects not rolling over into the long-term extension study ANB019-302 only.

[e] The primary endpoint will be evaluated on Day 29 (Week 4).