IMSIDOLIMAB

A Phase 3, Long-Term Extension Study to Evaluate the Safety and Efficacy of Imsidolimab (ANB019) in the Treatment of Adult Subjects with Generalized Pustular Psoriasis

Protocol Number: ANB019-302

Phase: III

Investigational New Drug (IND) Number: 136145

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Clinical Study Protocol

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: A Phase 3, Long-Term Extension Study to Evaluate the Safety and Efficacy of Imsidolimab (ANB019) in the Treatment of Adult Subjects with Generalized Pustular Psoriasis

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

Study Description: This is a Phase 3, long-term extension study to evaluate the safety and efficacy of imsidolimab in adult subjects with generalized pustular psoriasis (GPP). This study will also evaluate the pharmacokinetics (PK) of imsidolimab and explore the immunogenicity of imsidolimab in subjects with GPP.

To be eligible for this study, subjects must have participated in the preceding placebo-controlled Phase 3 study ANB019-301. In addition, subjects will be allowed to enter this long-term extension study if one of the following criteria is met:

- If they completed at least the Week 1 visit of the ANB019-301 study without the use of rescue/prohibited medication for GPP and needed rescue medication starting at Week 1 or later during the ANB019-301 study; or
- If they completed the Week 4 visit of the ANB019-301 study, and did not need or use rescue/prohibited medication for GPP during their entire participation in the ANB019-301 study.

The Day 1 visit of this study should ideally occur on the same day as the final study visit of the ANB019-301 study, in which case, subjects will enter this study directly after all assessments of the final ANB019-301 study visit are completed. Assessments that are common to both studies will be performed only once if the visits are on the same day. If scheduled on two separate days, the Day 1 visit of this study should occur no later than 1 week after completing the final study visit of the ANB019-301 study. No screening visit is required for this study.

During the treatment period, subjects will receive the treatment based on their status upon entry into this study (additional details of treatment administration are provided in Table 2):

- **Responders:** subjects who completed the Week 4 visit of the ANB019-301 study and have a Generalized Pustular Psoriasis Physician's Global Assessment (GPPPGA) score of 0 (clear) or 1 (almost clear) on Day 1 of this study.
  - o Randomized in a 1:1 ratio to receive a subcutaneous (SC) dose of imsidolimab 200 mg or placebo every 4 weeks starting on Day 1.

- **Partial responders:** subjects who completed the Week 4 visit of the ANB019-301 study but do not have a GPPPGA score of 0 (clear) or 1 (almost clear) on Day 1 of this study.
  - Will receive a SC dose of imsidolimab 200 mg every 4 weeks starting on Day 1.
- **Need for rescue therapy:** Subjects who exited the ANB019-301 study starting at the Week 1 visit (after evaluation of primary endpoint) or later to receive rescue therapy in this study.
  - Subjects who received placebo in the ANB019-301 study and need rescue therapy will receive an intravenous (IV) dose of imsidolimab 750 mg on Day 1, followed by a SC dose of imsidolimab 200 mg every 4 weeks.
  - Subjects who received imsidolimab in the ANB019-301 study will be treated on Day 1 at the discretion of the Investigator with any available therapy (such as retinoids, cyclosporine, methotrexate, corticosteroids, or other appropriate therapy).

Of note, the final treatment dose will be administered on Day 1009 (Week 144). The treatment period ends at the Day 1037 (Week 148) visit and will be followed by a safety follow-up period.

For scheduled onsite study visits, subjects will come to the study site to monitor safety and changes in disease activity on Day 1, Day 3 (applicable only for subjects receiving an IV dose on Day 1), Day 8 (Week 1) (applicable only for subjects receiving an IV dose on Day 1), Day 15 (Week 2), and Day 29 (Week 4), and then every 4 weeks during the treatment period. After Day 1037 (Week 148) visit (end of treatment [EOT]), subjects will enter the safety follow-up period and will be asked to come at Day 1065 (Week 152) and Day 1093 (Week 156 / end of study [EOS]) visits. Of note, subjects who were assigned to imsidolimab in the ANB019-301 study and receive other rescue therapy on Day 1 of this study will be asked to return for a final safety follow-up visit 12 weeks after receiving their study treatment dose in the ANB019-301 study. In this case, assessments described for the Day 1093 (Week 156) visit will be performed. In case of early termination (ET) during the study, subjects will be asked to come for an ET visit 12 weeks after their final study treatment dose. All procedures will be conducted in accordance with the Schedule of Activities (SoA) in Section 1.3.

In case an IV dose is administered, subjects will be allowed to leave the study site beginning 2 hours after the end of IV administration (end of the infusion) and with the Investigator's approval. In case of SC administration(s), subjects will be permitted to leave the study site 15 minutes after each SC administration and with the Investigator's approval.

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).

Disease activity will be evaluated for all subjects using GPPPGA, Pustulation Rating Scale (PRS), modified Japanese Dermatology Association (mJDA) severity index, Clinical Global Impression (CGI), Clinician Global Impression of Change (CGI-C), Generalized Pustular Psoriasis Area and Severity Index (GPPASI), total body surface area (BSA) affected with GPP, BSA affected with pustules (excluding palms and soles), 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 concurrent plaque psoriasis is present on Day 1 of the ANB019-301 study).

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 analysis of messenger ribonucleic acid (mRNA) expression will be collected at Day 169 (Week 24) visit. In addition, standardized photographs will be taken to document study outcome at the time points specified in the SoA.

Objectives: Primary Objective:

- To evaluate the long-term safety of imsidolimab in subjects with GPP who have participated in the ANB019-301 study

Secondary Objective:

- To evaluate the long-term efficacy of imsidolimab in subjects with GPP who have participated in the ANB019-301 study

Exploratory Objectives:

- To evaluate the PK of imsidolimab in subjects with GPP
- To evaluate the immunogenicity of imsidolimab
- To perform pharmacogenomic analysis
- To evaluate the effect of imsidolimab on plaque psoriasis, for subjects with concurrent plaque psoriasis on Day 1 of the ANB019-301 study

Endpoints: Safety Endpoints:

- 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

Secondary Efficacy Endpoints:

- Proportion of subjects with zero recurrence of GPP flare (defined by a GPPPGA ≥ 3 [moderate] in subjects who had previously achieved a GPPPGA score of 0 [clear] or 1 [almost clear]) through Week 24
- Proportion of subjects in remission (defined by a GPPPGA score of 0 [clear] or 1 [almost clear]) at Week 24, without intake of any rescue medications during the treatment period
- Time to first GPP flare recurrence
- Proportion of subjects with a GPPPGA score of 0 (clear) or 1 (almost clear) at Week 24
- Proportion of subjects with a PRS score of 0 (clear) or 1 (almost clear) at Week 24
- Time to first pustulation flare recurrence (defined by a PRS ≥ 3 [moderate] in subjects who had previously achieved a PRS score of 0 [clear] or 1 [almost clear])
- Proportion of subjects with a clinical response on the CGI scale at Week 24. Clinical response is defined as "Very much improved," "Much improved," and "Minimally improved" on CGI scale according to the mJDA severity index total score
- Proportion of subjects losing clinical response on the CGI scale (defined as subjects who had previously achieved clinical response defined as "minimally improved" or better on CGI scale according to the mJDA severity index total score and worsen to either "no change" or "worsened" on the CGI scale) at Week 24
- Change from Baseline in BSA affected with erythema with pustules as assessed by the mJDA severity index at Week 24
- Percent change from Baseline in BSA affected with erythema with pustules as assessed by the mJDA severity index at Week 24
- Change from Baseline in BSA affected with total erythema as assessed by the mJDA severity index at Week 24
- Percent change from Baseline in BSA affected with total erythema as assessed by the mJDA severity index at Week 24

Exploratory Efficacy Endpoints:

- Proportion of subjects with zero recurrence of GPP flare (defined by a GPPPGA ≥ 3 [moderate] in subjects who had previously achieved a GPPPGA score of 0 [clear] or 1 [almost clear]) through Week 52, Week 104, Week 148, and Week 156
- Proportion of subjects in remission (defined by a GPPPGA score of 0 [clear] or 1 [almost clear]) at Week 52, Week 104, Week 148, and Week 156, without intake of any rescue medications during the treatment period
- Proportion of subjects with a GPPPGA score of 0 (clear) or 1 (almost clear) at each visit except Week 24

- Proportion of subjects with a PRS score of 0 (clear) or 1 (almost clear) at each visit except Week 24
- Proportion of subjects with a clinical response on the CGI scale at each visit except Week 24. Clinical response is defined as "Very much improved," "Much improved," and "Minimally improved" on CGI scale according to the mJDA severity index total score
- Proportion of subjects losing clinical response on the CGI scale (defined as subjects who had previously achieved clinical response defined as "minimally improved" or better on CGI scale according to the mJDA severity index total score and worsen to either "no change" or "worsened" on the CGI scale) at each visit except Week 24
- Change from Baseline in BSA affected with erythema with pustules as assessed by the mJDA severity index at each visit except Week 24
- Percent change from Baseline in BSA affected with erythema with pustules as assessed by the mJDA severity index at each visit except Week 24
- Change from Baseline in BSA affected with total erythema as assessed by the mJDA severity index at each visit except Week 24
- Percent change from Baseline in BSA affected with total erythema as assessed by the mJDA severity index at each visit except Week 24
- Change from Baseline in BSA affected with edema as assessed by the mJDA severity index at each visit
- Percent change from Baseline in BSA affected with edema as assessed by the mJDA severity index at each visit
- Proportion of subjects with at least 3-point decrease from Baseline in pain NRS at each visit for subjects with a Baseline pain NRS of at least 3
- Change from Baseline in GPPPGA score at each visit
- Proportion of subjects with at least a 2-point decrease from Baseline in GPPPGA score at each visit
- Time to loss of response (defined by a GPPPGA score of $\geq$ 2 [mild] in subjects who had previously achieved a GPPPGA score of 0 [clear] or 1 [almost clear])
- Proportion of subjects with a maintenance of effect (defined by a GPPPGA score 0 [clear] or 1 [almost clear] at Week 24, Week 52, Week 104 and Week 148 in subjects who had previously achieved a GPPPGA score of 0 [clear] or 1 [almost clear])
- Change from Baseline in PRS score at each visit
- Proportion of subjects with at least a 2-point decrease from Baseline in PRS score at each visit
- Change from Baseline in mJDA severity index total score (sum of skin lesion total score and systemic manifestation 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, total erythema, and edema of the mJDA severity index at each visit

- 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) 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
- 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 in each response category for the CGI-C at each visit
- Proportion of subjects achieving an improvement of 50% from Baseline in GPPASI (GPPASI 50) at each visit
- Proportion of subjects achieving an improvement of 75% from Baseline in GPPASI (GPPASI 75) at each visit
- Time to loss of 50% of GPPASI improvement from Baseline in subjects who achieved GPPASI 75
- Change from Baseline in GPPPASI at each visit
- Percent change from Baseline in GPPPASI 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 pustule at each visit
- Percent change from Baseline in BSA (excluding palms and soles) affected with pustule at each visit
- Change from Baseline in EQ-5D-5L at Week 12, Week 24, Week 52, Week 104, Week 148 and Week 156
- Change from Baseline in DLQI at Week 12, Week 24, Week 52, Week 104, Week 148, and Week 156
- 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 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 12, Week 24, Week 52, Week 104, Week 148 and Week 156
- Proportion of subjects achieving "slightly satisfied", "somewhat satisfied" or "extremely satisfied" for the SSRS at Week 12, Week 24, Week 52, Week 104, Week 148 and Week 156
- Proportion of subjects receiving topical rescue medication from Week 16 to Week 24, Week 16 to Week 52, Week 16 to Week 104, Week 16 to Week 148, and Week 16 to Week 156

Other Exploratory Endpoints:

- Serum concentration of imsidolimab following administration to evaluate PK
- Presence of ADA to imsidolimab
- Optional blood genetic testing: mRNA
- Change from Baseline in PASI (for subjects with concurrent plaque psoriasis on Day 1 of the ANB019-301 study) at each visit
- Proportion of subjects achieving an improvement of 50% from Baseline in PASI (PASI 50) (for subjects with concurrent plaque psoriasis on Day 1 of the ANB019-301 study) at each visit
- Proportion of subjects achieving an improvement of 75% from Baseline in PASI (PASI 75) (for subjects with concurrent plaque psoriasis on Day 1 of the ANB019-301 study) at each visit

Study Population: Male and female subjects who participated in the ANB019-301 study will be allowed to enter in this study, if one of the following criteria is met:

- If they completed at least the Week 1 visit of the ANB019-301 study without the use of rescue/prohibited medication for GPP and needed rescue medication starting at Week 1 or later during the ANB019-301 study; or
- If they completed the Week 4 visit of the ANB019-301 study, and did not need or use rescue/prohibited medication for GPP during their entire participation in the ANB019-301 study.

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 either IV infusion or SC injection. The placebo contains no active ingredient and will be provided as a sterile, colorless to yellow, and clear to slightly opalescent solution for SC injection.

Imsidolimab may be administered as follows:

- IV dose of imsidolimab 750 mg (1-hour infusion duration) in polyvinyl chloride or polyolefin bags following dilution to a total volume of 100 mL with 0.9% sodium chloride; or
- SC dose of imsidolimab 200 mg.

Placebo may also be administered as SC dose in the same volume as imsidolimab.

During the treatment period, eligible subjects will receive the treatment as described below depending on the study status on Day 1 (refer to Section 4.1 for additional details on subject's status and Section 6.1.2 for additional details on treatment administration):

- Responders will be randomized in a 1:1 ratio to receive a SC dose of imsidolimab 200 mg or placebo every 4 weeks starting on Day 1;
- Partial responders will receive a SC dose of imsidolimab 200 mg every 4 weeks starting on Day 1;
- Subjects who received placebo in the ANB019-301 study and need rescue therapy will receive an IV dose of imsidolimab 750 mg on Day 1, followed by a SC dose of imsidolimab 200 mg every 4 weeks;
- Subjects who received imsidolimab in the ANB019-301 study and need rescue therapy will be treated on Day 1 at the discretion of the Investigator with any available therapy (such as retinoids, cyclosporine, methotrexate, corticosteroids, or other appropriate therapy).

Rescue Medication:

In case of flare (defined by GPPPGA ≥ 3 [moderate] in subjects who had previously achieved a GPPPGA score of 0 [clear] or 1 [almost clear]) after Day 1, the following treatments will be provided:

- Subjects assigned to placebo in this study will receive an IV dose of imsidolimab 750 mg followed by a SC dose of imsidolimab 200 mg every 4 weeks.
- Subjects assigned to imsidolimab in this study will be treated at the discretion of the Investigator with any available therapy (such as retinoids, cyclosporine, methotrexate, corticosteroids, or other appropriate therapy).

Subjects who experience a GPP flare between scheduled study visits may contact the study site to arrange an unscheduled visit.

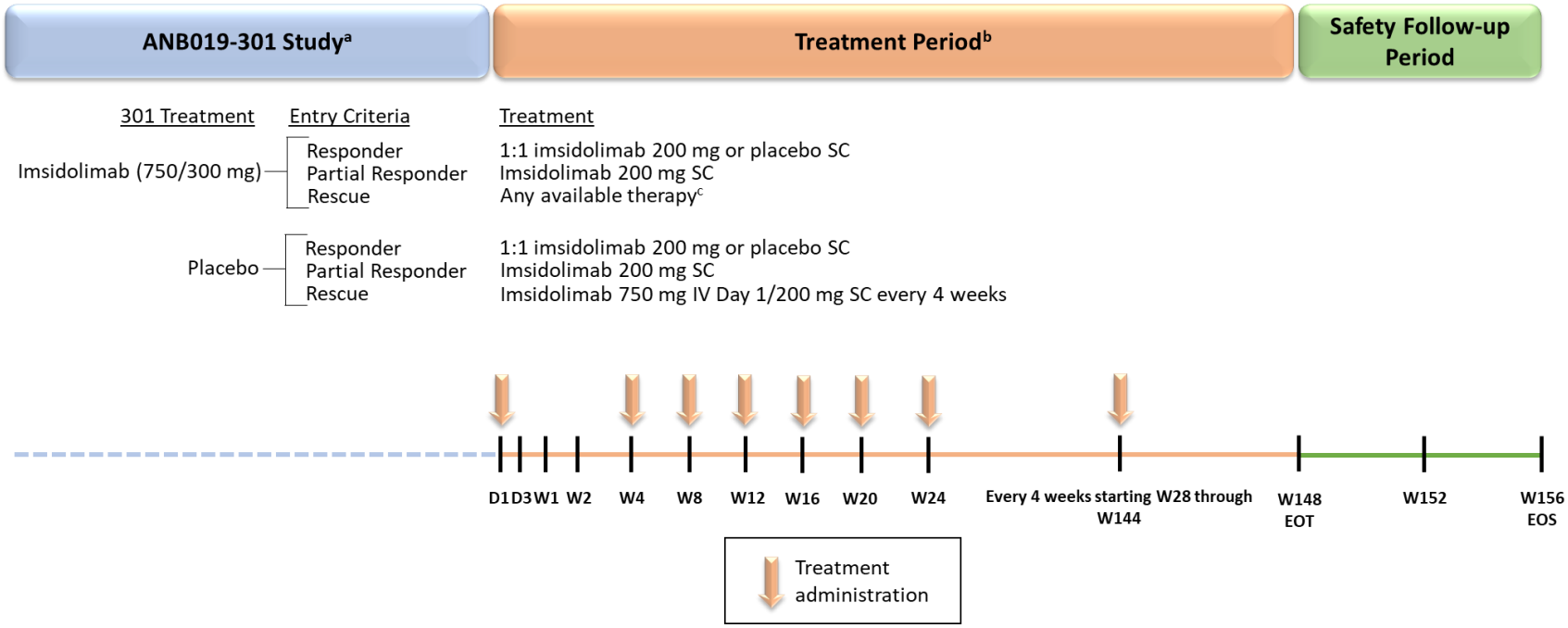
In addition, starting at Day 113 (Week 16), a subject who requires topical rescue medication, as judged by the Investigator and provided that he or she has a GPPPGA score of at least 3 (moderate severity), will be allowed to use topical rescue medications, such as corticosteroids, retinoid or vitamin A or D analog preparations, tacrolimus, calcineurin inhibitor, topical H1 and H2 antihistamines, tar preparations, or topical antimicrobials).

Additional details are provided in Table 2 and Section 6.5.3.

Subject Duration:	The maximum study duration per subject included in this study is approximately 156 weeks from first visit to last visit (including the treatment period and the safety follow-up period). However, subjects who were assigned to imsidolimab in the ANB019-301 study and receive other rescue therapy on Day 1 of this study will be asked to return for a final safety follow-up visit 12 weeks after receiving their study treatment dose in the ANB019-301 study. In this case, assessments described for the Day 1093 (Week 156) visit will be performed.

1.2 SCHEMA

Figure 1: Study Schema



Abbreviations: D, day; EOS, end of study; EOT, end of treatment; IV, intravenous; SC, subcutaneous; W, week.

[a] The Day 1 visit of this study should ideally occur on the same day as the final study visit of the ANB019-301 study, in which case, subjects will enter this study directly after all assessments of the final ANB019-301 study visit are completed. Assessments that are common to both studies will be performed only once if the visits are on the same day. If scheduled on two separate days, the Day 1 visit of this study should occur no later than 1 week after completing the final study visit of the ANB019-301 study. No screening visit is required for this study.

[b] Refer to Section 6.1.2 for specific visits were the study treatment needs to be administered and the treatment assignment depending on subject's status on Day 1.

[c] Subjects who were assigned to imsidolimab in the ANB019-301 study and receive other rescue therapy on Day 1 of this study will be asked to return for a final safety follow-up visit 12 weeks after receiving their study treatment dose in the ANB019-301 study. In this case, assessments described for the Day 1093 (Week 156) visit will be performed.