EMERGE Study

# A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ANB019 in the Treatment of Acneiform Rash in Subjects with Neoplasm Receiving EGFRi or MEKi Therapy

**Protocol Number: ANB019-207**

**Investigational New Drug (IND) Number: 136145**

**European Clinical Trials Database (EudraCT) Number: 2020-003494-22**

**Sponsor Name: AnaptysBio, Inc.**

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**San Diego, CA 92121, United States**

**Sponsor Medical Expert and Signatory:** [redacted]

**Amendment 2**

**05 August 2021**

 

## SPONSOR SIGNATURE PAGE

I confirm that I have read and approved this protocol in its entirety and will comply with the obligations as detailed in all applicable regulations and guidelines (eg, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] Good Clinical Practice [GCP] guidelines) and the protocol.

[redacted]

05 August 2021

**Date** (05 August 2021)

**AnaptysBio, Inc.**

## INVESTIGATOR'S AGREEMENT

PROTOCOL TITLE: A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ANB019 in the Treatment of Acneiform Rash in Subjects with Neoplasm Receiving EGFRi or MEKi Therapy

PROTOCOL NO: ANB019-207

VERSION: Amendment 2

This protocol is a confidential communication of the Sponsor. I confirm that I have read this protocol; I understand it; and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the investigator: Please SIGN and DATE (05 August 2021) this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to the Sponsor or designee.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

_____

## PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| Amendment 2 | 05 August 2021 |
| Amendment 1 | 11 February 2021 |
| Original Protocol (Version 1.0) | 28 September 2020 |

**Amendment 2**

**Date: 05 August 2021**

**Overall rationale for amendment:**

This amendment was prepared to address the following issues:

- Permit small editorial changes for clarity and correctness
- Update the name of the Sponsor medical expert and signatory, and address of the Sponsor
- Allow inclusion of subjects with benign neoplasm (not cancer)
- Revised eligibility criteria for body weight to $\geq$ 40kg
- Updated tuberculosis screening as inclusion criteria
- Clarified definition of childbearing potential in contraceptive use exclusion criteria
- Allow screening of subjects prior to rash onset
- Reduce the number of study visits by removing Week 1 and Week 6 visits
- Modify the list of study endpoints by removing percent change from Baseline from some endpoints and revised exploratory endpoints based on planned data collection
- Clarify the recommended order of assessments to be followed during the study visits
- Add an evaluation of the Fitzpatrick Skin Type Classification
- Reduce the number of electrocardiograms (ECGs) to be performed during the study
- Reduce the number of tape strip samples to be collected and clarify the location for sample collection
- Reduce the number of blood samples to be collected for pharmacokinetic (PK) evaluations
- Removal of noncompartmental analysis (NCA) due to limited PK sampling
- Update washout periods for prohibited treatments
- Add clarification related to vaccines allowed during the study
- Clarify if a subject were to discontinue early from the study, an early termination visit will be required
- Remove the possibility of subjects' replacement
- Clarify assessment of facial lesions
- Remove facsimile as an option to report serious adverse events (SAEs)
- Update the text to indicate local laboratory tests will be allowed at Screening for TB and viral serology testing

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Global | Small editorial changes and corrections. | To add clarity and implement corrections to text. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Global | Change language from final screening to Screening Part 2. | Change made to ensure clarity throughout document. |
| Global | Change language from cancer to neoplasm. | Change made to include subjects with neoplasm (not cancer). |
| Document Header; Title Page; Investigator's Agreement; Protocol Amendment Summary of Changes Table | Updated amendment number and date. | Administrative changes for Amendment 2. |
| Title Page; Sponsor Signature Page | Updated the name of the Sponsor medical expert and signatory, and address of the Sponsor. | To implement modification in study administrative structure. |
| Abbreviations; Section 1.3 Schedule of Activities; Section 1.1 Synopsis; Section 7.2 Subject Discontinuation/Withdrawal from the Study | Clarified that upon early discontinuation of study treatment, subjects must attend an early termination visit. | Change was made to clarify discontinuation/withdrawal from study. |
| Section 1.1 Synopsis; Section 1.3 Schedule of Activities; Section 4.1 Overall Design; Section 8.3.3 Pharmacokinetics, Table 15 Pharmacokinetic Sample Collection and Time Points | Removed visits at Week 1 (Day 8) and Week 6 (Day 43). Table 1 footnote edited to remove Day 1. | To reduce number of study visits required of subjects and align visit schedule with oncology visits. |
| Section 1.1 Synopsis; Section 3.3 Exploratory Objectives and Endpoints; Section 9.4.7 Analysis of the Exploratory Efficacy Endpoints | Removed percent change from Baseline in endpoints assessing change in acneiform rash modified MESTT grading scale at individual locations (face, scalp, chest, and back); acneiform rash CTCAE grading scale; IGA; and facial IGA. | These assessments use 4- to 6-point scales and percent change is not needed. |
| Section 1.1 Synopsis; Section 3.3 Exploratory Objectives and Endpoints; Section 9.4.7 Analysis of the Exploratory Efficacy Endpoints | Added endpoints based on change in facial papules and pustules as well as proportion of subjects achieving key categories in PGI-S/PGI-C. | Additional analyses added based on data previously specified for collection for proof-of-concept evaluation. |
| Section 1.3 Schedule of Activities | Clarified text to indicate the preferred rather than specific order for performing assessments, that subject-reported questionnaires and efficacy assessments must be performed before other assessments, and that | Change was made to provide flexibility around assessments while still adhering to specific guidelines. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| | photography may be performed any time predose provided it is before tape stripping. | |
| Section 1.3 Schedule of Activities; Section 8.2.1.1.1 Events Meeting the Adverse Event Definition | Removed ECG assessments at Day 1 (Week 0), Week 4, and Week 24. Reduced the number of blood samples to be collected for PK evaluations.<br><br>Revised text in section to read: "worsen from a prior assessment" instead of "Day 1". | Change was made to reduce number of assessments required of subjects.<br><br>Alignment between timepoints captured on the Schedule of Activities and text within protocol. |
| Section 1.3 Schedule of Activities | Indicated that tape strips will be collected on Day 1, Day 57, and Day 113 from both nonlesional and lesional skin. Removed tape strip collection on Day 15. | Change was made to allow comparison of lesional and nonlesional skin and reduce the number of visits for tape strip collection. |
| Section 1.3 Schedule of Activities | Removed Week 1 and Week 6 visits | Change was made to reduce the number of visits. |
| Section 1.3 Schedule of Activities | Removed photography collection at Week 2 (Day 15), added Week 4 (Day 29) for photography collection. | Photography is not collected at Week 2 (Day15). Photography will also be collected at Week 4 (Day 29). |
| Section 1.1 Synopsis; Section 1.2 Schema; Section 1.3 Schedule of Activities; Section 4.1 Overall Design; Section 5.1 Inclusion Criteria, Inclusion Criterion 3 | Updated study design and inclusion criteria to allow screening of subjects prior to rash onset and modify the screening procedures for those subjects. | Change was made in the inclusion criteria to allow screening of subjects prior to rash onset. The screening visit was updated and can be performed as one visit for subjects experiencing a rash or as two visits to follow subjects not experiencing a rash at the initial screening visit. |
| Section 1.3 Schedule of Activities; Section 8.3.1 Fitzpatrick Skin Type Classification; Section 10.1.9.1 Data Collection and Management Responsibilities; Section 11 References; Appendix 8 Fitzpatrick Skin Type Classification | Added the Fitzpatrick Skin Type Classification to the Screening activities. | Change was made to further classify skin type. |
| Title Page; Investigator's Agreement; Section 1.1 Synopsis; Section 2.1 Study Rationale; Section | Indicated that subjects with a diagnosed neoplasm were to be included in the study. | Change was made to be more inclusive of patients with different types of |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.1 Overall Design; Section 5.1 Inclusion Criteria, Inclusion Criteria 2 and 8; Exclusion Criteria 7, 10, 13j, and 21; Section 6.3 Measures to Minimize Bias: Randomization and Blinding; Section 6.5.2 Prohibited Medications or Procedures; Section 8.1.5 Systemic Therapy Induced Diarrhea Assessment Tool; Section 8.2.1 Adverse Events and Serious Adverse Events; Section 9.4.5.2 Statistical Analysis of Primary Endpoint | | neoplasm (ie, malignant[cancer] and benign neoplasms). |
| Section 5.1 Inclusion Criteria, Inclusion Criterion 7 | Revised body weight parameter. | Change was made to include body weight $\geq$ 40kg |
| Section 5.1 Inclusion Criteria, Inclusion Criterion 9 | Expanded on tuberculosis screening as inclusion criteria. | Tuberculosis screening criteria added as inclusion criteria (previously exclusionary criteria). |
| Section 5.1 Inclusion Criteria, Inclusion Criterion 10 | Clarified childbearing potential. | Change was made to clarify the definition of childbearing potential. |
| Section 5.2 Exclusion Criteria, Exclusion Criterion 6 | Clarified possible therapies for active infection and adjusted time window. | Added antifungal or antiviral therapy.<br><br>Changed treatment window to 2 weeks of Day 1. |
| Section 5.2 Exclusion Criteria, Exclusion Criterion 8 | Reduced window for history of opportunistic infection or parasitic infections. | Change was made from 6 months prior to Screening to 3 months. |
| Section 5.2 Exclusion Criteria, Exclusion Criterion 13 q; Table 3 | Added “other than used for treatment of neoplasm”. | Clarified marketed biologic agent. |
| Section 5.2 Exclusion Criteria, Exclusion Criterion 15 | Clarified periods of stable dosage. | Change was made to reduce the duration from 26 weeks to 12 weeks. |
| Section 5.2 Exclusion Criteria, Exclusion Criterion 13; Section 6.5.2 Prohibited Medications or Procedures; Table 3 | Clarified the periods of washout for prohibited medications. | Change was made to expand the period and use of prohibited medication prior to the study drug. |
| Section 6.5 Concomitant Therapy | Added the following: “Nonlive-attenuated vaccines, including those currently authorized for COVID-19 (eg, RNA-based vaccines, protein-based vaccines), are allowed during the | Change was made to clarify which COVID-19 vaccines are allowed during the study. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| | study. The Medical Monitor should be consulted to confirm that the vaccine planned/received is allowed and that subject participation in the study should be continued. Of note, vaccines, including those for COVID-19, should be captured as a concomitant medication and any related symptoms documented as AEs."<br><br>Removed language around concomitant treatments for other indications | <br><br><br><br><br><br><br><br><br><br>Defined in other sections. |
| Section 7.1 Discontinuation of Study Treatment | Removed definition of discontinuation from the study. | Text was removed from this section and clarified in Section 7.2 Subject Discontinuation/ Withdrawal from the Study. |
| Section 7.2 Subject Discontinuation/Withdrawal from the Study | Removed "Subjects withdrawing from the study prematurely for reasons other than a study treatment-related AE may be replaced at the discretion of the Sponsor." | To remove the possibility of subjects' replacement during the study. |
| Section 8.1.8 Facial Inflammatory Lesion Count | Clarified assessment timepoints at final screening and Day 1 visits.<br><br>Added the following explanation: "Only for the facial inflammatory lesion count, papules and pustules should be counted separately to attain the total inflammatory lesion count." | Change was made to clarify assessments. |
| Section 8.2.1.6.2 Reporting via Paper Case Report Form | Removed facsimile as a means of transmitting SAEs. | Facsimile is no longer being used. |
| Section 1.3, Section 8.2.7, Appendix 7 | Updated the text to indicate that local laboratory tests will also be allowed at Screening for TB and viral serology testing | Local laboratory tests will be allowed at TB screening and viral serology testing. |
| Section 8.3.5 Biomarkers Analysis | Deleted word "tube" from description of test strip labeling. | Tape strips are not collected in tubes. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 9.4.7 Analysis of the Exploratory Efficacy Endpoints | Removed two duplicated endpoints.<br>• Proportion of subjects achieving an IGA of clear (0) or almost clear (1) at each visit<br>• Proportion of subjects achieving a facial IGA of clear (0) or almost clear (1) at each visit | Change was made for clarity. |
| Section 9.4.9.1 Derivation of Pharmacokinetic Parameters | Due to minimal PK sampling, NCA will not be conducted. Updated text to reflect change. | Minimal PK sampling. |
| Section 9.4.12 Interim Analyses | Updated section header and text to indicate that interim *analyses* may be performed rather than interim *analysis.* | There are planned to be at least 2 interim analyses. |
| Tables 4-9 | Revised order of footer elements and added sources to table footers. | Administrative change. |

**Amendment 1**

**Date: 11 February 2021**

**Overall rationale for amendment:**

This amendment was prepared to address the following issues:

- Permit small editorial changes for correctness
- Clarify modifications to MESTT, use of CTCAE scoring and corresponding statistical analysis
- Permit (optional) home health visits during the COVID-19 pandemic, describe home nursing visit procedures, and acknowledge that COVID-19 measures only apply if they are in accordance with current, locally applicable recommendations/regulations
- Permit the use of remaining serum from samples collected for PK/immunogenicity endpoints to be retained for assay method development, troubleshooting, or validation
- Clarify timing for administration of live-attenuated vaccines after the subject completes the 12-week standard safety follow-up period of the study or after 12 weeks following the last administration of the study drug for subjects who discontinued from the study early
- Clarify timing requirements for use of hormonal contraceptives prior to and during study participation and to identify which oral hormonal contraceptives are permissible
- Permit enrollment of subjects treated with any commercially available EGFRi or MEKi therapy
- Include a 30-minute observation period of study subjects after application of each dose of ANB019 to identify any potential allergic/anaphylactic reaction
- Clarify timing of anti-drug antibody sample collection

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Global | Small editorial changes and corrections. | To add clarity and implement corrections to text. |
| Document Header/Footer; Document History | Added amendment number and date in the header. Added amendment number and date to the Document History table. | Administrative change for Amendment 1. |
| Title Page; Investigator's Agreement | Added amendment number. | Administrative change for Amendment 1. |
| Section 1.1 Synopsis (Study Population); Section 4.1 Overall Design; Section 5.1 Inclusion Criteria; Section 5.2 Exclusion Criteria; Section 6.5.2 Prohibited Medications or Procedures, Table 3 List of Prohibited Medications and Procedures | Updated text to clarify that subjects are eligible if they are treated with oral or injectable commercially available EGFRi or MEKi therapy. | Clarity of language for nonUS product usage/availability. |
| Section 1.1 Synopsis Protocol Summary Exploratory Endpoints; Section 3 Objectives and Endpoints; Section 9 Statistical Considerations | Updated secondary and exploratory endpoints; definitions of concomitant medications. | To add clarity and implement corrections to text. |
| Section 1.1 Synopsis Section (Study Description); Section 4.1 Study Design; Section 8.3.2 Pharmacokinetics; Section 8.3.3 Immunogenicity Assessments; Section 10.1.4 Future of Stored Specimens and Data | Updated text to clarify that remaining serum from samples collected for PK/immunogenicity endpoints may be retained for assay method development, troubleshooting, or validation. Samples will not be used for genetic analyses. | Alignment with AnaptysBio practices. |
| Section 1.3 Table 1 Schedule of Activities | Updated SoA to correct minor discrepancies and align with changes mentioned in this amendment. | To add clarity and implement corrections to text. |
| Section 1.3 Schedule of Activities; Section 4.2 Modifications to Study Conduct Due to the Coronavirus Disease 2019 (COVID-19) Pandemic; Section 7.3 Lost to Follow-Up | Updated text to:<br>Reflect that due to the COVID-19 restrictions, conducting optional home visits is permissible when on-site study visits are not feasible.<br>Clarified home nursing visit procedures.<br>Clarified that such modifications always must be in accordance with local regulations. | The COVID-19 pandemic may impact the ability to adhere to certain study procedures due to center closures, travel restrictions, and quarantines. |
| Section 2.3.1 Known Potential Risks; Section 6.1.2 Dosing and | Clarified that subjects should stay on-site for a 30-minute | Added clarity regarding observation of subject |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Administration, Table 2 Study Treatment Details | observation period to watch for a possible allergic/anaphylactic reaction after each dosing with ANB019. | following study drug administration. |
| Section 5.2 Exclusion Criteria; Section 6.5 Concomitant Therapy | Clarified period of time permissible for administration of live-attenuated vaccine - 12 weeks after the last administration of study drug. Also applies to subjects who terminate the study early. | During the 12-week follow up period, no study drug is administered; 12 weeks allows for at least 3 half-lives of study drug and is estimated to be a sufficient period after the last dose administration when a live vaccine can be safely administered. |
| Section 5.1 Inclusion Criteria; Section 12 Appendix 1, Contraceptive Guidance and Collection of Pregnancy Information | Clarified that hormonal contraceptives must be used at a stable regimen throughout the study. | Variability in hormonal contraceptive regimen may impact interpretation of possible exanthema. |
| Section 5.1 Inclusion Criteria; Section 6.5.2 Prohibited Medications or Procedures, Table 3 List of Prohibited Medications and Procedures; Section 12 Appendix 1, Contraceptive Guidance and Collection of Pregnancy Information | Clarified that drospirenone, chlormadinone acetate, or cyproterone acetate must be initiated and used at a stable dosage for at least 12 weeks prior to Day 1. | Alignment of prohibited medications and contraceptive guidance. |
| Section 8.1.10; Section 8.1.10 Table 8 Grading of Acneiform Rash According to Common Terminology Criteria for Adverse Events | Clarified assessment timepoints at final screening and Day 1 visits.<br><br>Updated Table 8 to include:<br>0 = No evidence of rash. | To add clarity and implement corrections to text. |
| Section 8.1.11 MASCC EGFRi Skin Toxicity Tool | Use of 'modified' MESTT in lieu of standard MESTT to record skin changes in 4 different body regions vs total skin changes combined. | To add clarity and implement corrections to text. |
| Section 8.1.11 Table 9 Grading of Acneiform Rash According to the MASCC EGFRi Skin Toxicity Tool | Updated Table 9 to include:<br>0 = No evidence of papules or pustules.<br>Updated Grade 1 definition to include presence of 5 papules and pustules (typographical error in the source document). | To clarify and implement corrections to text. |
| Section 8.1.12 Table 10 Grading of Paronychia According to Common | Updated Table 10 to include:<br>0 = No evidence of paronychia. | To clarify and implement corrections to text. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Terminology Criteria for Adverse Events | | |
| Section 8.1.12 Table 11 Grading of Dry Skin According to Common Terminology Criteria for Adverse Events | Updated Table 11 to include:<br>0 = No evidence of dry skin. | To add clarity and implement corrections to text. |
| Section 8.1.12 Table 12 Grading of Alopecia According to Common Terminology Criteria for Adverse Events | Updated Table 12 to include:<br>0 = No evidence of alopecia. | To add clarity and implement corrections to text. |
| Section 8.1.12 Table 13 Grading of Pruritus According to Common Terminology Criteria for Adverse Events | Updated Table 13 to include:<br>0 = No evidence of pruritus. | To add clarity and implement corrections to text |
| Section 8.2.5 Vital Signs | Clarified site methods for assessing body temperature (°C), pulse rate (bpm), blood pressure (mmHg), and respiratory rate (breaths/min) at the time points specified in SoA (Section 1.3). | To implement consistent methods for assessing vital signs across AnaptysBio protocols. |
| Section 8.3.3 Table 16 Anti-Drug Antibodies Sample Collection and Time Points | Updated Table 16 to delete Anti-Drug Antibody (ADA) sample collection times on Days 48 and 85 as per SoA. | To implement corrections to text and to align with SoA. |

## ABBREVIATIONS

| | |
|---|---|
| ADA | anti-drug antibody |
| ADL | activities of daily living |
| AE | adverse event |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| ATC | Anatomical Therapeutic Chemical |
| BSA | body surface area |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| CK | creatine kinase |
| $C_{max}$ | maximum observed concentration |
| CONSORT | Consolidated Standards of Reporting Trials |
| COVID-19 | Coronavirus Disease 2019 |
| CRO | contract research organization |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CV | coefficient of variation |
| cyIL-36R | cynomolgus monkey IL-36R |
| D | day |
| EC | Ethics Committee |
| ECG | electrocardiograms |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report forms |
| EDC | electronic data capture |
| EGFR | epidermal growth factor receptor |
| EGFRi | epidermal growth factor receptor inhibitor |
| EOS | end of study |
| ERK | extracellular signal-regulated kinase |
| ET | early termination |
| EudraCT | European Clinical Trials Database |
| FACT-EGFRi-18 | Functional Assessment of Cancer Therapy - Epidermal Growth Factor Receptor Inhibitor 18 |
| FSH | follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| GEE | Generalized Estimating Equations |
| GGT | gamma glutamyl transferase |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practices |
| GPP | generalized pustular psoriasis |
| $H_0$ | null hypothesis |
| hCG | human chorionic gonadotropin |
| HHS | Health and Human Services |
| HIPAA | Health Information Portability and Accountability Act |
| HRT | hormonal replacement therapy |
| hsCRP | high-sensitivity C-reactive protein |
| IA | interim analysis |
| IB | Investigator's Brochure |

| | |
|---|---|
| ICF | informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IGA | Investigator Global Assessment |
| IgG4 | immunoglobulin G4 |
| IL | interleukin |
| IL-36R | interleukin 36 receptor |
| IL-36Ra | IL-36R antagonist |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| ITT | Intent-to-Treat |
| IUD | intrauterine device |
| IUS | intrauterine hormone-releasing system |
| IV | intravenous |
| IWRS | Interactive Web Response System |
| KD | dissociation constant |
| LSM | least squares means |
| mAb | monoclonal antibody |
| MAD | multiple ascending dose |
| MAP | mitogen-activated protein |
| MAR | missing at random |
| MASCC | Multinational Association for Supportive Care in Cancer |
| MCH | mean corpuscular hemoglobin |
| MCHC | mean corpuscular hemoglobin concentration |
| MCV | mean corpuscular volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MEK | mitogen-activated protein/extracellular signal-regulated kinase kinase |
| MEKi | mitogen-activated protein/extracellular signal-regulated kinase kinase inhibitor |
| MESTT | MASCC EGFRi Skin Toxicity Tool |
| min | minute |
| MMRM | Mixed model of repeated measures |
| MNAR | Missing Not at Random |
| NaCl | sodium chloride |
| NCA | Noncompartmental analysis |
| NOAEL | no observed adverse effect level |
| NRS | Numeric Rating Scale |
| OTC | over-the-counter |
| PBMC | peripheral blood mononuclear cell |
| PCV | packed cell volume |
| PGI-C | Patient Global Impression of Change |
| PGI-S | Patient Global Impression of Severity |
| PK | pharmacokinetic |
| PPP | palmoplantar pustulosis |
| PT | preferred term |
| QC | quality control |
| RBC | red blood cell |
| SAD | single ascending dose |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SAS | statistical analysis system |
| SC | subcutaneous/subcutaneously |

| | |
|---|---|
| SD | standard deviation |
| SoA | Schedule of Activities |
| SOC | system organ class |
| SOP | Standard Operating Procedure |
| STIDAT | Systemic Therapy Induced Diarrhea Assessment Tool |
| $t_{1/2}$ | terminal half-life |
| TB | tuberculosis |
| TEAE | treatment-emergent adverse event |
| TK | toxicokinetic |
| $T_{max}$ | time to maximum observed concentration |
| ULN | upper limit of normal |
| URTI | upper respiratory tract infection |
| W | week |
| WBC | white blood cell |
| WHO | World Health Organization |
| WOCBP | woman of childbearing potential |

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## STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the protocol, applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines, and applicable local laws and regulations. The investigator will assure that no planned deviation from, or changes to the protocol will take place without prior agreement from the IND Sponsor and documented approval from the Institutional Review Board (IRB)/Ethics Committee (EC), except where necessary to eliminate an immediate hazard(s) to the study subjects. All personnel involved in the conduct of this study have completed ICH GCP Training.

The protocol, informed consent form(s) (ICFs), recruitment materials, and all subject materials will be submitted to the IRB/EC for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB/EC before the changes are implemented to the study. In addition, all changes to the consent form will be IRB/EC-approved; a determination will be made regarding whether a new consent needs to be obtained from subjects who provided consent, using a previously approved consent form.

# 1 PROTOCOL SUMMARY

## 1.1 SYNOPSIS

**Title:** A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ANB019 in the Treatment of Acneiform Rash in Subjects with Neoplasm Receiving EGFRi or MEKi Therapy

**Short Title:** Efficacy and Safety of ANB019 in Subjects with EGFRi/MEKi-Associated Acneiform Rash

**Study Description:** This study is a Phase 2a, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy, safety, and tolerability of ANB019 in the treatment of acneiform rash in subjects with neoplasm receiving epidermal growth factor receptor inhibitor (EGFRi) or mitogen-activated protein (MAP)/extracellular signal-regulated kinase (ERK) kinase inhibitor (MEKi). This study will also characterize the pharmacokinetic (PK) profile of ANB019 and explore the immune response to ANB019 in subjects with EGFRi/MEKi-associated acneiform rash.

Written informed consent will be obtained from each subject prior to initiating any study-related procedures.

Approximately 45 adult male and female subjects, aged 18 to 75 years, will be randomized in this study. To be eligible for the study, subjects must be receiving oral or injectable commercially available EGFRi or MEKi therapy at the Screening and Day 1 visits. Subjects can enter the initial screening regardless of their current acneiform rash status and severity (as described in Section 5.1). However, at the Screening Part 2 and at Day 1 visit, subjects must have an acneiform rash of Grade ≥ 2 as per the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, and ≥ 20 inflammatory lesions on the face. Randomization will be stratified based on acneiform rash CTCAE grade at Baseline and therapy the subject is receiving (EGFRi vs MEKi).

Subjects who enter the screening period without an acneiform rash or with an acneiform rash severity that does not meet the requirements of Inclusion (refer to Section 5.1) may remain in screening for up to 6 months and be reevaluated if/when an acneiform rash develops or worsens as long as they remain on EGFRi or MEKi therapy. Once the acneiform rash severity meets the requirements of Inclusion Criterion 3, a last screening visit (Screening Part 2; refer to Section 1.3) must be performed, within 15 days prior to Day 1, ideally within 1 week.

During the treatment period, eligible subjects will be randomized (2:1) to receive either ANB019 or placebo, subcutaneously (SC) administered at 4 time points. On Day 1, the subjects will receive a 400-mg dose of ANB019 or placebo. On Days 29, 57, and 85, the subjects will receive a 200-mg dose of ANB019 or placebo.

For scheduled study visits, subjects will come to the study center on up to 9 occasions to monitor changes in disease activity, PK (if applicable), safety, and tolerability: screening (depending on subject acneiform rash status, the screening visit may be planned either as 1 visit or 2 separate visits) and Days 1, 15, 29, 57, 85, 113 (end of treatment [EOT]/early termination [ET]), and 169 (end of study [EOS]). 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 57 (Week 8).

Disease activity will be evaluated for all subjects using facial inflammatory lesion count, acneiform rash CTCAE grading, acneiform rash modified Multinational Association for Supportive Care in Cancer (MASCC) EGFRi Skin Toxicity Tool (MESTT) grading, Investigator Global Assessment (IGA), facial IGA, pruritus Numeric Rating Scale (NRS), pain NRS, Patient Global Impression of Severity (PGI-S), Patient Global Impression of Change (PGI-C), number of nail folds with paronychia, and paronychia, dry skin, alopecia, and pruritus CTCAE grading. The subject's quality of life will be assessed using the Functional Assessment of Cancer Therapy - Epidermal Growth Factor Receptor Inhibitor 18 (FACT-EGFRi-18). Subject's gastrointestinal inflammation will be evaluated using the Systemic Therapy Induced Diarrhea Assessment Tool (STIDAT). Subject's level of functioning and daily living abilities will be evaluated to confirm eligibility using the Eastern Cooperative Oncology Group (ECOG) performance status.

In addition, standardized photographs of the face will be taken at the time points specified in the SoA to record inflammatory lesions for lesion counts analysis as supporting information for efficacy analyses.

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 [ADAs] to ANB019) will be collected on Day 1 before the administration of the study treatment and at the other time points specified in the SoA (see Section 1.3). Any remaining samples collected for PK and immunogenicity endpoints may be retained for assay method development, troubleshooting, or validation. The samples will not be used for any type of genetic analyses. Tape strips for biomarker analysis will be collected at the time points specified in the SoA.

Interim analyses (IAs) may be performed during the treatment period for assessment of all primary and secondary efficacy endpoints, and evaluation of all safety data available.

**Objectives:**

Primary Objective:

- To assess the efficacy of ANB019 compared with placebo in reduction of acneiform rash in subjects receiving EGFRi or MEKi therapy as measured by facial inflammatory lesion count

Secondary Objectives:

- To determine the effect of ANB019 compared with placebo on acneiform rash signs and symptoms, and quality of life in subjects receiving EGFRi or MEKi therapy
- To assess the safety and tolerability of ANB019 in subjects with acneiform rash receiving EGFRi or MEKi therapy

Exploratory Objectives:

- To further evaluate the effect of ANB019 compared with placebo on acneiform rash signs and symptoms, and quality of life in subjects receiving EGFRi or MEKi therapy
- To explore the effect of ANB019 on other EGFRi/MEKi adverse drug reactions (paronychia, dry skin, alopecia, and pruritus)
- To assess the effect of ANB019 on gastrointestinal inflammation in subjects with acneiform rash receiving EGFRi or MEKi therapy
- To explore the effect of ANB019 on cutaneous biomarkers
- To explore the effect of ANB019 on acneiform rash as measured by facial inflammatory lesion count using standardized photographs
- To describe the PK profile of ANB019 in subjects with acneiform rash receiving EGFRi or MEKi therapy
- To test for immunogenicity to ANB019

**Endpoints:**

Primary Endpoint:

- Change from Baseline in facial inflammatory lesion count (papules and pustules) at Week 8

Secondary Endpoints:

- Percent change from Baseline in facial inflammatory lesion count (papules and pustules) at Week 8
- Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash CTCAE grading scale at Week 8
- Time to first response of 1 grade improvement from Baseline on the acneiform rash CTCAE grading scale
- Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash modified MESTT grading scale (total score) at Week 8
- Time to first response of 1 grade improvement from Baseline on the acneiform rash modified MESTT grading scale (total score)

- Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash modified MESTT grading scale (facial assessment) at Week 8
- Time to first response of 1 grade improvement from Baseline on the acneiform rash modified MESTT grading scale (facial assessment)
- Change from Baseline in pruritus NRS at Week 8
- Percent change from Baseline in pruritus NRS at Week 8
- Change from Baseline in pain NRS at Week 8
- Percent change from Baseline in pain NRS at Week 8
- Change from Baseline in FACT-EGFRi-18 at Week 8
- 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 Endpoints:

- Change from Baseline in facial inflammatory lesion count (papules and pustules) at each visit other than Week 8
- Percent change from Baseline in facial inflammatory lesion count (papules and pustules) at each visit other than Week 8
- Change from Baseline in facial papule count at each visit
- Percent change from Baseline in facial papule count at each visit
- Change from Baseline in facial pustule count at each visit
- Percent change from Baseline in facial pustule count at each visit
- Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash CTCAE grading scale at each visit other than Week 8
- Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash modified MESTT grading scale (total score) at each visit other than Week 8
- Change from Baseline in pruritus NRS at each visit other than Week 8
- Percent change from Baseline in pruritus NRS at each visit other than Week 8
- Change from Baseline in pain NRS at each visit other than Week 8
- Percent change from Baseline in pain NRS at each visit other than Week 8
- Change from Baseline in FACT-EGFRi-18 at each visit other than Week 8
- Proportion of subjects achieving an improvement of 50% from Baseline in facial inflammatory lesion count (papules and pustules) at each visit
- Proportion of subjects achieving an improvement of 75% from Baseline in facial inflammatory facial lesion count (papules and pustules) at each visit
- Change from Baseline in acneiform rash CTCAE grading scale at each visit
- Change from Baseline in acneiform rash modified MESTT grading scale (total score) at each visit
- Percent change from Baseline in acneiform rash modified MESTT grading scale (total score) at each visit

- Change from Baseline in acneiform rash modified MESTT grading scale (facial assessment) at each visit
- Change from Baseline in acneiform rash modified MESTT grading scale (back assessment) at each visit
- Change from Baseline in acneiform rash modified MESTT grading scale (scalp assessment) at each visit
- Change from Baseline in acneiform rash modified MESTT grading scale (chest assessment) at each visit
- Change from Baseline in IGA at each visit
- Proportion of subjects achieving an IGA of clear (0) or almost clear (1) at each visit
- Proportion of subjects with at least 2-point decrease in IGA at each visit
- Change from Baseline in facial IGA at each visit
- Proportion of subjects achieving a facial IGA of none (0) or minimal (1) at each visit
- Proportion of subjects with at least 2-point decrease in facial IGA at each visit
- Proportion of subjects with at least 3-point decrease in pruritus NRS at each visit for subjects with a Baseline pruritus NRS of at least 3
- Proportion of subjects with at least 4-point decrease in pruritus NRS at each visit for subjects with a Baseline pruritus NRS of at least 4
- Proportion of subjects with at least 3-point decrease in pain NRS at each visit for subjects with a Baseline pain NRS of at least 3
- Proportion of subjects with at least 4-point decrease 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 the PGI-S and PGI-C at each visit
- Proportion of subjects achieving mild or clear skin according to the PGI-S at each visit
- Proportion of subjects achieving improvement (a little better, much better or very much better) according to the PGI-C at each visit
- Proportion of subjects receiving rescue medication from Week 4 through Week 24
- Proportion of subjects that do not require a dose reduction of EGFRi or MEKi therapy due to acneiform rash at each visit
- Proportion of subjects that do not require cessation of EGFRi or MEKi therapy due to acneiform rash at each visit
- Change from Baseline in number of nail folds with paronychia at each visit
- Proportion of subjects with paronychia, dry skin, alopecia, and pruritus of Grade 0 or 1 as per CTCAE grading scale at each visit
- Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash modified MESTT grading scale (facial assessment) at each visit
- Percent change from Baseline in facial inflammatory lesion count (papules and pustules) at each visit

- Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash modified MESTT grading scale (back assessment) at each visit
- Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash modified MESTT grading scale (scalp assessment) at each visit
- Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash modified MESTT grading scale (chest assessment) at each visit
- Time to first response of 1 grade improvement from Baseline on the acneiform rash modified MESTT grading scale (back assessment)
- Time to first response of 1 grade improvement from Baseline on the acneiform rash modified MESTT grading scale (scalp assessment)
- Time to first response of 1 grade improvement from Baseline on the acneiform rash modified MESTT grading scale (chest assessment)
- Change from Baseline in STIDAT at each visit
- Percent change from Baseline in STIDAT at each visit
- Skin tape strip biomarkers analysis including, but not limited to, IL-36 and Th-17
- Change from Baseline in inflammatory lesion counts as determined by standardized photographs at each visit
- Percent change from Baseline in inflammatory lesion counts as determined by standardized photographs at each visit
- Serum concentration following ANB019 administration and other parameters as appropriate will be determined to describe the PK profile of ANB019
- Presence of ADA to ANB019

**Study Population:** Approximately 45 adult male and female subjects, aged 18 to 75 years, will be randomized in this study. To be eligible for the study, subjects must be receiving oral or injectable commercially available EGFRi or MEKi therapy at the Screening and Day 1 visits. Subjects can enter the initial screening regardless of their current acneiform rash status and severity (as described in Section 5.1). However, at the Screening Part 2 and at Day 1 visit, subjects must have an acneiform rash of Grade ≥ 2 as per the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, and ≥ 20 inflammatory lesions on the face. Randomization will be stratified based on acneiform rash CTCAE grade at Baseline and the therapy the subject is receiving (EGFRi vs MEKi).

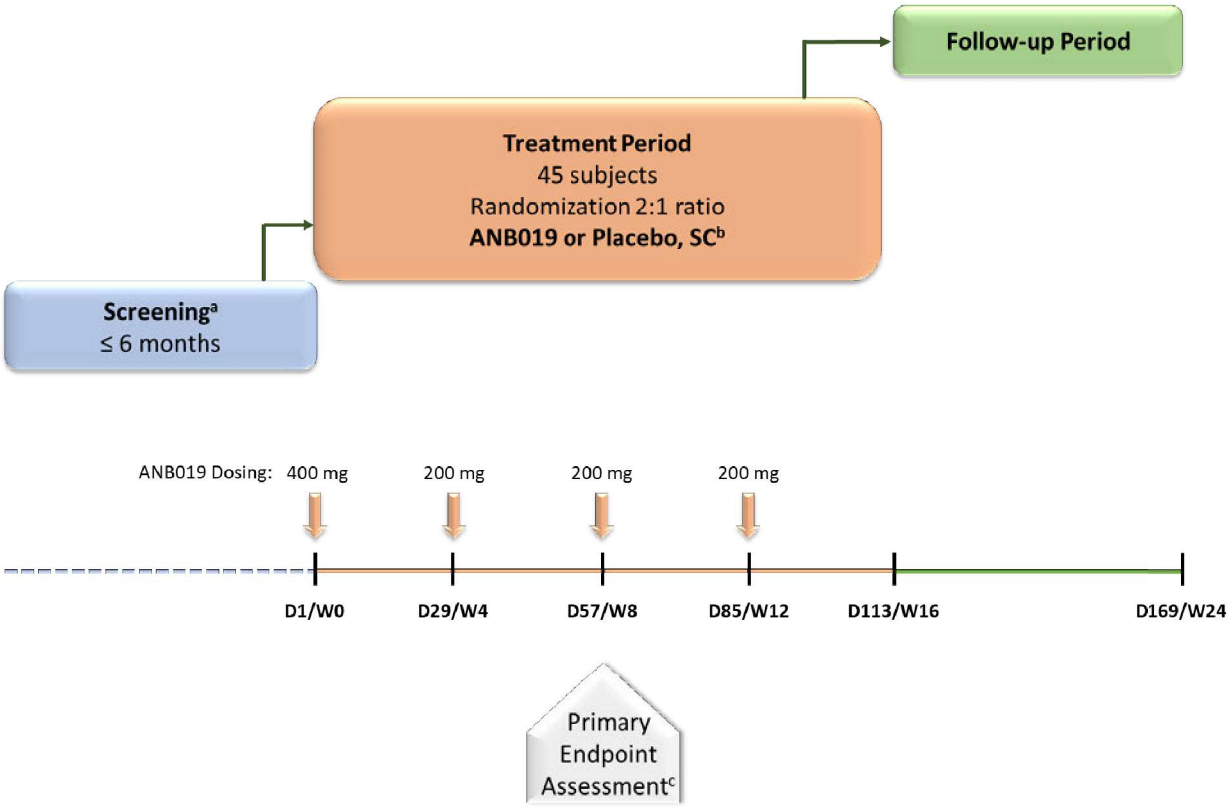
**Phase:** 2a

**Description of Study Sites Enrolling Subjects:** Approximately 20 study centers located in North America and Europe are expected to participate in this study.

| | |
|---|---|
| **Description of Study Treatments:** | ANB019 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 slightly yellowish, and clear to very slightly opalescent solution for injection.<br><br>During the treatment period, eligible subjects will be randomized (2:1) to receive either ANB019 or placebo, SC administered at 4 time points:<br><br>• Day 1: 400-mg dose of ANB019 or placebo (administered as 2 SC injections of ANB019 at 200 mg each or placebo)<br>• Days 29, 57, and 85: 200-mg dose of ANB019 or placebo<br><br>Of note, the placebo will be administered via SC injection(s) on the same schedule and in the same volumes as ANB019. |
| **Rescue Medication:** | A subject who has worsening or no improvement in facial inflammatory lesion count (papules and pustules), and/or worsening or no improvement of pain and/or itch, per the pruritus and pain NRSs will be eligible to receive rescue medication (ie, systemic antibiotics and low/medium potency topical corticosteroids [eg, hydrocortisone > 1%, triamcinolone 0.1%]) starting at Day 29 (Week 4). |
| **Study Duration:** | The estimated study duration is approximately 20 months from first subject screened until database lock. |
| **Subject Duration:** | The expected study duration per subject is up to approximately 12 months from the screening to last visit. The screening period may last up to 6 months depending on acneiform rash status and severity: an initial Screening will be planned for subjects without an acneiform rash or with an acneiform rash severity that does not meet the requirements of Inclusion Criterion 3 (refer to Section 5.1); once the acneiform rash severity meets the requirements of Inclusion Criterion 3, a last screening visit must be performed within 15 days prior to Day 1 (ideally within 1 week). The screening period will be followed by a 16-week treatment period and an 8-week follow-up period). |

## 1.2 SCHEMA

**Figure 1: Study Schema**




Abbreviations: D, day; SC, subcutaneously; W, week.
[a] Depending on subject acneiform rash status, the screening visit may be planned either as 1 visit (for subjects who already have an acneiform rash) or as 2 separate visits (for subjects not having an acneiform rash at the initial screening visit): Screening Part 1 and Screening Part 2. Screening Part 2 will only be performed once subject is having an acneiform rash. Screening Part 2 assessments must be performed within 15 days prior to Day 1 (ideally within 1 week) and safety evaluation results required to confirm eligibility must be obtained before randomization.
[b] During the treatment period, subjects will receive either ANB019 or placebo, SC administered at 4 time points: 400-mg dose of ANB019 or placebo on Day 1; 200-mg dose of ANB019 or placebo on Days 29, 57, and 85.
[c] The primary endpoint will be evaluated on Day 57 (Week 8).

## 1.3 SCHEDULE OF ACTIVITIES

Written informed consent will be obtained from each subject prior to initiating any study-related procedures.

To be eligible for the study, subjects must be receiving oral or injectable commercially available EGFRi or MEKi therapy at the Screening and Day 1 visits. Subjects can enter the initial screening regardless of their current acneiform rash status and severity (as described in Section 5.1). However, at the Screening Part 2 and at the Day 1 visit, subjects must have an acneiform rash of Grade ≥ 2 as per the CTCAE Version 5.0, and ≥ 20 inflammatory lesions on the face.

The screening period may last up to 6 months depending on acneiform rash status and severity: an initial Screening will be planned for subjects without an acneiform rash or with an acneiform rash severity that does not meet the requirements of Inclusion Criterion 3 (refer to Section 5.1); once the acneiform rash severity meets the requirements of Inclusion Criterion 3, a last screening visit must be performed within 15 days prior to Day 1 (ideally within 1 week). The screening period will be followed by a 16-week treatment period and an 8-week follow-up period). The screening period must not last for more than 6 months.

The screening evaluation will be performed according to the inclusion and exclusion criteria. If the subject fulfills all inclusion criteria and no exclusion criteria, he or she may be included in the study.

Table 1 provides a description of the procedures to be performed at each visit during the study.

Of note, the primary endpoint will be evaluated on Day 57 (Week 8).

Unless specified otherwise, the study assessments scheduled on Days 1, 15, 29, 57, and 85 must be performed before study treatment administration. The recommended order for performing the study assessments is as follows (applicable to all visits); however, subject-reported questionnaires and efficacy assessments must be conducted before other assessments:

- Subject-reported questionnaires
- Efficacy assessments (global assessments [eg, CTCAE, modified MESTT, IGA] should be performed before more quantitative assessments [eg, lesion count, nail folds with paronychia])
- Vital signs
- Physical examination
- ECG
- Photography (may be performed any time predose provided it is before tape stripping)
- Blood sample collections (for safety, PK, and ADA evaluations) do not have to follow a specific order, provided that they are performed after ECG
- Tape stripping

The Coronavirus Disease 2019 (COVID-19) pandemic may impact the ability to adhere to the study procedures described in Table 1 due to challenges that include, but are not limited to, subject preferences, center closures, travel restrictions, and quarantines. Please refer to Section 4.2 for more details on allowable, as necessary, modifications to the protocol due to COVID-19 restrictions, including conducting optional home visits when on-site study visits are considered not feasible. Such modifications in study conduct always must be in accordance with local regulations/mandates.

**Table 1: Schedule of Activities**

| | Screening Period (-6 months to -1 day) | | Treatment Period | | | | | | Follow-up Period |
|---|---|---|---|---|---|---|---|---|---|
| **Study visit** Window (days) | Screening[a] | | D1 W0 | D15 W2 (±2) | D29 W4 (±2) | D57 W8 (±4) | D85 W12 (±4) | D113 W16 (EOT/ET)[b] (±4) | D169 W24 (EOS) (±5) |
| | Part 1 Initial visit | Part 2 (-15 to -1) | | | | | | | |
| Informed consent | X | | | | | | | | |
| Demographics | X | X | | | | | | | |
| Fitzpatrick skin type classification | X[c] | | | | | | | | |
| Inclusion and exclusion criteria | X | X[d] | X[d] | | | | | | |
| Medical and surgical history | X | X | X | | | | | | |
| Height and weight[e] | X | X | X | | | | | X | X |
| Chest X-ray[f] | | X | | | | | | | |
| Physical examination[g] | | X | X | X | X | X | X | X | X |
| Vital signs[h] | | X | X | X | X | X | X | X | X |
| 12-lead ECG[i] | | X | | | | | | X | |
| Clinical laboratory assessments[j] | | X | X | X | X | X | X | X | X |
| TB screening (QuantiFERON®-TB Gold test)[j] | | X | | | | | | | |
| Viral serology[j] | | X | | | | | | | |
| FSH[j] | | X | | | | | | | |
| Serum pregnancy test (WOCBP only)[j] | | X | | | | | | | X |
| Urine pregnancy test (WOCBP only)[j] | | | X | X | X | X | X | X | |
| Blood samples for PK[k] | | | | X | X | X | X | X | X |
| Blood samples for ADA | | | X | | X | X | | X | X |
| ECOG[l] | | | X | | | | | | |
| IGA, facial IGA[l] | | | X | X | X | X | X | X | X |
| Facial inflammatory lesion count[l] | | X | X | X | X | X | X | X | X |
| Acneiform rash CTCAE grading[l] | | X | X | X | X | X | X | X | X |
| Acneiform rash modified MESTT[l] | | | X | X | X | X | X | X | X |

| | Screening Period (-6 months to -1 day) | | Treatment Period | | | | | | Follow-up Period |
|---|---|---|---|---|---|---|---|---|---|
| **Study visit** | **Screening[a]** | | **D1** | **D15** | **D29** | **D57** | **D85** | **D113** | **D169** |
| Window (days) | **Part 1** Initial visit | **Part 2** (-15 to -1) | **W0** | **W2** (±2) | **W4** (±2) | **W8** (±4) | **W12** (±4) | **W16 (EOT/ET)[b]** (±4) | **W24 (EOS)** (±5) |
| Pruritus and pain NRS[l] | | | X | X | X | X | X | X | X |
| FACT-EGFRi-18, PGI-S, PGI-C[l] | | | X | X | X | X | X | X | X |
| Number of nail folds with paronychia[l] | | | X | X | X | X | X | X | X |
| Paronychia, dry skin, alopecia, pruritus CTCAE grading[l] | | | X | X | X | X | X | X | X |
| STIDAT[l] | | | X | X | X | X | X | X | X |
| Tape strips collection[m] | | | X | | | X | | X | |
| Photography | | | X | | X | X | | X | X |
| Randomization | | | X | | | | | | |
| ANB019/placebo administration[n] | | | X | | X | X | X | | |
| AE/SAE review | X | X | Continuously | | | | | | |
| Concomitant medication review | X[o] | X[o] | Continuously | | | | | | |

Abbreviations: ADA, anti-drug antibody; AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; D, day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EGFRi, epidermal growth factor receptor inhibitor; EOT, end of treatment; ET, early termination; EOS, end of study; FACT-EGFRi-18, Functional Assessment of Cancer Therapy EGFRi 18; FSH, follicle-stimulating hormone; IGA, Investigator Global Assessment; MASCC, Multinational Association for Supportive Care in Cancer; modified MESTT, MASCC EGFRi Skin Toxicity Tool; NRS, Numeric Rating Scale; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; PK, pharmacokinetics; SAE, serious adverse event; SC, subcutaneous; SoA, Schedule of Activities; STIDAT, Systemic Therapy Induced Diarrhea Assessment Tool; TB, tuberculosis; W, week; WOCBP, woman of childbearing potential.

[a] Depending on subject acneiform rash status, the screening visit may be planned either as 1 visit (for subjects who already have an acneiform rash) or as 2 separate visits (for subjects not having an acneiform rash at the initial screening visit): Screening Part 1 and Screening Part 2. Screening Part 2 will only be performed once subject is having an acneiform rash. Screening Part 2 assessments must be performed within 15 days prior to Day 1 (ideally within 1 week) and safety evaluation results required to confirm eligibility must be obtained before randomization.

[b] The ET visit will include all procedures to be done at the EOT/ET visit (Day 113/Week 16 visit).

[c] If not collected at Screening, may be collected at any visit thereafter.

[d] At the Screening (Screening Part 2 for subjects not having an acneiform rash at the initial Screening) and Day 1 visits, the subjects will need to have an active acneiform rash of Grade ≥ 2 as per CTCAE Version 5.0, and ≥ 20 inflammatory lesions on the face.

[e] Height will be measured at Screening only (Screening Part 1 for subjects not having an acneiform rash).

[f] Refer to Section 8.2.3 for details regarding the chest X-ray. A chest X-ray (both posterior-anterior and lateral views) must be done during the screening prior to Day 1 unless the report from a chest X-ray or a chest CT scan, done within 6 months before the first administration of study drug, and read by a qualified radiologist is already available.

[g] Refer to Section 8.2.4 for details regarding the complete physical examination.

[h] Refer to Section 8.2.5 for details and instructions regarding vital signs.

[i] Refer to Section 8.2.6 for details and instructions regarding the ECG. In addition to the time points specified in the SoA, ECGs may be performed at any time during the study if, in the opinion of the investigator, it is clinically warranted.

[j] The FSH testing is performed for postmenopausal women with at least 12 months of amenorrhea without an alternative medical cause to confirm they meet not of childbearing potential criteria. Additional pregnancy testing may be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected. Local laboratory tests will also be allowed at Screening for TB and viral serology testing. Refer to Appendix 7 for details and instructions regarding clinical laboratory parameters and refer to Appendix 1 for the WOCBP definition.

[k] Blood sample for PK will be collected prior to SC administration. In addition, samples for PK will also be collected on Days 15, 29, 57, 85, 113, and 169 (refer to Table 15).

[l] Refer to Section 8.1 for details and instructions regarding ECOG, facial inflammatory lesion count, acneiform rash CTCAE, acneiform rash modified MESTT, IGA, facial IGA, pain and pruritus NRSs, FACT-EGFRi-18, PGI-S, PGI-C, nail folds with paronychia, paronychia, dry skin, alopecia, and pruritus CTCAE grading, and STIDAT. The IGA/facial IGA assessment must be performed prior to the facial lesion count assessment. PGI-C is not to be performed at Day 1.

[m] Tape strips will be collected on Day 1, Day 57, and Day 113 from nonlesional and lesional skin.

[n] During the treatment period, subjects will receive either ANB019 or placebo, SC administered at 4 time points: 400-mg dose of ANB019 or placebo on Day 1; 200 mg dose of ANB019 or placebo on Days 29, 57, and 85.

[o] At screening, prior medications should be reviewed and documented. Refer to Section 6.5.

# 2 INTRODUCTION

## 2.1 STUDY RATIONALE

This study is designed to evaluate the efficacy and safety of multiple doses of ANB019 in the treatment of acneiform rash in subjects with neoplasm who are currently receiving an EGFRi or MEKi therapy.

### 2.1.1 ACNEIFORM RASH

Targeted drugs and biologics that inhibit the activity of the Epidermal Growth Factor Receptor (EGFR) and MAP/ERK kinase (MEK) are frequently used for the treatment of neoplasms, including solid tumors such as lung, head and neck, colon, and pancreatic cancers. They offer several advantages over less specific chemotherapy. However, they often induce cutaneous toxicities as EGFR and MEK are highly expressed in the skin (Yano 2003, Manousaridis 2013). One of the most frequently seen cutaneous AEs of EGFRi is an acneiform rash (also called papulopustular rash) that occurs in up to 85% of patients (Lacouture 2018, Segaert 2005). This dermatologic AE is also one of the most frequently observed following treatment with MEKi, likely because MEK is a downstream mediator of EGFR (Manousaridis 2013). This eruption usually begins on the face a few weeks after initiation of EGFRi/MEKi therapy, can be extremely painful and pruritic, and can spread over to the entire body (Lacouture 2018, Manousaridis 2013). The impact of targeted therapies, such as EGFRi/MEKi, on quality of life can be very important and has been reported to be higher than the impact of nontargeted therapies, such as chemotherapy (Rosen 2013). Moreover, the severity of the acneiform rash often requires modification of the neoplasm treatment regimen (Lacouture 2018).

The pathophysiology of the EGFRi/MEKi-induced acneiform rash is not fully understood. Studies have shown that the inflammatory infiltrate of the skin rash induced by EGFRi is composed of T cells, dendritic cells, neutrophils, macrophages, and mast cells (Lichtenberger 2013). This is also accompanied by an increase in the expression of several proinflammatory chemokines such as CCL2, CCL5, CCL27, and CXCL14, and a decrease in antibacterial peptides that favors bacterial proliferation (Lichtenberger 2013). Recently, increased expression of interleukin (IL)-36γ and IL-8 has been reported in lesions of acneiform eruption associated with EGFR/MEK inhibition (Satoh 2020).

Current treatments for the acneiform rash induced by EGFRi/MEKi include topical and systemic antibiotics and corticosteroids, but the efficacy of these treatments is limited (Lacouture 2011, Farahnik 2016, Manousaridis 2013). In severe cases (eg, acneiform rash of Grade 2 or 3 as per CTCAE grading), dose reduction or cessation of EGFRi/MEKi may be required despite the use of antibiotics and corticosteroids (Boone 2007, Manousaridis 2013). There is a definite need for more efficacious and specific treatments for the management of acneiform rash induced by EGFRi/MEKi.

### 2.1.2 ANB019

ANB019 is a high-affinity, humanized, immunoglobulin G4 (IgG4) monoclonal antibody (mAb) that specifically binds IL-36 receptor (IL-36R) and antagonizes IL-36 signaling. The IL-36 cytokines (IL-36α, IL-36β, and IL-36γ) engage with IL-36R to initiate signaling events leading to proinflammatory responses. Interleukin 36 signaling is counter-balanced by IL-36R antagonist (IL-36Ra), an IL-36 receptor antagonist that binds to IL-36R and competes with activity of IL-36 cytokines. Inhibition of IL-36 signaling, by targeting IL-36R with a specific mAb, may represent a novel strategy to control the pathological inflammatory cascade driven by IL-36 pathway activation.

ANB019 is currently being studied as a potential first-in-class therapy for generalized pustular psoriasis (GPP), palmoplantar pustulosis (PPP), and other inflammatory diseases where the IL-36 pathway might

play a pathogenic role. Of note, generalized pustular psoriasis is characterized by a very extensive pustular rash.

### 2.1.3 STUDY RATIONALE

It has recently been shown that IL-36γ drives skin toxicity induced by EGFRi and MEKi (Satoh 2020). Gene expression profiling using biopsies from patients presenting the acneiform rash has shown an increase in expression of IL-36γ and IL-8. Interleukin-36 is known to induce the production of IL-8, a potent chemotactic factor for neutrophils. This could explain the presence of pustules in the acneiform rash. Interestingly, administration of an anti-IL-8 antibody has been reported to suppress the acneiform rash induced by SC injection of an anti-EGFR monoclonal antibody in healthy volunteers (Bangsgaard 2012).

The importance of the IL-36 pathway in the pathophysiology of the acneiform rash and the improvement induced by anti-IL-8 antibodies in the healthy volunteer model of acneiform eruption strongly suggest that ANB019 could improve or even suppress the acneiform rash induced by EGFRi/MEKi. Therefore, inhibition of IL-36γ signaling by blocking IL-36R with ANB019 may provide a novel strategy to control the intense inflammatory reaction of acneiform rash induced by EGFRi/MEKi therapy in patients with neoplasms.

## 2.2 BACKGROUND

### 2.2.1 NONCLINICAL STUDIES

ANB019 exhibits strong inhibitory activity for human as well as cynomolgus monkey IL-36R (cyIL-36R) cell populations. Nonclinical data obtained from studies with ANB019 in primary human and cynomolgus monkey cells and from in vivo nonhuman primate studies demonstrated that:

- ANB019 shows reactivity with human and cyIL-36R (dissociation constant [KD] of 67.9 ± 31.4 pM and 80.0 ± 49.6 pM, respectively), but not with mouse or rat IL-36R.
- In primary human and cynomolgus monkey cell populations, keratinocytes, peripheral blood mononuclear cells (PBMCs), and human whole blood, ANB019 inhibited IL-36R mediated release of IL-8.
- The terminal half-life ($t_{1/2}$) of ANB019 in cynomolgus monkeys was 304 hours after single intravenous (IV) dose administration, and 310 hours after a single SC dose administration at 10 mg/kg, with bioavailability approximately 76% consistent with the anticipated PK characteristics for a human IgG4 scaffold mAb in the cynomolgus monkey.
- Repeat-dose, Good Laboratory Practice (GLP) toxicity and toxicokinetic (TK) studies of 4, 13, and 26 weeks in duration have been conducted with ANB019 administered by weekly SC and IV injection in cynomolgus monkeys. There were only minor treatment-related injection site findings in the 4-week repeat-dose study. Treatment-related effects in the 13-week toxicity study included increased observations of nonformed feces and prolapsed rectum, and protozoa in the stomachs of cynomolgus monkeys; the latter being consistent with the mechanism of action of an immune-modulator in cynomolgus monkeys (Dubey 2002). Weekly administrations of vehicle-control article, 30 mg/kg/dose ANB019 via SC injection, or 60 mg/kg/dose ANB019 via SC or IV bolus injection, to male and female sexually mature cynomolgus monkeys during the 26-week toxicity and TK study was well tolerated. ANB019-related effects were limited to a low incidence of liquid feces not considered AEs for animals administered 60 mg/kg/dose IV. Thus, the no observed adverse effect level (NOAEL) is 60 mg/kg/dose administered by SC or IV injection.

These data provide a strong scientific rationale for advancing ANB019 through clinical development.

A detailed description of the physical, chemical, and pharmaceutical properties of ANB019 and nonclinical studies is provided in the Investigator's Brochure (IB).

### 2.2.2 CLINICAL STUDIES

Currently, two clinical studies (ANB019-001 and ANB019-005) have been completed. Study ANB019-001 was a Phase 1, first-in-human, single ascending dose (SAD) and multiple ascending dose (MAD) study in healthy volunteers and in subjects with psoriasis. Study ANB019-005 was a Phase 1, ethno-bridging study, a single-dose safety, tolerability, PK, and immunogenicity study of ANB019 in healthy Japanese and Caucasian subjects. A detailed description of the safety and tolerability, and PK/pharmacodynamic (PD) results of these two Phase 1 clinical studies is provided in the IB.

In addition, two Phase 2a studies (ANB019-002 and ANB019-003) to evaluate clinical activity and safety of ANB019 in GPP and PPP are completed and ongoing, respectively. Study ANB019-002 was a single-arm, multiple-dose study to be conducted in subjects with active GPP. Study ANB019-003 was a randomized, placebo-controlled, multiple-dose study to be conducted in subjects with PPP.

## 2.3 RISK/BENEFIT ASSESSMENT

### 2.3.1 KNOWN POTENTIAL RISKS

No major toxicities were observed in the 4-week repeat-dose toxicity study in cynomolgus monkeys. The main finding consisted of minor, injection site reactions associated with the SC route of administration and not considered AEs.

In cynomolgus monkeys, treatment-related effects observed in the 13-week repeat-dose toxicity study included protozoa in the stomach, an increase in nonformed feces, and prolapsed rectum observations; the latter observation was not considered dose-related. The increase in protozoa in the stomach has been observed in monkeys treated with immune-modulating drugs (Dubey 2002) and is consistent with the putative mechanism of action of ANB019. During the 26-week repeat-dose toxicity study, ANB019-related effects were limited to a low incidence of liquid feces. In the monkeys, the increased incidence of protozoa, nonformed feces, and prolapsed rectum were not considered AEs as they responded to veterinarian intervention. In humans, gastrointestinal infections can be clinically monitored and, in the case of most protozoa, are readily treatable even in the context of immunocompromised individuals (Farthing 2006).

One female monkey receiving 60 mg/kg ANB019 IV was found moribund on Study Day 34. The cause of death was not determined and had an uncertain relationship to ANB019 but could be due to treatment-related immune modulation. However, data published on IL-36R deficient humans shows no deleterious effect on general health and normal immune function is broadly preserved, indicating that inhibition of the IL-36R, apart from disease modification, does not generally compromise host defenses. Similar to other immune-modulating treatment paradigms, subjects should be closely monitored for any clinical gastrointestinal manifestations including infections and evaluated on an ongoing basis. If a gastrointestinal infection is suspected, the subject should be treated as clinically indicated.

In the ANB019-001 study in healthy adults, single doses of ANB019 up to 750 mg administered by IV infusion or SC injection to 32 healthy adults in the SAD part of the Phase 1 study were generally well tolerated with a similar number of treatment-emergent adverse events (TEAEs) reported in subjects receiving ANB019 or placebo, 29 subjects (81%) and 11 subjects (92%), respectively. The most frequently reported AEs were upper respiratory tract infection (URTI) (10 [28%] ANB019; 6 [50%] placebo),

headache (10 [28%] ANB019; 3 [25%] placebo), and viral URTI (4 [11%] ANB019; 1 [8%] placebo). Additionally, multiple doses of ANB019 up to 300 mg administered by IV infusion once weekly for 4 weeks to 18 healthy adults were also well tolerated. Overall, TEAEs occurred in 16 subjects (89%) receiving ANB019 and in 3 subjects (50%) receiving the placebo. The most common AEs were headache (7 [39%] ANB019; 1 [17%] placebo) and URTI (3 [17%] ANB019; 1 [17%] placebo).

In ANB019-005, single doses of ANB019 up to 750 mg administered by IV infusion or SC injection to 32 healthy Japanese and Caucasian adults were generally well tolerated. The most common TEAEs were alanine aminotransferase (ALT) increased (3 subjects [9.4%]) and aspartate aminotransferase (AST) increased (2 subjects [6.3%]).

To date, 1 SAE of sepsis was reported in the completed ANB019-002 study in subjects with GPP; the SAE was considered possibly related to the study drug. The subject had a medical history of sepsis and experienced the SAE after the 750 mg IV dose administration. Antibiotic treatment rapidly resolved the sepsis episode with complete subject recovery. Further details of ANB019 clinical studies are in the IB.

As allergic or anaphylactic reactions may occur in any subjects treated with mAbs, subjects should be observed during study drug administration and for a period of 30 mins after each dose administration. Subjects with true allergic/anaphylactic reactions should not receive further doses of the monoclonal antibody. Symptoms of an apparent allergic reaction to the drug, also known as ‘cytokine release syndrome’, vary dramatically but can include:

- Mild to moderate fever, chills, headache, nausea, and vomiting
- Moderate to severe symptoms such as edema, hypotension, and pulmonary infiltrates (eg, blood and mucus in the lung)

Such reactions should be managed as clinically indicated and according to standard clinical practice.

### 2.3.2 KNOWN POTENTIAL BENEFITS

Subjects with EGFRi/MEKi-associated acneiform rash may or may not receive direct benefit from participating in this study. An improvement in the acneiform rash as a result of participating in the study, may be observed if subjects are randomized to the active study treatment.

Participation in this study also may help generate future benefit for larger groups of patients with EGFRi/MEKi-associated acneiform rash if ANB019 proves to be successful in treating this manifestation.

### 2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

All quality, pharmacology and toxicology data, and satisfactory safety and tolerability data demonstrated in nonclinical and clinical studies are considered sufficient to expect a positive benefit/risk ratio for the treatment of EGFRi/MEKi-associated acneiform rash with ANB019, and therefore to initiate this study.

The risk to subjects in this study will be minimized by compliance with the eligibility criteria, proper study design, and close monitoring.

# 3 OBJECTIVES AND ENDPOINTS

## 3.1 PRIMARY OBJECTIVE AND ENDPOINT

| Primary Objective | Primary Endpoint |
|---|---|
| • To assess the efficacy of ANB019 compared with placebo in reduction of acneiform rash in subjects receiving EGFRi or MEKi therapy as measured by facial inflammatory lesion count | • Change from Baseline in facial inflammatory lesion count (papules and pustules) at Week 8 |

## 3.2 SECONDARY OBJECTIVES AND ENDPOINTS

| Secondary Objectives | Secondary Endpoints |
|---|---|
| • To determine the effect of ANB019 compared with placebo on acneiform rash signs and symptoms, and quality of life in subjects receiving EGFRi or MEKi therapy | • Percent change from Baseline in facial inflammatory lesion count (papules and pustules) at Week 8<br>• Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash CTCAE grading scale at Week 8<br>• Time to first response of 1 grade improvement from Baseline on the acneiform rash CTCAE grading scale<br>• Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash modified MESTT grading scale (total score) at Week 8<br>• Time to first response of 1 grade improvement from Baseline on the acneiform rash modified MESTT grading scale (total score)<br>• Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash modified MESTT grading scale (facial assessment) at Week 8<br>• Time to first response of 1 grade improvement from Baseline on the acneiform rash modified MESTT grading scale (facial assessment)<br>• Change from Baseline in pruritus NRS at Week 8<br>• Percent change from Baseline in pruritus NRS at Week 8<br>• Change from Baseline in pain NRS at Week 8<br>• Percent change from Baseline in pain NRS at Week 8<br>• Change from Baseline in FACT-EGFRi-18 at Week 8 |
| • To assess the safety and tolerability of ANB019 in subjects with acneiform rash receiving EGFRi or MEKi therapy | • 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 |

## 3.3 EXPLORATORY OBJECTIVES AND ENDPOINTS

| Exploratory Objectives | Exploratory Endpoints |
|---|---|
| • To further evaluate the effect of ANB019 compared with placebo on acneiform rash signs and symptoms, and quality of life in subjects receiving EGFRi or MEKi therapy | • Change from Baseline in facial inflammatory lesion count (papules and pustules) at each visit other than Week 8<br>• Percent change from Baseline in facial inflammatory lesion count (papules and pustules) at each visit other than Week 8<br>• Change from Baseline in facial papule count at each visit<br>• Percent change from Baseline in facial papule count at each visit<br>• Change from Baseline in facial pustule count at each visit<br>• Percent change from Baseline in facial pustule count at each visit<br>• Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash CTCAE grading at each visit other than Week 8<br>• Proportion of subjects with an improvement of at least 1 grade from Baseline in modified MESTT grading scale at each visit other than Week 8<br>• Change from Baseline in pruritus NRS at each visit other than Week 8<br>• Percent change from Baseline in pruritus NRS at each visit other than Week 8<br>• Change from Baseline in pain NRS at each visit other than Week 8<br>• Percent change from Baseline in pain NRS at each visit other than Week 8<br>• Change from Baseline in FACT-EGFRi-18 at each visit other than Week 8<br>• Proportion of subjects achieving an improvement of 50% from Baseline in facial inflammatory lesion count (papules and pustules) at each visit<br>• Proportion of subjects achieving an improvement of 75% from Baseline in facial inflammatory lesion count (papules and pustules) at each visit<br>• Change from Baseline in acneiform rash CTCAE grading scale at each visit<br>• Change from Baseline in acneiform rash modified MESTT grading scale (total score) at each visit<br>• Percent change from Baseline in acneiform rash modified MESTT grading scale (total score) at each visit |

| | |
|---|---|
| | • Change from Baseline in acneiform rash modified MESTT grading scale (facial assessment) at each visit<br>• Change from Baseline in acneiform rash modified MESTT grading scale (back assessment) at each visit<br>• Change from Baseline in acneiform rash modified MESTT grading scale (scalp assessment) at each visit<br>• Change from Baseline in acneiform rash modified MESTT grading scale (chest assessment) at each visit<br>• Change from Baseline in IGA at each visit<br>• Proportion of subjects achieving an IGA of none (0) or almost minimal (1) at each visit<br>• Proportion of subjects with at least 2-point decrease in IGA at each visit<br>• Change from Baseline in facial IGA at each visit<br>• Proportion of subjects achieving a facial IGA of none (0) or minimal (1) at each visit<br>• Proportion of subjects with at least 2-point decrease in facial IGA at each visit<br>• Proportion of subjects with at least 3-point decrease in pruritus NRS at each visit for subjects with a Baseline pruritus NRS of at least 3<br>• Proportion of subjects with at least 4-point decrease in pruritus NRS at each visit for subjects with a Baseline pruritus NRS of at least 4<br>• Proportion of subjects with at least 3-point decrease in pain NRS at each visit for subjects with a Baseline pain NRS of at least 3<br>• Proportion of subjects with at least 4-point decrease in pain NRS at each visit for subjects with a Baseline pain NRS of at least 4<br>• Proportion of subjects in each response category for the PGI-S and PGI-C at each visit<br>• Proportion of subjects achieving mild or clear skin according to the PGI-S at each visit<br>• Proportion of subjects achieving improvement (a little better, much better, or very much better) according to the PGI-C at each visit<br>• Proportion of subjects receiving rescue medication from Week 4 through Week 24<br>• Proportion of subjects that do not require a dose reduction of EGFRi or MEKi therapy due to acneiform rash at each visit<br>• Proportion of subjects that do not require cessation of EGFRi or MEKi therapy due to acneiform rash at each visit<br>• Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash modified MESTT |

| Exploratory Objectives | Exploratory Endpoints |
|---|---|
| | grading scale (facial assessment) at each visit other than Week 8<br>• Percent change from Baseline in facial inflammatory lesion count (papules and pustules) at each visit other than Week 8<br>• Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash modified MESTT grading scale (back assessment) at each visit<br>• Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash modified MESTT grading scale (scalp assessment) at each visit<br>• Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash modified MESTT grading scale (chest assessment) at each visit<br>• Time to first response of 1 grade improvement from Baseline on the acneiform rash modified MESTT grading scale (back assessment)<br>• Time to first response of 1 grade improvement from Baseline on the acneiform rash modified MESTT grading scale (scalp assessment)<br>• Time to first response of 1 grade improvement from Baseline on the acneiform rash modified MESTT grading scale (chest assessment) |
| • To explore the effect of ANB019 on other EGFRi/MEKi adverse drug reactions (paronychia, dry skin, alopecia, and pruritus) | • Change from Baseline in number of nail folds with paronychia at each visit<br>• Proportion of subjects with paronychia, dry skin, alopecia, and pruritus of Grade 0 or 1 as per CTCAE grading scale at each visit |
| • To assess the effect of ANB019 on gastrointestinal inflammation in subjects with acneiform rash receiving EGFRi or MEKi therapy | • Change from Baseline in STIDAT at each visit<br>• Percent change from Baseline in STIDAT at each visit |
| • To explore the effect of ANB019 on cutaneous biomarkers | • Skin tape strip biomarkers analysis including, but not limited to, IL-36 and Th-17 |
| • To explore the effect of ANB019 on acneiform rash as measured by facial inflammatory lesion count using standardized photographs | • Change from Baseline in inflammatory lesion counts as determined by standardized photographs at each visit<br>• Percent change from Baseline in inflammatory lesion counts as determined by standardized photographs at each visit |
| • To describe the PK profile of ANB019 in subjects with acneiform rash receiving EGFRi or MEKi therapy | • Serum concentration following ANB019 administration and other parameters as appropriate will be determined to describe the PK profile of ANB019 |

| Exploratory Objectives | Exploratory Endpoints |
|---|---|
| • To test for immunogenicity to ANB019 | • Presence of ADA to ANB019 |

# 4 STUDY DESIGN

## 4.1 OVERALL DESIGN

This study is a Phase 2a, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy, safety, and tolerability of ANB019 in the treatment of acneiform rash in subjects with neoplasm receiving EGFRi or MEKi. This study will also characterize the PK profile of ANB019 and explore the immune response to ANB019 in subjects with EGFRi/MEKi-associated acneiform rash.

Written informed consent will be obtained from each subject prior to initiating any study-related procedures.

Approximately 45 adult male and female subjects, aged 18 to 75 years, will be randomized in this study. To be eligible for the study, subjects must be receiving oral or injectable commercially available EGFRi or MEKi therapy at the Screening and Day 1 visits. Subjects can enter the initial screening regardless of their current acneiform rash status and severity (as described in Section 5.1). However, at the Screening Part 2 and at Day 1, subjects must have an acneiform rash of Grade ≥ 2 as per CTCAE Version 5.0, and ≥ 20 inflammatory lesions on the face. Randomization will be stratified based on acneiform rash CTCAE grade at Baseline and therapy the subject is receiving (EGFRi vs MEKi).

The expected study duration per subject is up to approximately 12 months from the screening to last visit. Subjects who enter the screening period without an acneiform rash or with an acneiform rash severity that does not meet the requirements of Inclusion Criterion 3 (refer to Section 5.1) may remain in Screening for up to 6 months and be reevaluated if/when an acneiform rash develops or worsens as long as they remain on EGFRi or MEKi therapy. Once the acneiform rash severity meets the requirements of Inclusion Criterion 3, a last screening visit (Screening Part 2; refer to Section 1.3) must be performed, within 15 days prior to Day 1, ideally within 1 week. The screening period will be followed by a 16-week treatment period and an 8-week follow-up period.

During the treatment period, eligible subjects will be randomized (2:1) to receive either ANB019 or placebo, SC administered at 4 time points. On Day 1, the subjects will receive a 400-mg dose of ANB019 or placebo. On Days 29, 57, and 85, the subjects will receive a 200-mg dose of ANB019 or placebo. Refer to Section 6.1.2 for additional details on study treatment administration.

For scheduled study visits, subjects will come to the study center up to 9 occasions to monitor changes in disease activity, PK (if applicable), safety, and tolerability: screening (depending on subject acneiform rash status, the screening visit may be planned either as 1 visit or 2 separate visits) and Days 1, 15, 29, 57, 85, 113, and 169 (EOS/ET). All procedures will be conducted in accordance with the SoA in Section 1.3. Of note, the primary endpoint will be evaluated on Day 57 (Week 8).

Disease activity will be evaluated for all subjects using facial inflammatory lesion count, acneiform rash CTCAE grading, acneiform rash modified MESTT grading, IGA, facial IGA, pruritus NRS, pain NRS, PGI-S, PGI-C, number of nail folds with paronychia, and paronychia, dry skin, alopecia, and pruritus CTCAE grading. The subject's quality of life will be assessed using the FACT-EGFRi-18. Subject's gastrointestinal inflammation will be evaluated using the STIDAT. Subject's level of functioning and daily living abilities will be evaluated to confirm eligibility using the ECOG performance status.

In addition, standardized photographs of the face will be taken at the time points specified in the SoA to record inflammatory lesions for lesion counts analysis as supporting information for efficacy analyses.

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

Blood samples to determine PK and immunogenicity (presence of ADA to ANB019) will be collected on Day 1 before the administration of the study treatment and at the other time points specified in the SoA (see Section 1.3). Any remaining samples collected for PK and immunogenicity endpoints may be retained for assay method development, troubleshooting, or validation. The samples will not be used for any type of genetic analyses. Tape strips for biomarker analysis will be collected at the time points specified in the SoA.

Interim analyses (IAs) may be performed during the treatment period for assessment of all primary and secondary efficacy endpoints, and evaluation of all safety data available.

## 4.2 MODIFICATIONS TO STUDY CONDUCT DUE TO THE CORONAVIRUS DISEASE 2019 (COVID-19) PANDEMIC

As a consequence of the COVID-19 pandemic that has had a worldwide impact, including cases in North America and Europe, control measures in place in different regions may impact the ability to adhere to some of the study procedures described in this protocol. Due to challenges that include, but are not limited to, subject preferences, site closures, travel restrictions, and quarantines, some modifications to study conduct during the COVID-19 pandemic may be necessary to ensure study continuity, including conducting optional home visits when on-site study visits are considered not feasible. Such modifications in study conduct always must be in accordance with local regulations/mandates.

The following are allowable, as necessary, modifications to study conduct during the COVID-19 pandemic.

- Prior to a study visit at the site, the subject may be contacted and screened for potential exposure or infection to COVID-19 per site, local, or federal requirements. If the subject is suspected to be exposed or infected with COVID-19, the on-site visit should either be re-scheduled or a virtual visit may be performed instead, as applicable.
- In the event that a subject cannot attend their regularly scheduled study visits in person due to COVID-19 necessitating a limit on in-person contact, the investigator may perform safety and efficacy assessments by phone or video, with home nursing visit support for procedures that cannot be done virtually. The investigator may use the technology platform that is currently available to them. Suggested platforms include Apple FaceTime, Zoom for Healthcare, Facebook Messenger video chat, Microsoft Teams, Google Hangouts video, and Skype. Home nursing visit support may be used in addition to phone or video at visits that require procedures that cannot be done via phone or video alone, such as but not limited to, ECG, PK draws, clinical laboratory draws, study drug administration. The home nurse will collect the lab samples and perform all applicable study assessments that are possible during a home visit, including collection of adverse events and concomitant medications. During the COVID-19 period, if any data are collected at a home visit, it will be recorded by the home nurse in the source documents and the originals will be sent back to the site for data entry into the electronic data capture system for storage/archiving.
- Clinical laboratory tests (chemistry and hematology) and pregnancy tests may be performed by local laboratory, if home nursing visits are not possible and sample collection cannot be performed at the study site due to COVID-19 related limitations, including but not limited to site closure. Abnormal laboratory results should be promptly communicated to the Medical Monitor. Subjects' anonymity must be maintained when communicating results to the Medical Monitor.
- At home investigational product administration by home health nurses may be done.
- Source documentation should note that the visit was performed virtually (not face-to-face) and note the name of the local lab where laboratory tests were done.

- If certain study procedures or assessments cannot be completed per the schedule of events, the reason for the missed assessment (ie, laboratory tests, vital signs, physical examinations, etc) must be noted in the source documentation (eg, COVID-19), captured in the protocol deviations documentation, and reported to the IRB/EC, as applicable.

A detailed assessment of COVID-19 related risk and mitigation measures will be documented in the appropriate study plans.

## 4.3 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The effective treatment of EGFRi/MEKi-associated acneiform rash remains an unmet medical need. The efficacy of available treatments (including topical and systemic antibiotics and corticosteroids) is limited and many patients with severe acneiform rash require dose reduction or cessation of EGFRi or MEKi therapy despite the use of these treatments.

In this context, the development of agents with new mechanisms of action is considered important for future clinical practice. As ANB019 offers the potential for inhibition of IL-36 signaling by blocking IL-36R, it may provide a novel strategy for treatment of patients with EGFRi/MEKi-associated acneiform rash, for whom increased lesional expression of IL-36γ has been reported.

The proposed design is considered appropriate for assessing the efficacy, safety, and tolerability of ANB019 compared with placebo in subjects with EGFRi/MEKi-associated acneiform rash.

In this study, randomization will ensure random allocation of subjects to treatment arms to reduce bias. Randomization will be stratified based on acneiform rash CTCAE grade at Baseline and therapy the subject is receiving (EGFRi vs MEKi). Because efficacy assessments of EGFRi/MEKi-associated acneiform rash have a high degree of subjectivity, the study will be double-blinded. The highest degree of subject and assessor (investigator or designee) blinding should be sought to achieve credible inference. A placebo-controlled period in this Phase 2a study will control for confounding factors, such as potential investigator bias, and ensure that the statistical procedures can be appropriately applied. In addition, the use of a placebo will help interpret the result of the study, because a spontaneous improvement of EGFRi/MEKi-associated acneiform rash is expected in several subjects. However, subjects with limited improvement of EGFRi/MEKi-associated acneiform rash will have access to rescue medication starting from Week 4, as judged by the investigator.

## 4.4 JUSTIFICATION FOR DOSE

During the treatment period, ANB019 will be SC administered as a 400 mg dose on Day 1, followed by a 200 mg dose on Days 29, 57, and 85.

The doses selected for the study demonstrated a favorable safety and tolerability profile in a Phase 1 study conducted in healthy volunteers. In addition, ANB019 demonstrated linear PK with an estimated terminal half-life ($t_{1/2}$) of approximately 28 days at all doses tested with persistent pharmacodynamic activity. The loading dose of 400 mg SC administered on Day 1 was chosen to achieve maximum observed concentration ($C_{max}$) soon after dosing in order to provide optimal potential benefit to subjects with EGFRi/MEKi-associated acneiform rash and to reach steady-state concentrations rapidly following 200-mg SC dosing. The treatment period duration is expected to provide better clinical outcome, thus potentially benefiting subjects with EGFRi/MEKi-associated acneiform rash and further assessing the long-term efficacy and safety of ANB019.

## 4.5 END OF STUDY DEFINITION

A subject is considered to have completed the study if he or she has completed all periods of the study including the last specified visit (Day 169 [Week 24]/ET) shown in the SoA (see Section 1.3).

The end of the study is defined as completion of the last visit or procedure shown in the SoA by the last subject included the study.

# 5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

It is imperative that subjects fully meet all the inclusion criteria and none of the exclusion criteria.

## 5.1 INCLUSION CRITERIA

To be eligible to participate in this study, a subject must meet all of the following criteria, either at the Screening and Day 1 visits, or only at one of the specified visits (Screening or Day 1) as noted in the criterion:

1. Male and female subject aged 18 to 75 years (inclusive) at the time of signing the informed consent.
2. Subject is treated with an oral or injectable commercially available EGFRi or MEKi therapy (alone or in combination) for a diagnosed neoplasm.
3. Subject has EGFRi/MEKi-related acneiform rash of Grade ≥ 2 as per CTCAE Version 5.0, and ≥ 20 inflammatory lesions on the face at the Screening Part 2 visit and on Day 1.
4. Subject has an ECOG performance score between 0 and 2 at Day 1.
5. Subject has a life expectancy of ≥ 6 months at Day 1.
6. Subject meets the following laboratory criteria at the Screening Part 2:
   a) Hemoglobin ≥ 90 g/L (≥ 9 g/dL);
   b) White blood cell count ≥ 3.0 × 109/L (≥ 3.0 × 103/µL);
   c) Platelets ≥ 100 × $10^9$/L (≥ 100 × $10^3$/µL);
   d) Serum creatinine ≤1.5 × upper limit of normal (ULN) or creatinine clearance ≥ 50 mL/min;
   e) ALT and AST ≤ 2.5 × ULN with no liver metastases and ≤ 5 x ULN in presence of liver metastases;
   f) Total bilirubin ≤ 1.5 × ULN. Subjects with known Gilbert's disease who have serum bilirubin < 3 × ULN may be included;
   g) Absolute neutrophils count > 1.5 × 103/µL.
7. Subject has a body weight ≥ 40kg.
8. Subject has no clinically significant medical condition (other than neoplasm) or physical/laboratory/ECG/vital signs abnormality that would, in the opinion of the investigator, put the subject at undue risk or interfere with interpretation of study results.
9. Subject meets the following tuberculosis (TB) screening criteria:
   a) Has no history of latent or active TB before screening, with an exception for subjects who have a history of latent TB that provide documentation of having completed appropriate treatment for latent TB before the first administration of study drug. The investigator must verify the adequacy of previous anti-TB treatment based on current local TB treatment guidelines and provide appropriate documentation.
   b) Has no signs or symptoms suggestive of active TB upon medical history and/or physical examination.
   c) Has had no recent close contact with a person with active TB, based on information provided by the subject.
   d) Has a negative QuantiFERON®-TB test result obtained during screening prior to Day 1.
   Note: a QuantiFERON®-TB test is not required at Screening for subjects with a history of latent TB who have previously completed appropriate TB treatment as described above in Inclusion Criterion 9a.

Note: A negative tuberculin skin test (as per local guidelines) may be required if the QuantiFERON®-TB test is not approved/registered in that country or the tuberculin skin test is mandated by local health authorities. If the tuberculin skin test is positive, but is suspected to be a false positive, a confirmation by a specialist will be required to exclude latent/active TB based on local guidelines. A subject whose first screening QuantiFERON-TB® test result is indeterminate may have the test repeated once.

e) Has no more than 1 indeterminate QuantiFERON®-TB test result during screening.
f) Has the report from a qualified radiologist of a chest X-ray performed within 6 months before Day 1 that shows no abnormalities suggestive of a current active infection, including TB. A chest CT scan is also acceptable if already available. If not performed with 6 months before Day 1, a chest X-ray must be performed at Screening.

10. Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
Contraception and pregnancy:
    a) A male subject who is sexually active with a female of childbearing potential and has not had a vasectomy must agree to use contraception as detailed in Appendix 1 of this protocol during the treatment period and for at least 220 days (which includes the duration of relevant exposure plus the duration of sperm cycle) after the last study treatment administration and refrain from donating sperm during this period.
    b) Female subjects:
        i) A woman of childbearing potential (WOCBP) is eligible to participate if she has a negative serum pregnancy test (beta-human chorionic gonadotropin) at Screening and a negative urine pregnancy test at Day 1 (see Appendix 1), is not breastfeeding, and if heterosexually active agrees to follow the contraceptive guidance in Appendix 1 during the treatment period and for at least 6 months after receiving the study treatment, and refrains from donating oocytes for assisted reproduction during this period. The female subject's selected form of contraception must be effective by the time the female subject enters into the study at Day 1 (eg, hormonal contraception should be initiated at least 28 days before Day 1).
        ii) A woman not of childbearing potential is eligible to participate if she meets the criteria in Appendix 1.

    Note: If a female participant's childbearing potential changes after start of the study (eg, a woman who is not heterosexually active becomes active, a premenarchal woman experiences menarche), she must begin practicing a highly effective method of birth control, as described above.

11. Subject is willing to participate and is capable of giving written informed consent, which must be personally signed and dated by the subject and obtained prior to any study-related activities.
12. Subject must be willing to comply with all study procedures and must be available for the duration of the study.

## 5.2 EXCLUSION CRITERIA

A subject who meets any of the following criteria at the screening and/or Day 1 visits, as applicable, will be excluded from participation in this study:

1. Subject has clinical evidence of an infection of their EGFRi/MEKi-associated acneiform rash (eg: cellulitis, impetigo), according to the investigator's evaluation.
2. Subject has other medical conditions which may interfere with the investigators' ability to evaluate the subject's response to therapy, as judged by the investigator.

3. Subject has significant skin disease other than EGFRi/MEKi-induced acneiform rash that, in the opinion of the investigator, would interfere with the study assessments.
4. Subject has a history of clinically significant (as determined by the investigator) cardiac, pulmonary, neurologic, gastrointestinal, endocrine, hematological, renal, hepatic, cerebral or psychiatric disease, or other major uncontrolled disease that makes them unsuitable for the study.
5. Subject has a history of chronic or recurrent infectious disease, including but not limited to upper and lower respiratory infection (eg, sinusitis, bronchitis, and bronchiectasis), urinary tract infection (eg, recurrent pyelonephritis), and skin infection (eg, abscesses, infected skin wounds, or ulcers) within 6 months prior to Screening. Note: A subject with a history of localized oral or genital herpes simplex that, in the opinion of the investigator, is well-controlled will be eligible for study participation.
6. Subject has a history or any evidence of active infection (eg, bronchopulmonary, urinary, or gastrointestinal) that required systemic antibiotic, antifungal or antiviral therapy within 2 weeks of Day 1, excluding localized oral or genital herpes simplex that, in the opinion of the investigator, is well-controlled.
7. Subject has any factors (other than related to neoplasm) that would predispose the subject to develop an infection in the investigator's opinion.
8. Subject has a history of an opportunistic infection (eg, *Pneumocystis carinii*, aspergillosis, or mycobacteria other than tuberculosis [TB]) or parasitic infections (eg, helminths, protozoa, *Trypanosoma cruzi*) within 3 months prior to Screening.
9. Subject has a history of a herpes zoster infection within 2 months prior to Screening.
10. Subject has any history of known or suspected congenital or acquired immunodeficiency state, or condition that would compromise the subject's immune status (eg, history of splenectomy) not related to their neoplasm diagnosis or treatment.
11. Subject had any major surgery within 2 weeks of Day 1.
12. Subject has a history of any significant drug allergy or reaction (such as anaphylaxis or hepatotoxicity) to polysorbate 20, a component of ANB019 formulation, or the inactive ingredients (excipients).
13. For subjects with prior use of the following therapies or procedures, the specified washouts between last dose of prohibited medication (or date of procedure) and Day 1 will apply:
    a) Over-the-counter (OTC) topical medication that can have an effect on acneiform rash, including topical anti-inflammatory medications, or antibacterial/antiseptic soap or wash:
        i) If used consistently without any alteration in dosage for at least 14 days prior to Day 1: subject may agree to either continue at current dosage over the entire course of the study OR discontinue the treatment at least 1 day prior Day 1.
        ii) If dosing initiated or dosage was changed less than 14 days prior to Day 1, the treatment must be discontinued at least 1 day prior to Day 1.
    b) Topical corticosteroids that can have an effect on acneiform rash:
        i) If used consistently without any alteration in dosage for at least 14 days prior to Day 1: subject may agree to either continue at current dosage over the entire course of the study OR discontinue the treatment at least 1 day prior to Day 1.
        ii) If dosing initiated or dosage was changed less than 14 days prior to Day 1, the treatment must be discontinued at least 1 day prior to Day 1.
        Note: Topical hydrocortisone ≤ 1% is allowed throughout the study.
    c) Topical retinoids (eg: tretinoin, tazarotene, adapalene, dapsone) or other prescription topical medications that can have an effect on acneiform rash:

i) If used consistently without any alteration in dosage for at least 14 days prior to Day 1: subject may agree to either continue at current dosage over the entire course of the study OR discontinue the treatment at least 1 day prior to Day 1.
ii) If dosing initiated or dosage was changed less than 14 days prior to Day 1, the treatment must be discontinued at least 1 day prior to Day 1.

d) Topical antimicrobials (eg, clindamycin, erythromycin):
i) If used consistently without any alteration in dosage for at least 14 days prior to Day 1: subject may agree to either continue at current dosage over the entire course of the study OR discontinue the treatment at least 1 day prior to Day 1.
ii) If dosing initiated or dosage was changed less than 14 days prior to Day 1, the treatment must be discontinued at least 1 day prior to Day 1.

e) Topical agents (on the regions affected by the rash) that could affect pruritus (eg, topical antipruritic agents):
i) If used consistently without any alteration in dosage for at least 14 days prior to Day 1: subject may agree to either continue at current dosage over the entire course of the study OR discontinue the treatment at least 1 day prior to Day 1.
ii) If dosing initiated or dosage was changed less than 14 days prior to Day 1, the treatment must be discontinued at least 1 day prior to Day 1.

f) Systemic agents that could affect pruritus (such as oral antihistaminic, gabapentin, pregabalin, doxepin, and aprepitant):
i) If used consistently without any alteration in dosage for at least 14 days prior to Day 1: subject may agree to either continue at current dosage over the entire course of the study OR discontinue the treatment at least 1 day prior to Day 1.
ii) If dosing initiated or dosage was changed less than 14 days prior to Day 1, the treatment must be discontinued at least 1 day prior to Day 1.

g) Oral antibiotic therapy for EGFRi/MEKi-associated acneiform rash:
i) If used consistently without any alteration in dosage for at least 14 days prior to Day 1: subject may elect to either remain on the therapy at current dosage for the entire duration of the study OR discontinue the treatment at least 1 day prior to Day 1.
ii) If dosing initiated or dosage was changed less than 14 days prior to Day 1, a washout period of 1 day is required prior to Day 1.

h) Other systemic antiacne drugs not mentioned in other exclusion criteria:
i) If used consistently without any alteration in dosage for at least 14 days prior to Day 1: subject may agree to either continue at current dosage over the entire course of the study OR discontinue the treatment at least 1 day prior to Day 1.
ii) If dosing initiated or dosage was changed less than 14 days prior to Day 1, the treatment must be discontinued at least 1 day prior to Day 1.

i) Intramuscular corticosteroid injections: must be discontinued at least 28 days prior to Day 1.

j) Oral corticosteroids: must be discontinued at least 7 days prior to Day 1.
Note: Corticosteroids used to prevent nausea, vomiting, or hypersensitivity reactions related to treatment of neoplasm (eg, dexamethasone) are allowed.
Note: Intranasal corticosteroids and inhaled corticosteroids are allowed.
Note: Eye and ear drops containing corticosteroids are also allowed.

k) Facial procedures (eg, chemical peel, laser, microdermabrasion): must be discontinued at least 4 weeks prior to Day 1.

l) Photodynamic therapy or phototherapy with blue or red light: must be discontinued at least 14 days prior to Day 1.

m) Androgen receptor blockers (such as spironolactone or flutamide): must be discontinued at least 14 days prior to Day 1.
n) Oral retinoid (eg, isotretinoin) or vitamin A supplements > 10,000 U/d: must be discontinued at least 14 days prior to Day 1.
o) Investigational nonbiologic drug: must be discontinued at least 14 days or 5 half-lives (whichever is longer) prior to Day 1.
p) Investigational biologic agent: must be discontinued at least 12 weeks or 5 half-lives (whichever is longer) prior to Day 1.
q) Marketed biologic agent (excluding any use for diagnosed neoplasm): must be discontinued at least 12 weeks or 5 half-lives (whichever is longer) prior to Day 1.

14. Subject has had previous treatment with anti-IL-36R antibody.
15. Subject has used drospirenone, chlormadinone acetate, or cyproterone acetate alone or as a component of an oral contraceptive, unless initiated and used at a stable dosage for at least 12 weeks prior to Day 1.
16. Subject has received live or live-attenuated vaccine within 12 weeks prior to Day 1.
    Note: Nonlive vaccines for currently authorized COVID-19 (eg, RNA-based vaccines, protein-based vaccines, and nonreplicating viral vector-based vaccines) are allowed during the study.
17. Subject has had excessive sun exposure or has used tanning booths within 4 weeks prior to Day 1 or is not willing to minimize natural and artificial sunlight exposure during the study. Use of sunscreen products and protective apparel are recommended when sun exposure cannot be avoided, except within 3 hours prior to the study visit.
18. Subject has a known history of clinically significant drug or alcohol abuse in the last year prior to Day 1, or other factors limiting the ability to cooperate and to comply with the study protocol, as determined by the investigator.
19. Subject is a pregnant or lactating woman, or a woman who intends to become pregnant during the study period.
20. Subject has any other physical, mental, or medical conditions, which, in the opinion of the investigator, make study participation inadvisable or could confound study assessments.
21. Subject has clinically significant abnormality on chest X-ray at screening, or on chest X-ray or any other chest imaging within 6 months prior to screening with the exception of the neoplasm (including primary or metastatic tumor, if applicable).
22. Subject has any clinically significant abnormalities on 12-lead ECG at screening.
23. Subject has a positive blood screen for hepatitis C antibody and hepatitis C RNA, antibodies to hepatitis B core antigens, hepatitis B surface antigen, or human immunodeficiency virus 1 and 2 antibodies.
24. Subject is not able to tolerate SC drug administration.

## 5.3 LIFESTYLE CONSIDERATIONS

Subjects can apply an emollient of their choice (without pharmacological active ingredient) and topical hydrocortisone ≤ 1% on their skin, including on the acneiform eruption as desired throughout the study. For subjects who use make-up, facial moisturizers, creams, lotions, cleansers, and/or sunscreens, the same product brands/types should be used at the same frequency throughout the study. However, these products (including emollient and topical hydrocortisone) must not be applied within 3 hours prior to the study visits. Every effort should be made to keep the same products throughout the study. In case a subject applied these products on the face on a visit day, they will be instructed to wash their face at least 3 hours before the visit and not reapply these products on the face before the visit.

Subjects should continue with their regular facial skin care habits (including shaving) during the study but must not wash or shave their face within 3 hours prior to study the visit.

The commercial name of the selected emollient(s) will be recorded in the source document and the electronic case report form (eCRF). No other products may be applied to the acneiform eruption during the study, unless deemed necessary by the investigator as described in Section 6.5.3.

## 5.4 SCREEN FAILURES

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria not met, and any SAE.

Individuals who do not meet the eligibility criteria for participation in this study (screen failure) may be rescreened once after discussion with the Medical Monitor and if deemed appropriate. However, subjects without an acneiform rash or with an insufficient acneiform rash severity at the initial screening who are still not eligible after the 6-month screening period, will be considered screen failures and should not be rescreened.

Rescreened subjects should not be assigned the same subject number as for the initial screening. All procedures planned at the screening visit, including signature of a new consent form, will be performed.

## 5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

The recruitment and retention strategies for the study will be covered in other study plans.

# 6 STUDY TREATMENT

Study treatment is defined as any investigational treatment or placebo intended to be administered to a clinical study subject according to the study protocol.

## 6.1 STUDY TREATMENT ADMINISTRATION

### 6.1.1 STUDY TREATMENT DESCRIPTION

ANB019 is a humanized IgG4 (S228P)/kappa mAb that belongs in the class of anti-IL-36R mAb.

ANB019 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 slightly yellowish, and clear to very slightly opalescent solution for injection. Detailed administration instructions will be provided in the Pharmacy Manual.

During the treatment period, eligible subjects will be randomized (2:1) to receive either ANB019 or placebo, SC, administered at 4 time points:

- Day 1: 400-mg dose of ANB019 or placebo (administered as 2 SC injections of ANB019 at 200 mg each or placebo)
- Days 29, 57, and 85: 200-mg dose of ANB019 or placebo

Of note, the placebo will be administered via SC injection(s) on the same schedule and in the same volumes as ANB019. Further information will be provided in the Pharmacy Manual.

### 6.1.2 DOSING AND ADMINISTRATION

Study treatment dosing and administration details are provided in Table 2.

**Table 2: Study Treatment Details**

| | | |
|---|---|---|
| **Study Treatment Name:** | ANB019<br>Anti-interleukin 36 receptor monoclonal antibody | Placebo |
| **Dosage Form:** | Solution for injection | Solution for injection |
| **Source of procurement:** | AnaptysBio, Inc. | AnaptysBio, Inc. |
| **Study Treatment Description:** | ANB019 will be provided as a sterile, colorless to yellow, and clear to slightly opalescent solution supplied in a single use, 2R, Type I glass vial with a fill volume of 1 mL. Each vial contains 100 mg of ANB019 at a concentration of 100 mg/mL. | The placebo contains no active ingredient and will be provided as a sterile, colorless to slightly yellowish, and clear to very slightly opalescent solution supplied in a single use, 2R, Type I glass vial with a fill volume of 1 mL. |
| **Dosage Formulation:** | ANB019 study treatment is formulated as: 100 mg/mL ANB019 in 25 mM histidine, 60 mM NaCl, 145 mM sorbitol, and 0.02% v/v polysorbate 20 at pH 6.0. | The placebo is formulated as: 25 mM histidine, 60 mM NaCl, 145 mM sorbitol, and 0.02% v/v polysorbate 20, at pH 6.0. |

**Table 2: Study Treatment Details (Continued)**

| | | |
|---|---|---|
| **Unit Dose Strength(s)/ Dosage Level(s):** | Subjects assigned to ANB019 during the treatment period will receive the following doses:<br>Day 1: 400-mg dose, administered as 2 mL × 2 SC injections of ANB019 at 200 mg each.<br>Days 29, 57, and 85: 200-mg dose, administered as 2 mL × 1 SC injection of ANB019 at 200 mg. | Subjects assigned to placebo during the treatment period will receive an equivalent volume of placebo SC administered on Days 1, 29, 57, and 85.<br>Day 1: 2 mL × 2 SC injections of placebo.<br>Days 29, 57, and 85: 2 mL × 1 SC injection of placebo. |
| **Route of Administration:** | SC injection (4 doses during the treatment period) | SC injection (4 doses during the treatment period) |
| **Dosing Instructions:** | ANB019 and placebo should be administered by clinic staff trained in best practices for SC administration of study treatments.<br>For SC injections, ANB019 and placebo should be prepared by drawing up the required dosing volume into suitable-sized syringe and attaching a dosing needle. No further dilution is required.<br>The preferred anatomical site of SC administration is the abdomen; however, the injection may be made in the upper arm, if needed.<br>An observation period of approximately 30 minutes after each dose should be included.<br>The same anatomical site should be used throughout the entire study for a given subject (ie, do not administer one dose into the upper arm and at a subsequent visit or dose, administer the next dose into the abdomen).<br>Subsequent doses should be rotated within an anatomical site (ie, if the upper left abdominal quadrant is used as the initial site of administration, then the next administration at a subsequent visit should be rotated to the upper right quadrant). Of note, on Day 1 the 2 SC injections should not be rotated within the anatomical site (ie, if the upper left abdominal quadrant is used for the first injection, then the second injection should be administered in the same quadrant).<br>Subcutaneous injections should not be given into moles, scars, tattoos, or areas where the skin is tender, bruised, red, hard, or not intact.<br>Prior to SC needle insertion, the skin will be pinched between the thumb and index finger to separate the subcutaneous layer from the muscle.<br>The needle is to be injected at a 45 to 90-degree angle to the skin.<br>The plunger will be pressed gently until the entire dose is delivered to the SC space and the needle will be held in place (fully depressed) for 10 seconds after the injection is administered.<br>The needle will be removed and then the skin pinch released; any leakage or backflow of fluid from the administration site onto the surface of the skin will be noted and documented in the eCRF.<br>The site of administration is NOT to be massaged by either the clinic staff or by the subject for at least 60 minutes after drug administration. | |

Abbreviations: eCRF, electronic case report form; NaCl, sodium chloride; SC, subcutaneous; v/v, volume to volume.

The contents of the label will be in accordance with all applicable regulatory requirements.

## 6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatments received, and any discrepancies are to be reported and resolved before use of the study treatment.

Only subjects randomized in the study may receive study treatment and only authorized study site staff may supply or administer study treatment. Further guidance and information for the administration of the study treatment are provided in the Pharmacy Manual.

All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study center staff.

ANB019 vials must be refrigerated at 2°C to 8°C (36°F to 46°F) until the day of use. ANB019 must not be used beyond the re-test or expiration date provided by the manufacturer. Vial contents should not be frozen, shaken, or diluted. ANB019 vials undiluted may be stored at room temperature (8°C to 25°C [46°F to 77°F]) for up to 8 hours. Vials are intended for single use only; therefore, any remaining solution should not be used and should be discarded after study treatment accountability and reconciliation.

The investigator is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual.

The investigator, a member of the study center staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study medication using the Drug Accountability Form. These forms must be available for inspection at any time.

## 6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This study is randomized, double-blind, and placebo-controlled. The blind will be maintained throughout the study with limited and controlled access to the randomization code.

All subjects will be assigned a unique subject identification number at the time of screening. On Day 1, after verification that all inclusion and no exclusion criteria have been met, the subjects will be randomized in a 2:1 ratio to receive ANB019 or placebo. As subjects become eligible, they will be assigned unique randomization numbers, which will be used to assign the allocated treatment based on a randomization schedule. Randomization will be stratified based on acneiform rash CTCAE grade at Baseline and therapy the subject is receiving (EGFRi vs MEKi). Ideally, the study should include at least 25% of subjects from each neoplasm therapy at Baseline (EGFRi and MEKi).

The Sponsor, investigator, and subjects will be blinded to treatment assignment of ANB019 or placebo. An unblinded pharmacist will be responsible for study treatment dispensing.

Once the subject has provided an informed consent and meets all inclusion and no exclusion criteria, the study site will request the treatment assignment using a central Interactive Web Response System (IWRS).

The process for breaking the blind will be handled through the IWRS. Unblinding is undertaken by a predetermined process to ensure that participating subject and study team are not unblinded unnecessarily and the study results are not compromised. Unblinding of treatment assignment during the study should occur only if it is necessary to know what treatment the subject received during the

placebo-controlled period. Unblinding should occur if the investigator deems identification of the study treatment is necessary for the purpose of providing urgent subject care, and knowledge of the subject's treatment assignment (ANB019 or placebo) will alter subsequent care (emergency unblinding).

In the event that emergency unblinding is necessary, the investigator must ensure that the unblinding of the treatment code is performed in a discreet manner and the treatment is disclosed only to those persons involved with the direct medical care of the subject. Subjects for whom the blind has been broken will be discontinued from treatment at the time of unblinding. After discontinuation from treatment, subjects should remain in the study but proceed directly into the safety follow-up period. The investigator must provide the reason for unblinding to the Sponsor's Medical Monitor according to the Sponsor instructions following emergency unblinding.

The Sponsor and the contract research organization (CRO) must be notified when a subject and/or investigator is unblinded during the study. The IWRS will create the blinded and/or unblinded notification when the blind is broken, which can be sent via email as per the user role of IWRS. The unblinding will be captured in the IWRS audit trail. Pertinent information regarding the circumstances of unblinding of a subject's treatment code must be documented in the subject's source documents.

## 6.4 STUDY TREATMENT COMPLIANCE

Study treatment compliance in this study will be under the direct control of the investigator; the study treatment will be administered on site.

The prescribed dosage, timing, and mode of administration may not be changed. Any departures from the intended regimen must be recorded in the eCRFs.

For the study treatment administrations, date/time of administration, site of administration, and dose administered (entire dose/incomplete dose) will be documented in the eCRF.

## 6.5 CONCOMITANT THERAPY

Any medication or vaccine (including OTC or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment and receives during the study must be recorded on the eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose, route, and frequency

In addition, all prior medications used to treat EGFRi/MEKi-associated acneiform rash and any other medications taken within 6 months prior to enrollment (Day 1) must be recorded in the eCRF. Live and live-attenuated vaccines may be utilized after subjects complete the safety follow-up period of the study. During the follow-up period, no study drug is administered and 12 weeks (at least three half-lives of study drug) is estimated to be a sufficient period after the last dose administration when a live or live-attenuated vaccine can be safety administered. If a subject terminates the study early, live or live-attenuated vaccines may be utilized 12 weeks after last dose of study drug administration. Nonlive and nonlive-attenuated vaccines, including those currently authorized for COVID-19 (eg, RNA-based vaccines, protein-based vaccines, and nonreplicating viral vector-based vaccines), are allowed during the study. The Medical Monitor should be consulted to confirm that the vaccine planned/received is allowed and that subject participation in the study should be continued. Of note, vaccines, including those for COVID-19, should be captured as a concomitant medication and any related symptoms documented as AEs.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

### 6.5.1 PERMITTED THERAPIES

Use of topical bland emollients (without pharmacological active ingredients) and topical hydrocortisone ≤ 1% on the skin, including on lesions, will be permitted throughout the study, except within 3 hours prior to the study visits.

Use of make-up, facial moisturizers, creams, lotions, cleansers, and/or sunscreens will be permitted throughout the study, except within 3 hours prior to the study visits.

Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.

### 6.5.2 PROHIBITED MEDICATIONS OR PROCEDURES

Prohibited medications/therapy are listed below. The use of a prohibited medication/therapy (unless conditions for use of rescue medications have been met) is a protocol violation and must be recorded in the eCRF. If treatment with any of these prohibited medications is essential, then the investigator must notify the Medical Monitor in order to make a decision as to whether the subject will be withdrawn from the study.

All medications and procedures listed in Table 3 are prohibited from at least 1 day prior to Day 1 until the end of study, unless the specific requirements for continued use stated in the table were met.

**Table 3: List of Prohibited Medications and Procedures**

| Treatment |
|---|
| OTC topical medications that can have an effect on acneiform rash, including topical anti-inflammatory medications, corticosteroids, or antibacterial/antiseptic soap or wash are prohibited unless the subject has agreed to continue at their current dosage over the entire course of the study and the look-back stipulated in EC-13(a) and 13(b) was met (was used consistently without any alteration in dosage for at least 14 days prior to Day 1).<br><br>Topical retinoids (eg, tretinoin, tazarotene, adapalene, dapsone) or other prescription topical medications that can have an effect on acneiform rash, unless the subject has agreed to continue at their current dosage over the entire course of the study and the look-back stipulated in EC-13(c) was met (was used consistently without any alteration in dosage for at least 14 days prior to Day 1).<br><br>Topical antimicrobials (eg, clindamycin, erythromycin), unless the subject has agreed to continue at their current dosage over the entire course of the study and the look-back stipulated in EC-13(d) was met (was used consistently without any alteration in dosage for at least 14 days prior to Day 1).<br><br>Topical agents (on the regions affected by the rash) or systemic agents that could affect pruritus (such as oral antihistaminic, gabapentin, pregabalin, doxepin, and aprepitant), unless the subject has agreed to continue at their current dosage over the entire course of the study and the look-back stipulated in EC-13(e) and 13(f) was met (was used consistently without any alteration in dosage for at least 14 days prior to Day 1).<br><br>Other systemic antiacne drugs not mentioned in other exclusion criteria, unless the subject has agreed to continue at their current dosage over the entire course of the study and the look-back stipulated in EC-13(h) was met (was used consistently without any alteration in dosage for at least 14 days prior to Day 1). |
| Oral antibiotic therapy for EGFRi/MEKi-associated acneiform rash, unless the subject has agreed to continue at their current dosage over the entire course of the study and the look-back stipulated in EC-13(g) was met (was used consistently without any alteration in dosage for at least 14 days prior to Day 1). |

| Treatment |
|---|
| Oral corticosteroids or injectable corticosteroids, unless used to prevent nausea, vomiting, or hypersensitivity reactions related to neoplasm therapy (eg, dexamethasone).<br>Note: Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed. |
| Facial procedure (eg, chemical peel, laser, microdermabrasion) |
| Photodynamic therapy or phototherapy with blue or red light |
| Androgen receptor blockers (such as spironolactone or flutamide) |
| Live and Live-attenuated vaccines |
| Oral retinoid (eg, isotretinoin) or vitamin A supplements >10,000 Units/day |
| Investigational nonbiologic drugs |
| Investigational biologic agent |
| Marketed biologic agent (other than used for treatment of neoplasm) |

### 6.5.3 RESCUE MEDICATION

A subject who has worsening or no improvement in facial inflammatory lesion count (papules and pustules), and/or worsening or no improvement of pain and/or itch, per the pruritus and pain rating scales, will be eligible to receive rescue medication (ie, systemic antibiotics and low/medium potency topical corticosteroids [eg, hydrocortisone > 1%, triamcinolone 0.1%]) starting at Day 29 (Week 4).

Subjects who take protocol-stipulated rescue medication can continue taking study treatment and remain in the study if the rescue medication is started at Day 29 (Week 4) or later. However, subjects who start taking a permitted rescue medication prior to Day 29 (Week 4) or subjects who start taking prohibited medications will be discontinued from study treatment and the study. The investigator must notify the Medical Monitor to confirm whether the subject will be withdrawn from the study.

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

## 6.6 DOSE MODIFICATION

No dose modification is allowed in this study. Study treatment can be interrupted temporarily or permanently if deemed necessary as per the investigator's discretion.

## 6.7 TREATMENT AFTER THE END OF THE STUDY

All subjects will return to the study site for the EOS (Day 169/Week 24) or ET visit for final safety and EOS assessments. After this visit, subjects should be treated according to the clinical judgment of the subject's physician. Any SAE or pregnancy occurring through the EOS visit should be reported to the pharmacovigilance unit (see Section 8.2.1) and followed up until an outcome is determined.

# 7 STUDY TREATMENT DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

## 7.1 DISCONTINUATION OF STUDY TREATMENT

The subject's eligibility criteria will be checked prior to administration of the study treatment on Day 1. If a clinically significant finding or AE/SAE is identified after enrollment, the investigator or qualified designee will determine if the subject can receive the study treatment and continue in the study and if any change in subject management is needed.

### 7.1.1 TEMPORARY INTERRUPTION

Study treatment can be interrupted temporarily for any individual subject in case of an AE as per the investigator's discretion. The Medical Monitor should be informed. Re-starting of study treatment can be done after discussion with the Medical Monitor.

### 7.1.2 RE-CHALLENGE

In case the study drug was interrupted due to an AE that was deemed at least possibly related, the study treatment can be reintroduced at the next scheduled administration visit at the investigator's discretion and after discussion with the Medical Monitor. In case of positive re-challenge, the study treatment should be withdrawn permanently.

## 7.2 SUBJECT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

A subject may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

In case of early discontinuation of study treatment, the subject will be required to attend an early termination ET (EOT/ET - Week 16) visit (see the SoA in Section 1.3). After completion of the ET visit, the subject should then return for a final follow-up visit (EOS - Week 24) 12 weeks after receiving their last dose of study treatment. Additional follow-up visit(s) may also be scheduled to follow any ongoing AE. Subjects must discontinue study treatment under the following circumstances: any SAE or significant AE, which, in the opinion of the investigator, warrants study discontinuation for safety reasons, or pregnancy occurring during the treatment period, which should be followed up until outcome.

The following events are considered sufficient reasons for discontinuing a subject from the study treatment:

- Pregnancy (refer to Appendix 1 and Section 8.2.1.8)
- Significant deviation/lack of compliance with protocol
- Any significant AE, laboratory abnormality, or other medical condition or situation occurs, such that continued participation in the study would not be in the best interest of the subject, in the opinion of the investigator
- Disease progression which requires discontinuation of the study treatment
- Discontinuation of use of EGFRi/MEKi therapy
- Withdrawal of consent
- Lost to follow-up
- Use of any prohibited medication or treatment that, in the opinion of the investigator, necessitates the subject being withdrawn (refer to Section 6.5.2)
- Termination of the subject participation by the investigator or Sponsor

The reason for subject discontinuation or withdrawal from the study will be recorded on the eCRF.

If a subject withdraws from the study, he or she may request destruction of any samples taken and not tested, and the investigator must document this in the study center study records.

See SoA (see Section 1.3) for data to be collected at the time of study discontinuation and follow-up, and for any further evaluations that need to be completed.

## 7.3 LOST TO FOLLOW-UP

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study center.

The following actions must be taken if a subject fails to return to the clinic for a required study visit (unless this is required by the COVID-19 restrictions and virtual visits are scheduled instead):

- The study center must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study. If the re-scheduled visit falls within the next visit's window, then the visit should be considered a missed visit and the subject should come in for the next scheduled visit as planned. Missed visits must be captured in the eCRFs and will be recorded as a protocol deviation.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study.

# 8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (see Section 1.3). Assessments scheduled on the day of study treatment administration must be performed prior to the study treatment administration unless otherwise noted. There are visits where the protocol requires more than 1 procedure to be completed at the same time point. When indicated, the procedure must follow the specific order of events; refer to the SoA (Section 1.3) for instructions.

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the subject should continue or discontinue in the study.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened, and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the subject's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (see Section 1.3).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

## 8.1 EFFICACY ASSESSMENTS

Clinical evaluations of EGFRi/MEKi-associated acneiform rash will be performed by an experienced and qualified dermatologist (board-certified or equivalent). To assure consistency and reduce variability, the same assessor should perform all assessments on a given subject, whenever possible (especially at Day 1 and Day 57 [Week 8]).

### 8.1.1 SUBJECT ASSESSMENTS OF PRURITUS AND PAIN

The intensity of pruritus and pain will be assessed at the visits specified in the SoA (see Section 1.3) using an NRS. This will be evaluated by asking subjects to assign a numerical score representing of the worst intensity over the last 24 hours of their symptoms (pruritus or pain) on a scale from 0 to 10, with 0 indicating no symptoms and 10 indicating the worst imaginable symptoms (Phan 2012, Verweyen 2019, modified from Farrar 2001).

These assessments will be completed by the subject on a worksheet prior to any efficacy and safety evaluations at every study visit. The 2 scales are presented in Appendix 2.

### 8.1.2 FUNCTIONAL ASSESSMENT OF CANCER THERAPY - EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITOR 18

The FACT-EGFRi-18 will be assessed at the visits specified in the SoA (see Section 1.3). The FACT-EGFRi-18 is a subject-reported outcomes questionnaire developed to assess the effect of EGFRi-induced dermatologic toxicities on health-related quality of life. It is an 18-item Likert-scaled questionnaire, arranged in three dimensions: physical (seven items), social/emotional (six items), and functional well-being (five items) (Wagner 2013). To provide a better fit for scale items, the item groups

are reorganized in skin, nail, and hair side effect domains. The response scores ranged from 0 (not at all) to 4 (very much).

The FACT-EGFRi-18 will be completed by the subject on a worksheet prior to any efficacy and safety evaluations. The questionnaire is self-explanatory and handed to the subject who is asked to fill it in without the need for a detailed explanation. The FACT-EGFRi-18 is presented in Appendix 3.

### 8.1.3 PATIENT GLOBAL IMPRESSION OF SEVERITY

The PGI-S will be assessed at the visits specified in the SoA (see Section 1.3). It is a single-item question, which asks the subject to rate the current severity of the acneiform rash. The response options are “Clear skin”, “Mild”, “Moderate”, “Severe”.

The PGI-S will be completed by the subject on a worksheet prior to any safety and efficacy evaluations. The questionnaire is self-explanatory and handed to the subject who is asked to fill it in without the need for a detailed explanation. The PGI-S (modified from Yalcin 2003) is presented in Appendix 4.

### 8.1.4 PATIENT GLOBAL IMPRESSION OF CHANGE

The PGI-C will be assessed at the visits specified in the SoA (see Section 1.3). The PGI-C is a single-item, self-administered questionnaire, which asks the subject to rate the change in their symptom severity (“Very much better” to “Very much worse”).

The PGI-C will be completed by the subject on a worksheet prior to any safety and efficacy evaluations. The questionnaire is self-explanatory and handed to the subject who is asked to fill it in without the need for a detailed explanation. The PGI-C (modified from Yalcin 2003) is presented in Appendix 5.

### 8.1.5 SYSTEMIC THERAPY INDUCED DIARRHEA ASSESSMENT TOOL

The STIDAT will be assessed at the visits specified in the SoA (see Section 1.3). The STIDAT is a questionnaire that was developed to evaluate the severity of systemic therapy-induced diarrhea, a common side effect experienced by more than half of patients with neoplasm (Liu 2017; http://creativecommons.org/licenses/by/4.0/). The STIDAT will be used in the present study to assess the severity of gastrointestinal inflammation.

The STIDAT assesses patient’s perception of having diarrhea, daily number of bowel movements, daily number of diarrhea episodes, antidiarrheal medication use, the presence of urgency, abdominal discomfort, fecal incontinence, patient’s perception of diarrhea severity, and quality of life.

The STIDAT will be completed by the subject on a worksheet prior to any efficacy and safety evaluations. The questionnaire is self-explanatory and is first handed to the subject who is asked to fill in without the need for a detailed explanation. The STIDAT is presented in Appendix 6.

### 8.1.6 FACIAL INVESTIGATOR GLOBAL ASSESSMENT

The facial IGA of the acneiform rash severity will be assessed at the visits specified in the SoA (see Section 1.3). The facial IGA will be used to evaluate the current state of the acneiform rash on the face only. It is a 5-point morphological assessment of facial acneiform rash severity. The facial IGA is a global evaluation that should be performed at arm’s length distance from the subject and must be performed before the facial inflammatory lesion count. A detailed description of the facial IGA scale (a modified IGA scale from ACZONE FDA guidance. https://www.fda.gov/media/104718/download) is provided in Table 4.

**Table 4: Facial Investigator Global Assessment Scale**

| Grade | Definition | Description |
|---|---|---|
| 0 | None | No evidence of facial rash |
| 1 | Minimal | A few inflammatory lesions (papules/pustules) are present |
| 2 | Mild | Several inflammatory lesions (papules/pustules) are present |
| 3 | Moderate | Many inflammatory lesions (papules/pustules) are present |
| 4 | Severe | Significant degree of inflammatory disease |

Source: modified IGA scale from ACZONE FDA guidance
https://www.fda.gov/media/104718/download

### 8.1.7 INVESTIGATOR GLOBAL ASSESSMENT

The IGA of the acneiform rash severity will be assessed at the visits specified in the SoA (see Section 1.3). The IGA will be used to evaluate the current state of the acneiform rash on the entire body. It is a 5-point morphological assessment of overall acneiform rash severity. The IGA is a global evaluation that should be performed at arm's length distance from the subject and must be performed before the facial inflammatory lesion count. A detailed description of IGA scale (a modified IGA scale from Pascoe 2015) is provided in Table 5.

**Table 5: Investigator Global Assessment Scale**

| Grade | Definition | Description |
|---|---|---|
| 0 | Clear | Residual hyperpigmentation and erythema may be present |
| 1 | Almost clear | A few small papules |
| 2 | Mild | Easily recognizable; less than half the body is involved |
| 3 | Moderate | More than half the body is involved; many papules and pustules |
| 4 | Severe | Entire body is involved; covered with numerous papules and pustules |

Source: modified IGA scale from Pascoe 2015.

### 8.1.8 FACIAL INFLAMMATORY LESION COUNT

The number of facial inflammatory lesions (papules and pustules) on the face (excluding the neck and scalp area) will be counted at the visits specified in the SoA (see Section 1.3), according to the definitions presented in Table 6. These definitions were adapted from the FDA guidance for acne vulgaris. To be eligible for this study, subjects must have ≥ 20 inflammatory lesions on the face at the Screening Part 2 and Day 1 visits.

Subjects will be examined in a well-lit room and without the aid of magnifying instruments. Total number of facial inflammatory lesions and number of each type of lesions (papule, pustule) should be reported. Only for the facial inflammatory lesion count, papules and pustules should be counted separately to attain the total inflammatory lesion count.

**Table 6: Definition of Inflammatory Lesions**

| Type of Lesion | Definition |
|---|---|
| Papule | A small, solid elevation 5 mm or less in diameter |
| Pustule | A small, circumscribed elevation of the skin that contains yellow-white exudate |

Source: adapted from the FDA guidance for acne vulgaris.
https://www.fda.gov/media/71152/download

### 8.1.9 NAIL FOLDS WITH PARONYCHIA

The number of nail folds with paronychia will be counted at the visits specified in the SoA (see Section 1.3), according to the definitions presented in Table 7.

**Table 7: Definition of Paronychia**

| Type of Lesion | Definition |
|---|---|
| Paronychia | Disorder characterized by an infectious process (ie, edema, erythema, disruption of the cuticle) involving the soft tissues around the nail |

Source: Lacouture 2010

### 8.1.10 ACNEIFORM RASH – COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

The severity of acneiform rash will be assessed at the visits specified in the SoA (see Section 1.3) using the CTCAE Version 5.0. The acneiform rash CTCAE grading scale of the acneiform rash severity is a 6-point scale ranging from 0 to 5 (where 0 = no evidence of rash and 5 = death, respectively). A detailed description of the CTCAE grading scale for acneiform rash is provided in Table 8. To be eligible for this study, subjects must have EGFRi/MEKi-related noninfected acneiform rash CTCAE ≥ Grade 2 at Screening Part 2 and Day 1 visits. Of note, subjects with less than 10% body surface area (BSA) covered with papules and/or pustules, but with limiting instrumental activities of daily living (ADL) will be considered Grade 2.

**Table 8: Grading of Acneiform Rash According to the Common Terminology Criteria for Adverse Events**

| Grade | Definition |
|---|---|
| 0 | No evidence of rash |
| 1 | Papules and/or pustules covering < 10% BSA, which may or may not be associated with symptoms of pruritus or tenderness |
| 2 | Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL; papules and/or pustules covering > 30% BSA with or without mild symptoms |
| 3 | Papules and/or pustules covering > 30% BSA with moderate or severe symptoms; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated |
| 4 | Life-threatening consequences; papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated |

| | |
|---|---|
| 5 | Death |

Abbreviations: ADL, activities of daily living; BSA, body surface area; IV, intravenous.

Of note, a semi-colon indicates 'or' within the description of the grade.
Source: CTCAE v5.0 – November 27, 2017
U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

### 8.1.11 MASCC EGFRi SKIN TOXICITY TOOL

The severity of acneiform rash will be assessed at the visits specified in the SoA (see Section 1.3) using a modified MESTT. The MESTT was designed to characterize the specific dermatological toxicities observed with EGFRi therapy (Lacouture 2010). A "modified MESTT" will be utilized wherein the 3-point scale will be evaluated individually for the face, scalp, chest, and back, and then these individual grades will be summed for a total score between 4-12. A detailed description of the acneiform rash modified MESTT grading scale is provided in Table 9.

**Table 9: Grading of Acneiform Rash According to the MASCC EGFRi Skin Toxicity Tool**

| Grade | Definition |
|---|---|
| 1 | 1A: papules or pustules ≤ 5; OR 1 area of erythema or edema < 1cm in size<br>1B: papules or pustules ≤ 5; OR 1 area of erythema or edema < 1cm in size; AND pain or pruritus |
| 2 | 2A: papules or pustules 6-20; OR 2-5 areas of erythema or edema < 1cm in size<br>2B: Papules or pustules 6-20; OR 2-5 areas of erythema or edema < 1cm in size; AND pain, pruritus, or effect on emotions or functioning |
| 3 | 3A: papules or pustules > 20; OR more than 5 areas of erythema or edema < 1cm in size<br>3B: papules or pustules > 20; OR more than 5 areas of erythema or edema < 1cm in size; AND pain, pruritus, or effect on emotions or functioning |

Abbreviations: EGFRi, epidermal growth factor receptor inhibitor; MASCC, Multinational Association for Supportive Care in Cancer.
Source: ©MASCC, Multinational Association for Supportive Care in Cancer™
https://www.mascc.org/MESTT

### 8.1.12 PARONYCHIA, DRY SKIN, ALOPECIA, AND PRURITUS COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

The severity of paronychia, dry skin, alopecia, and pruritus will be assessed at the visits specified in the SoA (see Section 1.3) using the corresponding CTCAE grade (CTCAE v5.0 – November 27, 2017. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute). https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. A detailed description of the CTCAE grading scales is provided in

Table 10 for paronychia, Table 11 for dry skin, Table 12 for alopecia, and Table 13 for pruritus. Of note, a semi-colon indicates 'or' within the description of the grades.

**Table 10: Grading of Paronychia According to Common Terminology Criteria for Adverse Events**

| Grade | Definition |
|---|---|
| 0 | No evidence of paronychia |
| 1 | Nail fold edema or erythema; disruption of the cuticle |
| 2 | Local intervention indicated; oral intervention indicated (eg, antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL |
| 3 | Operative intervention indicated; IV antibiotics indicated; limiting self-care ADL |

Abbreviations: ADL, activities of daily living; IV, intravenous.

**Table 11: Grading of Dry Skin According to Common Terminology Criteria for Adverse Events**

| Grade | Definition |
|---|---|
| 0 | No evidence of dry skin |
| 1 | Covering < 10% BSA and no associated erythema or pruritus |
| 2 | Covering 10–30% BSA and associated with erythema or pruritus; limiting instrumental ADL |
| 3 | Covering > 30% BSA and associated with pruritus; limiting self-care ADL |

Abbreviations: ADL, activities of daily living; BSA, body surface area.

**Table 12: Grading of Alopecia According to Common Terminology Criteria for Adverse Events**

| Grade | Definition |
|---|---|
| 0 | No evidence of alopecia |
| 1 | Hair loss of < 50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss but it does not require a wig or hair piece to camouflage |
| 2 | Hair loss of ≥ 50% normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact |

**Table 13: Grading of Pruritus According to Common Terminology Criteria for Adverse Events**

| Grade | Definition |
|---|---|
| 0 | No evidence of pruritus |
| 1 | Mild or localized; topical intervention indicated |
| 2 | Widespread and intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL |
| 3 | Widespread and constant; limiting self-care ADL or sleep; systemic corticosteroid or immunosuppressive therapy indicated |

Abbreviations: ADL, activities of daily living.

### 8.1.13 EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Subject's level of functioning will be assessed at the visits specified in the SoA (see Section 1.3) using the ECOG performance status (Oken 1982; ECOG-ACRIN Cancer Research Group). The ECOG performance scale is a 6-point scale ranging from 0 to 5.

A detailed description of the scale is provided in Table 14.

**Table 14: Eastern Cooperative Oncology Group Performance Status**

| Grade | Definition |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work) |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours |
| 3 | Capable of only limited self-care; confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled; cannot carry on any self-care; totally confined to bed or chair |
| 5 | Dead |

## 8.2 SAFETY ASSESSMENTS

### 8.2.1 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

#### 8.2.1.1 DEFINITION OF ADVERSE EVENTS

An AE is any untoward medical occurrence in a subject temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment that does not necessarily have a causal relationship with this treatment.

##### 8.2.1.1.1 EVENTS MEETING THE ADVERSE EVENT DEFINITION

Events meeting the AE definition include:

- Any abnormal laboratory test results (hematology, biochemistry, or urinalysis) or other safety assessments (eg, ECG, vital signs measurements), including those that worsen from a prior assessment, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition (including neoplasm).
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

"Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or

clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

#### 8.2.1.1.2 EVENTS NOT MEETING THE ADVERSE EVENT DEFINITION

Events not meeting the AE definition include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease (acneiform rash and neoplasm), unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

### 8.2.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or Sponsor, it results, at any dose, in any of the following outcomes:

- **Death**
- **Life-threatening adverse event** – The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- **Inpatient hospitalization or prolongation of existing hospitalization** – In general, hospitalization signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition (including neoplasm) that did not worsen from Baseline is not considered an AE.
- **Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions** – The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Congenital anomaly/birth defect**
- **Other important medical events** – Events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Examples of such medical events include invasive or malignant cancers, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

#### 8.2.1.3 CLASSIFICATION OF AN ADVERSE EVENT

##### 8.2.1.3.1 SEVERITY OF EVENT

The intensity of an AE is an estimate of the relative severity of the event. The investigator will make an assessment of intensity for each AE and SAE reported during the study based on his or her clinical experience and familiarity with the literature. The following definitions are to be used to rate the severity of an AE:

- **Mild** – Events require minimal or no treatment, are easily tolerated by the subject, causing minimal discomfort, and do not interfere with the subject's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning and sufficient discomfort to the subject.
- **Severe** – Events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious". An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE (Section 8.2.1.2), NOT when it is rated as severe.

##### 8.2.1.3.2 RELATIONSHIP TO STUDY TREATMENT

All AEs must have their relationship to study treatment assessed by the investigator who examines and evaluates the subject based on temporal relationship and his or her clinical judgment. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. The investigator will also consult the IB in his or her assessment. The degree of certainty about causality will be graded using the categories below. In a clinical study, the study treatment must always be suspect.

- **Unrelated** – Clinical event incontrovertibly not related to the study treatment.
- **Unlikely to be related** – Clinical event with an incompatible time relationship to study treatment administration which makes a causal relationship improbable, and in which an underlying condition or other drugs or chemicals provides plausible explanations.
- **Possibly related** – Clinical event with a reasonable time relationship to study treatment administration, and that is unlikely to be attributed to concurrent condition or other drugs or chemicals.
- **Related** – Clinical event with plausible time relationship to study treatment administration and that cannot be explained by concurrent condition or other drugs or chemicals.

For each AE/SAE, the investigator must document in the medical notes that he or she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the pharmacovigilance unit. However, it is very important that the

investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the pharmacovigilance unit within 24 hours of awareness of the event.

The investigator may change his or her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

#### 8.2.1.3.3 EXPECTEDNESS

The pharmacovigilance unit will be responsible for determining whether an AE is expected or unexpected as interpreted through the IB. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study treatment.

### 8.2.1.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions will be captured on the appropriate eCRF. Information to be collected includes event description, date of onset, clinician's assessment of severity, seriousness, relationship to study treatment (assessed only by those with the training and authority to make a diagnosis), action taken, and outcome of the event. All AEs occurring while on study must be documented appropriately regardless of relationship (see Section 8.2.1.3.2). All AEs will be followed to adequate resolution or stabilization.

Study site personnel will note the occurrence and nature of each subject's medical condition(s) present prior to the informed consent signature in the appropriate section of the source document and eCRF. During the study, site personnel will note any change in the condition(s) and the occurrence and nature of any AE. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

Should a subject experience an AE at any time after the informed consent signature until the end of participation in the study, the event will be recorded as an AE in the source document and eCRF. Any SAE related to the study participation (eg, screening procedure) will be recorded in the source document and eCRF from the time consent is given to participate in the study until the end of participation in the study (EOS/ET visit).

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he or she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the pharmacovigilance unit.

Any medical condition that is present at the time that the subject is first screened will be considered as medical history and not reported as an AE. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE/SAE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The investigator is responsible for appropriate medical care of subjects during the study. After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent

visits/contacts. The investigator also remains responsible for following through with an appropriate health care option for all AEs that are ongoing at the end of the study. The subject should be followed until the event is resolved or stable. If an AE is ongoing at the end of study, the follow-up duration is left to the discretion of the investigator. Follow-up frequency will be performed at the discretion of the investigator.

Whenever possible, clinically significant abnormal laboratory results are to be reported using the diagnostic that resulted in the clinically significant abnormal laboratory results and not the actual abnormal test.

#### 8.2.1.5 ADVERSE EVENT REPORTING

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant AE/SAE information (including event term, start and stop dates, severity, relationship to study treatment, outcome, if serious or nonserious) in the eCRF. Each event must be recorded separately.

It is not acceptable for the investigator to send photocopies of the subject's medical records to the pharmacovigilance unit in lieu of completion of the AE/SAE eCRF page.

There may be instances when copies of medical records for certain cases are requested by the pharmacovigilance unit. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the pharmacovigilance unit.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the pharmacovigilance unit to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded in the originally completed eCRF.

#### 8.2.1.6 SERIOUS ADVERSE EVENT REPORTING

Prompt notification by the investigator to the pharmacovigilance unit of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met. All SAEs will be recorded and reported to the pharmacovigilance unit within 24 hours of awareness. The investigator will submit any updated SAE data to the pharmacovigilance unit within 24 hours of receipt of the information as outlined in the Safety Reporting Instructions that will be provided to the sites and in the study Safety Management Plan.

The pharmacovigilance unit will inform the Medical Monitor, the Sponsor, and Innovaderm within 1 business day of awareness of a new SAE. The pharmacovigilance unit will process and evaluate all SAEs as soon as the reports are received. For each SAE received, the pharmacovigilance unit, in consultation with the Sponsor if needed, will make a determination as to whether the criteria for expedited reporting to relevant regulatory authorities have been met.

The Sponsor or designee has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor or

designee will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/EC, and investigators.

Investigator safety reports must be prepared for suspected unexpected SAEs according to local regulatory requirements and pharmacovigilance unit policy and forwarded to investigators, as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the pharmacovigilance will review and then file it along with the IB and will notify the IRB/EC, if appropriate according to local requirements.

If a subject dies while participating in the study, the investigator will provide the pharmacovigilance unit with a copy of any postmortem findings.

#### 8.2.1.6.1 REPORTING VIA AN ELECTRONIC DATA COLLECTION TOOL

The primary mechanism for reporting an SAE to the pharmacovigilance unit will be the electronic data capture (EDC) clinical database.

If the electronic system is unavailable, then the study center will use the back-up paper SAE Report Form. The study center will then enter the SAE data into the EDC system as soon as it becomes available.

After the study is completed and the database is locked, the tooled system will be taken off-line to prevent the entry of new data or changes to existing data.

If a study center receives a report of a new SAE from a subject or receives updated data on a previously reported SAE after the EDC system is locked, then the study center can report this information on a paper SAE form and email the form to the pharmacovigilance unit.

Contacts for SAE reporting can be found in SAE form and Safety Reporting Instructions that will be provided to the sites.

#### 8.2.1.6.2 REPORTING VIA PAPER CASE REPORT FORM

In rare circumstances, and in the absence of EDC or email, notification by telephone is acceptable for notifying the pharmacovigilance unit of an SAE. Once the EDC is available, the SAE must be reported in the system within 24 hours of it becoming available.

Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

Contacts for SAE reporting can be found in Safety Reporting Instructions that will be provided to the sites.

### 8.2.1.7 REPORTING EVENTS TO SUBJECTS

Not applicable.

### 8.2.1.8 REPORTING OF PREGNANCY

If a female subject or a female partner of a male subject becomes pregnant during the study and up to 28 days after the end of the subject participation, the subject should inform the study center as soon as possible.

If a pregnancy is reported, the investigator should inform the pharmacovigilance unit within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 1.

If a pregnancy occurs, it will be followed up to determine the outcome, but no longer than 6 to 8 weeks after the estimated delivery date, where consent has been obtained to do so.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs and must be reported in 24 hours of awareness as described in Section 8.2.1.6.

#### 8.2.1.9 TREATMENT OF OVERDOSE

For this study, any dose of ANB019 or placebo administered in a volume exceeding the planned dosing detailed in Table 2 (Dose Strength[s]/Dosage Level[s]) will be considered an overdose. For ANB019, this means a dose greater than 400 mg received within a 24-hour time period on Day 1 and greater than 200 mg on Days 29, 57, and 85.

In the improbable event of a suspected overdose, the following procedures should be executed:

- Administration is to be discontinued.
- The subject is to be monitored clinically.
- Supportive measures are to be undertaken as clinically indicated.
- Electrocardiography and clinical laboratory evaluations (ie, blood glucose, hepatic enzymes, creatinine, blood urea nitrogen, creatine kinase (CK), and complete blood count) are to be performed and followed until all values return to Baseline levels and AEs subside, if applicable.

No information on overdose, maximum tolerated dose, or dose-limiting toxicities for ANB019 has been established at this time and since there are no known antidotes for ANB019, the treatment of overdose is at investigator's discretion.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the subject for any AE/SAE and laboratory abnormalities and follow-up until resolution.
3. Obtain a serum sample for PK analysis soon after the dose for SC administration.
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

### 8.2.2 HEIGHT AND WEIGHT

Height will be measured only at screening and weight will be measured at the time points specified in the SoA (see Section 1.3).

### 8.2.3 CHEST X-RAY

Bidirectional posterior-anterior and lateral view chest X-ray will be performed during Screening (Section 1.3) unless the report from a qualified radiologist of a chest X-ray performed within 6 months before Day 1 shows no abnormalities suggestive of a current active infection, including TB, is available. A chest CT scan is also acceptable if already available.

### 8.2.4 PHYSICAL EXAMINATIONS

Complete physical examinations will be performed at the time points indicated in the SoA (see Section 1.3).

A complete physical examination will include assessments of general appearance; skin; head/neck; pulmonary, cardiovascular, gastrointestinal, lymphatic, and musculoskeletal system; extremities; eyes; nose; throat; and neurologic status.

A detailed examination of the skin should be performed at the time points indicated in the SoA for the efficacy assessments.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

### 8.2.5 VITAL SIGNS

Body temperature (°C), pulse rate (bpm), blood pressure (mmHg), and respiratory rate (breath/min) will be assessed at the time points specified in SoA (see Section 1.3).

Blood pressure and pulse rate will be assessed in a seated position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (eg, television, cell phones).

Vital signs including body temperature, respiratory rate, and pulse rate (after at least 5 minutes rest) should be measured once. Arterial blood pressure should be measured twice (at intervals of at least 5 minutes), using a validated device.

### 8.2.6 ELECTROCARDIOGRAMS

A single 12-lead ECG will be obtained at the time points specified in the SoA (see Section 1.3) using a validated ECG machine that automatically calculates the heart rate and measures RR, PR, QRS, QT, QTcB, and QTcF intervals.

The ECG will be reviewed by the central ECG laboratory team and the instructions and guidelines for collection (eg, equipment), transmission, and archiving of ECG data will be provided in the ECG Manual.

The ECG will be reviewed by the investigator or an authorized representative who is experienced in the evaluation of ECGs and assessed for clinical significance.

The investigator evaluation will take precedence over the central ECG laboratory for safety evaluation.

The ECG individual data (with the exception of clinical significance that will be reported as AE) does not need to be entered into the EDC.

### 8.2.7 CLINICAL SAFETY LABORATORY ASSESSMENTS

See Appendix 7 for the list of clinical laboratory tests to be performed and the SoA (see Section 1.3) for the timing and frequency of the tests.

A central laboratory will be used to perform all laboratory tests except urine pregnancy dipstick which will be assessed by the study center staff. Local laboratory tests will be allowed in the event that the central laboratory results will not be available immediately and the investigator needs to make an immediate decision for any safety concerns based on laboratory results. Local laboratory tests will also be allowed at Screening for TB and viral serology testing. If local laboratory is used for TB and viral serology, sample must be sent to central laboratory for analysis as well.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.

All laboratory tests with values considered clinically significantly abnormal during the study and including the subject's last study visit (EOS) should be repeated until the values return to normal or Baseline, or are no longer considered clinically significant or judged medically stabilized by the investigator or Medical Monitor.

If such values do not return to normal/Baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the Sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 7, must be conducted in accordance with the Laboratory Manual and the SoA.

If laboratory values from nonprotocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the investigator (eg, SAE or AE), then the results must be recorded in the eCRF.

## 8.3 OTHER ASSESSMENTS

### 8.3.1 FITZPATRICK SKIN TYPE CLASSIFICATION

The Fitzpatrick skin type (Fitzpatrick 1988; Attwa 2016; Wallace 2017; Zalaudek 2007) will be evaluated at Screening as described in Appendix 8. If not collected at Screening, the Fitzpatrick skin type may be collected at any visit thereafter.

### 8.3.2 PHOTOGRAPHY

Standardized photographs of acneiform rash on the face will be performed at the time points mentioned in the SoA (see Section 1.3) for facial inflammatory lesion count analysis. Further guidance and information on the standardized photographs are provided in a separate manual and/or Statistical Analysis Plan (SAP).

### 8.3.3 PHARMACOKINETICS

Whole blood will be obtained from each subject for the determination of ANB019 concentrations in human serum to enable modeling PK parameters. Samples will be collected according to the SoA (see Section 1.3) and Table 15. Each serum sample will be divided into 2 aliquots (1 each for primary and a back-up). Samples collected for analyses of ANB019 serum concentration may also be used to correlate exposure to safety or efficacy as well as supportive analysis for dose justification. Any remaining serum from samples collected for PK endpoints may be retained for assay method development, troubleshooting, or validation. The samples will not be used for any type of genetic analyses.

The actual date and time (24-hour clock) of the blood sample collection will be recorded in the subject's eCRF. The details of blood sample collection, sample tube labeling, sample preparation, storage, and shipping procedures will be described in a separate manual.

The measurement of the concentrations of ANB019 will be performed using a validated assay method under the supervision of the Sponsor. The analytical methods used to measure concentrations of ANB019 will be described in a separate bioanalytical report.

Only samples within the stability window of the assay will be analyzed.

While PK samples must be collected from subjects assigned to the placebo arm to maintain the blinding of treatment assignment, PK assay results for these subjects are not needed for the safe conduct or proper interpretation of this study. These samples may not be analyzed unless needed to investigate if a dosing error has occurred. Personnel at the bioanalytical laboratory performing PK assays will be unblinded, clinical study team members, and study center staff (with the exception of the unblinded pharmacist) will remain blinded to treatment for the duration of the study. Data may be de-identified for quality review. Additional details on de-identification or unblinding of the PK data, if applicable, will be described in a separate plan.

Drug concentration information that may unblind the study will not be reported to study site or blinded personnel until the study has been unblinded. Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and study files but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

**Table 15**: **Pharmacokinetic Sample Collection and Time Points**

| Study Visit | Pharmacokinetic Sample Time Point (Serum) |
|---|---|
| Day 15 | Anytime |
| Day 29 | Predose |
| Day 57 | Predose |
| Day 85 | Predose |
| Day 113 | Anytime |
| Day 169 | Anytime |

### 8.3.4 IMMUNOGENICITY ASSESSMENTS

Anti-drug antibodies (ADAs) to ANB019 will be evaluated in serum samples collected from all subjects according to the SoA (see Section 1.3) and Table 16. Additionally, serum samples should also be collected at the final visit from subjects who discontinued study treatment or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee. Each serum sample will be divided into 2 aliquots (1 each for primary and a back-up). Any remaining serum from samples collected for immunogenicity endpoints may be retained for assay method development, troubleshooting, or validation. The samples will not be used for any type of genetic analyses.

The detection and characterization of ADAs will be performed using a validated assay method by or under the supervision of the Sponsor.

Serum samples will be tested in a multi-tiered approach. A validated screening assay for antibodies binding to ANB019 will be initially used to assess serum samples. Samples that are determined putative positive in the screening assay will then be subjected to a confirmatory assay to demonstrate that antibodies are specific to ANB019. Samples that are identified as positive in the confirmatory assay will be further characterized in a validated titer assay and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to study treatment and/or to further characterize the immunogenicity of study treatment.

Samples that are confirmed positive for antibodies binding to ANB019 may be further characterized for their ability to neutralize the activity of the study treatment using a validated neutralizing antibody assay method and the presence and/or titer of ADAs may be correlated to safety and PK data.

**Table 16: Anti-Drug Antibodies Sample Collection and Time Points**

| Study Visit | Anti-Drug Antibodies Sample Time Point (Serum) |
|---|---|
| Day 1 | Predose |
| Day 29 | Predose |
| Day 57 | Predose |
| Day 113 | Anytime |
| Day 169 | Anytime |

### 8.3.5 BIOMARKERS ANALYSIS

Tape strips samples will be collected from nonlesional and lesional skin according to the SoA (see Section 1.3) to measure cutaneous biomarkers including but not limited to IL-36R, Th-17 cytokines such as IL-17A, and markers of neutrophils and dendritic cells infiltration.

The actual date and time of the sample collection will be recorded in the subject's eCRF. The details of tape strips collection, sample labeling, sample preparation, storage, and shipping procedures will be described in a separate Laboratory Manual.

The measurement of tape strips biomarkers may be performed by an additional third party (eg, a university investigator) designated by the Sponsor.

# 9 STATISTICAL CONSIDERATIONS

## 9.1 STATISTICAL HYPOTHESES

The primary analysis for this study is to compare the mean change from Baseline in facial inflammatory lesion count for ANB019 with placebo at Week 8 of the double-blind treatment period, at a two-sided alpha = 0.05 level. Any testing being performed for the secondary or exploratory endpoints will be considered exploratory in nature based on a two-sided alpha = 0.05.

$H_0$: $\mu_{ANB019} - \mu_{Placebo} = 0$ vs. $H_A$: $\mu_{ANB019} - \mu_{Placebo} \neq 0$

## 9.2 SAMPLE SIZE DETERMINATION

The primary efficacy endpoint is the change from Baseline in facial inflammatory lesion count at Week 8. The null hypothesis ($H_0$) to be tested is that the mean change from Baseline in lesion count is the same for ANB019 and placebo. Treatment arm sample sizes of 30 (ANB019) and 15 (placebo) achieve 80% power to reject $H_0$ of equal means if the population mean difference is -10.6 (ANB019 – placebo), with a common standard deviation (SD) within both groups of 11.7, and significance level (alpha) of 0.05 using a two-sided two-sample equal-variance t-test.

## 9.3 POPULATIONS FOR ANALYSES

The analysis sets are defined in Table 17.

**Table 17: Analysis Sets**

| Analysis Set | Description |
|---|---|
| **Intent-to-Treat (ITT) Analysis Set** | The ITT Analysis Set will include all randomized subjects. In this analysis set, treatment will be assigned based upon the treatment arm to which subjects were randomized regardless of which treatment they receive. ITT Analysis Set will be used for efficacy data analyses. |
| **Safety Analysis Set** | The safety analysis set will include all randomized subjects who receive 1 dose of ANB019 or placebo. The safety analysis set will be used for all safety analyses. Subjects will be analyzed as treated. If a subject receives both treatments, they will be analyzed in the ANB019 group. |
| **Per Protocol Analysis Set** | The Per Protocol analysis set will include all subjects in the ITT Analysis Set who do not have major protocol violations that would affect the evaluation of the primary efficacy endpoint. Per Protocol analysis set will be used for a sensitivity analysis of the primary endpoint and for some secondary endpoints. |
| **PK Analysis Set** | The PK Analysis Set will include all ANB019-treated subjects in the safety analysis set who have at least 1 quantifiable post-dose PK sample available and who do not have events or protocol deviations or events with the potential to affect PK concentrations. The PK Analysis Set will be used for all PK analyses. |

Abbreviations: ITT, Intent-to-Treat; PK, pharmacokinetic

## 9.4 STATISTICAL ANALYSES

### 9.4.1 GENERAL APPROACH

The statistical analysis will be performed using statistical analysis system (SAS®) Version 9.4 or higher. All details regarding the statistical analysis will be described in the SAP.

The default summary statistics for continuous variables include number of contributing observations, mean, SD, median, minimum, and maximum. For PK parameters, coefficient of variation (CV) and geometric mean will also be presented, as appropriate.

For categorical variables, the number and percentage (percentage of subjects in each category relative to the total number of subjects in the relevant analysis set or relative to the total number of subjects in the relevant analysis set with assessments available [where appropriate]) in each category will be the default summary presentation.

Unless otherwise specified, “Baseline” is defined as the last observed value of the parameter of interest prior to the first intake of study treatment (this includes unscheduled visits). For numerical variables, change from Baseline will be calculated as the difference between the value of interest and the corresponding Baseline value.

Point estimates of treatment differences will be accompanied with 2 sided 95% confidence intervals (CIs), where applicable.

In the case of normality assumption violations, appropriate transformations or nonparametric methods may be used for analysis.

All data will be presented in by-subject listings.

### 9.4.2 SUBJECT DISPOSITION

A tabular presentation of the subject disposition will be provided. It will include the number of subjects consented, screened, randomized, treated, completed as well as the number of dropouts with reasons for discontinuation, and major protocol deviations or violations.

A listing will be presented to describe dates of screening, assigned treatment, screen failed with reason, completion or early withdrawal, and the reason for early discontinuation, if applicable, for each subject. A list of protocol deviations/violations will be identified and discussed with the investigator/Sponsor in a dry run to categorize as major or minor with decisions of exclusion from analysis sets prior to unblinding.

During the COVID-19 pandemic, protocol deviations related to COVID-19 will be documented and information on how they will be handled in the analyses will be detailed in the SAP.

### 9.4.3 BASELINE DESCRIPTIVE STATISTICS

Subject characteristics obtained at Baseline will be summarized for all subjects taking ANB019 or placebo.

Summaries will include descriptive statistics for continuous variables (sample size [n], mean, SD, median, minimum, and maximum) and for categorical variables (n, frequency, and percentage).

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) latest version and listed for all subjects.

### 9.4.4 CONCOMITANT MEDICATION

All medications will be coded using the World Health Organization (WHO) Drug Dictionary and Anatomical Therapeutic Chemical (ATC) system. Each medication will be classified as prior medication if it is stopped prior to the first dose of study treatment, or as concomitant medication if it is ongoing at the time of the first dose or is started after the first dose of study treatment. Prior, concomitant, and rescue medications will be summarized descriptively with a by-subject listing.

To handle the issue of rescue medication use, the efficacy data on and after the use rescue medication will be set to missing in the efficacy analysis.

### 9.4.5 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint is the change from Baseline in facial inflammatory lesion count (papules and pustules) at Week 8.

#### 9.4.5.1 PRIMARY ESTIMAND

The primary estimand, comprising of four components, is defined as follows:

a) The target population is reflected by the patients that are eligible to be included in the clinical trial based on the inclusion/exclusion criteria in the protocol. The ITT Analysis Set will include all randomized subjects. For the analysis, treatment will be assigned based upon the treatment arm to which subjects were randomized regardless of which treatment they receive.
b) The primary variable is the facial inflammatory lesion count (papules and pustules) of an individual subject at Week 8.
c) To handle intercurrent events such as use of rescue medications, the hypothetical strategy for estimand will be used. Data collected following receipt of rescue medication (if any) will be considered missing in the analysis.
d) The population-level summary measure for the primary endpoint is mean change from Baseline in facial inflammatory lesion count (papules and pustules) at Week 8. The estimator for between-group comparison of the primary endpoint will be the difference in the primary endpoint between ANB019 and placebo at Week 8.

#### 9.4.5.2 STATISTICAL ANALYSIS OF PRIMARY ENDPOINT

A general linear mixed model repeated measures (MMRM) analysis will be used to estimate the least squares means (LSM) and associated standard errors for the change from Baseline in facial inflammatory lesion count (papules and pustules) at Week 8. The model will include change from Baseline in facial inflammatory lesion count (papules and pustules) at Week 8 as the dependent variable, fixed effects for treatment arm, visit, and the treatment by visit interaction, and the Baseline value of response, and the stratification factors (ie, acneiform rash CTCAE grade at Baseline and therapy the subject is receiving [EGFRi vs MEKi]) as covariates. An unstructured covariance structure will be used. The difference between LSMs (ANB019 – placebo) at Week 8 will be presented along with the associated 95% CI and p-value. The ITT Analysis Set will be used for the primary efficacy analysis.

The possible effect of any covariates as well as investigation of subgroup analyses will be performed by minimally including the stratification factors of Baseline acneiform rash CTCAE grade (2 vs 3 or 4) and type of neoplasm therapy (EGFRi or MEKi).

#### 9.4.5.3 HANDLING OF MISSING DATA

The method for handling missing data for the primary variable will be MMRM, which is based on the statistical assumption of missing at random (MAR). Based on the hypothetical strategy for handling rescue medication use, data will be set to missing and will be considered missing in the analysis on or after the rescue medication use. All other missing values will be implicitly handled in MMRM. Sensitivity analysis under Missing Not at Random (MNAR) will be described in the next section.

#### 9.4.5.4 SENSITIVITY ANALYSIS

As a sensitivity analysis of the primary analysis under MNAR, placebo Multiple Imputation (pMI) method will be conducted. The pMI assumes that the statistical behavior of ANB019-treated patients and placebo-treated patients after the occurrence of intercurrent events will be the same as if patients were treated with placebo. In the context of efficacy data, pMI is a specific form of a Missing Not at Random (MNAR) analysis and expected to yield a conservative estimate for efficacy.

As an additional sensitivity analysis to assess the results from the ITT population, per protocol analysis of the primary efficacy endpoint will also be performed.

### 9.4.6 ANALYSIS OF THE SECONDARY EFFICACY ENDPOINTS

Following are the secondary efficacy endpoints:

- Percent change from Baseline in facial inflammatory lesion count (papules and pustules) at Week 8
- Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash CTCAE grading scale at Week 8
- Time to first response of 1 grade improvement from Baseline on the acneiform rash CTCAE grading scale
- Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash modified MESTT grading scale (total score) at Week 8
- Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash modified MESTT grading scale (facial assessment) at Week 8
- Time to first response of 1 grade improvement from Baseline on the acneiform rash modified MESTT grading scale (total score)
- Time to first response of 1 grade improvement from Baseline on the acneiform rash modified MESTT grading scale (facial assessment)
- Change from Baseline in pruritus NRS at Week 8
- Percent change from Baseline in pruritus NRS at Week 8
- Change from Baseline in pain NRS at Week 8
- Percent change from Baseline in pain NRS at Week 8
- Change from Baseline in FACT-EGFRi-18 at Week 8

All secondary endpoints will be analyzed on the ITT Analysis Set. Between-treatment differences will be reported with corresponding 95% CIs and p-values. Secondary endpoints will be analyzed using the methods described in section 9.4.6.1 (continuous endpoints), section 9.4.6.2(categorical endpoints), and section 9.4.6.3 (time-to-event endpoints).

#### 9.4.6.1 CONTINUOUS ENDPOINTS

Summary statistics will be provided for absolute scores and change from Baseline to specified time points of facial inflammatory lesion count, acneiform rash CTCAE, acneiform rash modified MESTT (by body region), IGA, pruritus and pain NRS, and FACT-EGFRi-18; change and percent change from Baseline by visit and treatment arm also will be shown. A by-subject listing will be presented for each assessment, by visit.

MMRM method for longitudinal continuous data will be used for testing, with treatment group as main effect, with visit and interaction of treatment by visit as factors, and with Baseline values of response and the stratification factors (ie, acneiform rash CTCAE grade at Baseline and therapy the subject is receiving [EGFRi vs MEKi]) as covariates.

#### 9.4.6.2 CATEGORICAL ENDPOINTS

Frequency and percentages for each response Yes/No for categorical endpoints related to inflammatory lesion count, acneiform rash CTCAE, acneiform rash modified MESTT (by body region and total score), IGA, pruritus and pain NRS, subjects that do not require dose reduction of EGFRi or MEKi therapy, and rescue medication will be presented separately by visit for both treatment arms. Subjects with missing scores, dose reduction data, or rescue medication data at a given visit will be considered to have not met the criteria of interest (ie, nonresponse). Estimates of the difference between treatments (ANB019 and placebo) will be presented along with 95% CIs.

Treatment arms will be compared using Cochran–Mantel–Haenszel chi-squared test, adjusted for stratification factors (ie, acneiform rash CTCAE grade at Baseline and therapy the subject is receiving [EGFRi vs MEKi]). Robustness analyses involving repeated measures Generalized Estimating Equations (GEE) may also be used.

#### 9.4.6.3 TIME-TO-EVENT ENDPOINTS

Summary statistics such as median and 95% CI for time-to-event endpoints will be estimated using Kaplan-Meier Method. The statistical comparison of the time-to-event endpoints between treatment groups will be performed using Cox regression.

### 9.4.7 ANALYSIS OF THE EXPLORATORY EFFICACY ENDPOINTS

Following are the exploratory efficacy endpoints:

- Change from Baseline in facial inflammatory lesion count (papules and pustules) at each visit other than Week 8
- Percent change from Baseline in facial inflammatory lesion count (papules and pustules) at each visit other than Week 8
- Change from Baseline in facial papule count at each visit
- Percent change from Baseline in facial papule count at each visit
- Change from Baseline in facial pustule count at each visit
- Percent change from Baseline in facial pustule count at each visit
- Proportion of subjects with an improvement of at least 1 grade from Baseline in acneiform rash CTCAE grading at each visit other than Week 8
- Proportion of subjects with an improvement of at least 1 grade from Baseline in modified MESTT grading scale (total score) at each visit other than Week 8
- Proportion of subjects with an improvement of at least 1 grade from Baseline in modified MESTT grading scale (facial assessment) at each visit other than Week 8

- Proportion of subjects with an improvement of at least 1 grade from Baseline in modified MESTT grading scale (back assessment) at each visit
- Proportion of subjects with an improvement of at least 1 grade from Baseline in modified MESTT grading scale (scalp assessment) at each visit
- Proportion of subjects with an improvement of at least 1 grade from Baseline in modified MESTT grading scale (chest assessment) at each visit
- Time to first response of 1 grade improvement from Baseline on the acneiform rash modified MESTT grading scale (back assessment)
- Time to first response of 1 grade improvement from Baseline on the acneiform rash modified MESTT grading scale (scalp assessment)
- Time to first response of 1 grade improvement from Baseline on the acneiform rash modified MESTT grading scale (chest assessment)
- Change from Baseline in pruritus NRS at each visit other than Week 8
- Percent change from Baseline in pruritus NRS at each visit other than Week 8
- Change from Baseline in pain NRS at each visit other than Week 8
- Percent change from Baseline in pain NRS at each visit other than Week 8
- Change from Baseline in FACT-EGFRi-18 at each visit other than Week 8
- Proportion of subjects achieving an improvement of 50% from Baseline in facial inflammatory lesion count (papules and pustules) at each visit
- Proportion of subjects achieving an improvement of 75% from Baseline in facial inflammatory lesion count (papules and pustules) at each visit
- Change from Baseline in acneiform rash CTCAE grading scale at each visit
- Change from Baseline in acneiform rash modified MESTT grading scale (total score) at each visit
- Percent change from Baseline in acneiform rash modified MESTT grading scale (total score) at each visit
- Change from Baseline in acneiform rash modified MESTT grading scale (facial assessment) at each visit
- Change from Baseline in acneiform rash modified MESTT grading scale (back assessment) at each visit
- Change from Baseline in acneiform rash modified MESTT grading scale (scalp assessment) at each visit
- Change from Baseline in acneiform rash modified MESTT grading scale (chest assessment) at each visit
- Change from Baseline in IGA at each visit
- Proportion of subjects achieving an IGA of clear (0) or almost clear (1) at each visit
- Proportion of subjects with at least 2-point decrease in IGA at each visit
- Change from Baseline in facial IGA at each visit
- Proportion of subjects achieving a facial IGA of none (0) or minimal (1) at each visit
- Proportion of subjects with at least a 2-point decrease in facial IGA at each visit
- Proportion of subjects with at least a 3-point decrease in pruritus NRS at each visit for subjects with a Baseline pruritus NRS of at least 3
- Proportion of subjects with at least a 4-point decrease in pruritus NRS at each visit for subjects with a Baseline pruritus NRS of at least 4
- Proportion of subjects with at least a 3-point decrease in pain NRS at each visit for subjects with a Baseline pain NRS of at least 3

- Proportion of subjects with at least a 4-point decrease 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 the PGI-S and PGI-C at each visit
- Proportion of subjects achieving mild or clear skin according to the PGI-S at each visit
- Proportion of subjects achieving improvement (a little better, much better, or very much better) according to the PGI-C at each visit
- Proportion of subjects receiving rescue medication from Week 4 through Week 24
- Proportion of subjects that do not require a dose reduction of EGFRi or MEKi therapy due to acneiform rash at each visit
- Proportion of subjects that do not require cessation of EGFRi or MEKi therapy due to acneiform rash at each visit
- Change from Baseline in number of nail folds with paronychia at each visit
- Proportion of subjects with paronychia, dry skin, alopecia, and pruritus of Grade 0 or 1 as per CTCAE grading scale at each visit
- Change from Baseline in STIDAT at each visit
- Percent change from Baseline in STIDAT at each visit
- Change from Baseline in inflammatory lesion counts as determined by standardized photographs at each visit
- Percent change from Baseline in inflammatory lesion counts as determined by standardized photographs at each visit

Note: Reference to each visit in the exploratory endpoints excludes the visits covered by the primary and secondary endpoints.

Methods for analyzing the above continuous and categorical efficacy endpoints will mirror the methods described in Section 9.4.6.1, 9.4.6.2, and 9.4.6.3, respectively.

### 9.4.8 SAFETY ANALYSES

Following are the safety and tolerability endpoints:

- Assessment of AEs, SAEs, AEs leading to study discontinuation, and AEs leading to study drug withdrawal
- Vital signs
- 12-lead ECG
- Clinical safety laboratory tests (hematology, biochemistry, and urinalysis)

All safety analyses will be performed on the safety analysis set.

#### 9.4.8.1 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A TEAE is defined as:

- A new event that occurs during or after first dose of study treatment or,
- Any event present at Baseline that worsens in either intensity or frequency after first dose of study treatment.

AEs will be coded using the MedDRA and only TEAEs will be summarized. Number of events and percentage will be tabulated by preferred term (PT) and system organ class (SOC). Multiple occurrences of an AE for a subject will only be counted once per SOC and PT. Percentages will be determined relative to the subjects in the safety analysis set for the given treatment arm.

If the intensity or seriousness of the AE changes, the overall intensity or seriousness will be the maximum intensity or seriousness of the multiple occurrences. The TEAEs, SAEs, TEAEs leading to treatment discontinuation, and TEAEs leading to withdrawal of subject will be tabulated for each treatment arm.

All AE data will be listed for each subject.

Summaries over SOC and PT of TEAEs, TEAEs leading to death, SAEs, and TEAEs that led to discontinuation from the study or study treatment will be presented by treatment. Summaries will also be presented by relatedness to the study treatment and the severity of the TEAE.

#### 9.4.8.2 12-LEAD ELECTROCARDIOGRAM, VITAL SIGNS, AND CLINICAL SAFETY LABORATORY TESTS

Summaries and listings of data for vital signs and safety laboratory tests result (hematology, biochemistry, and urinalysis) will be presented. Appropriate descriptive statistics will be summarized for the observed value at each scheduled assessment and for the corresponding change from Baseline.

For hematology and biochemistry tests, listings of subject data will also flag up any abnormal or out-of-range values. Clinically significant changes in the laboratory test parameters will be summarized and listed. Hematology and biochemistry data will be reported in System International units.

Descriptive statistics will be used to present the safety outcomes including weight, 12-lead ECGs, vital signs, and clinical laboratory test results.

Change from Baseline will also be summarized for vital signs, and clinical laboratory tests results.

All ECG data results (normal/abnormal) will be summarized using frequency and percentage. Clinically significant abnormalities will be presented in by-subject listings.

### 9.4.9 PHARMACOKINETIC ANALYSES

ANB019 PK drug concentrations will be listed and summarized for each sampling time point using appropriate descriptive statistics and applied on the PK Analysis Set.

#### 9.4.9.1 DERIVATION OF PHARMACOKINETIC PARAMETERS

Noncompartmental analysis (NCA) will not be conducted due to minimal PK sampling. However, observed PK parameters or other presentations PK information may be presented at the discretion of the PK scientist. Further details of PK analysis, data handling, analysis procedures, and data reporting will be detailed in a separate analysis plan.

#### 9.4.9.2 PHARMACOKINETIC CONCENTRATION DATA ANALYSIS

A subject listing of all concentration-time data following SC injections will be presented by subject and scheduled sample collection time.

Concentration data of ANB019 will be summarized by day and nominal time point using the number of observations, arithmetic mean, SD, CV, minimum, median, maximum, and geometric mean.

Mean trough (predose samples on Days 29) concentrations-time data will be graphically displayed for samples collected at the visits specified in the SoA (see Section 1.3) to visually assess time to attainment of steady state. Time to steady state may also be explored by using inferential statistics, if deemed appropriate.

#### 9.4.9.3 PHARMACOKINETIC PARAMETER DATA ANALYSIS

Noncompartmental analysis (NCA) will not be conducted due to minimal PK sampling.

#### 9.4.9.4 POPULATION PHARMACOKINETICS ANALYSIS

Pharmacokinetic data from the study may also be used for population PK and exposure-response analyses. If done, a separate analysis plan will be prepared, and results will be reported separately from the Clinical Study Report (CSR).

### 9.4.10 IMMUNOGENICITY ANALYSES

Observed values for ADA levels/status will be listed by-subject and summarized with descriptive statistics based on the safety analysis set.

The incidence of ADA positive, treatment-emergent, and treatment-boosted will be shown by treatment group. A treatment-emergent ADA result is one with any positive post-treatment ADA value when the Baseline ADA result is negative. A treatment-boosted ADA result is any post-Baseline positive ADA result that is at least four times greater than the Baseline value (when positive). If data permits, correlation will be analyzed between ADA levels and safety and efficacy endpoints, as well as ADA impact on ANB019 exposure.

Frequency and percentage of ADA response will be presented and listed and correlated to safety and PK endpoints and correlated to safety and PK endpoints.

### 9.4.11 BIOMARKER ANALYSES

Tape strip biomarkers (including but not limited to IL-36R and Th-17 cytokine) analysis will be performed by a third party designated by the Sponsor. A separate analysis plan will be created for the biomarker analyses.

### 9.4.12 PLANNED INTERIM ANALYSES

Interim analyses may be performed during the treatment period for assessment of the primary and secondary efficacy endpoints, and evaluation of all safety data available.

The rationale for IAs is to assist in making decisions for potential future development of this treatment. No adjustments to the current protocol are planned as a result of the IAs; therefore, overall alpha in the analysis of the primary analysis is expected to be maintained at 0.05, two-sided.

Full details of the IAs, including procedures for maintaining the study blind for key personnel and the confidentiality of the results, will be described in the SAP.

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

After reading the protocol, each investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative. The study will not start at any study site at which the investigator has not signed the protocol.

### 10.1.1 INFORMED CONSENT PROCESS

#### 10.1.1.1 CONSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO SUBJECTS

An ICF describing in detail the study treatments, study procedures, and risks will be given to the subjects, and written documentation of informed consent is required prior to starting any study-related procedures. The following materials will be submitted to the IRB/EC with this protocol: subject self-reported questionnaires, ICF, IB, and other relevant documents (eg, advertisements).

#### 10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Each informed consent document must adhere to the ethical principles stated in the Declaration of Helsinki and will include the elements required by FDA regulations in 21 Code of Federal Regulations (CFR) Part 50, as well as the elements required by the ICH GCP guideline, and applicable federal and local regulatory requirements. The consent form will be IRB/EC-approved, and the subject will be asked to read and review the document.

The investigator or his/her representative will explain the research study to the subject and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The subject will sign the informed consent document prior to any procedures being done specifically for the study.

Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the subjects for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the subject undergoes any study-specific procedures. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The medical record must include a statement that written informed consent was obtained before the subject was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study. Subjects who are rescreened are required to sign a new ICF.

### 10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study subjects, investigator, the IND Sponsor, and

regulatory authorities, as applicable. If the study is prematurely terminated or suspended, the investigator will promptly inform study subjects and the IRB/EC and will provide the reason(s) for the termination or suspension. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Scientific or corporate reasons

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Sponsor, IRB/EC and/or regulatory authorities.

### 10.1.3 CONFIDENTIALITY AND PRIVACY

Subject confidentiality and privacy are strictly held in trust by the participating investigators, their staff, and the Sponsor and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

All research activities will be conducted in a setting as private as possible. The investigator must assure that the subjects' anonymity will be maintained and that subjects' identities are protected from unauthorized parties. On CRFs or other documents submitted to the Sponsor, subjects should not be identified by their names, but by an identification code. The investigator should keep a subject log relating codes with the names of subjects. The investigator should maintain in strict confidence documents not for submission to the Sponsor (eg, subjects' written consent forms).

The study monitor, other authorized representatives of the Sponsor, and representatives of the IRB/EC, regulatory agencies, or pharmaceutical company supplying study treatment may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the applicable legal or regulatory requirements, the reviewing IRB/EC, Institutional policies, or Sponsor requirements.

Study subject research data, which are for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the data management company responsible for data management, analysis, and reporting. This will not include the subject's contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical study centers and by data management research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived by the Sponsor.

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without written prior permission from the Sponsor. Authorized regulatory officials and Sponsor personnel (or their representatives) will be allowed

full access to inspect and copy the records. All study investigational product, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor. Subjects will only be identified by unique subject numbers on eCRFs. Every subject will be given a copy of each version of the ICF that he or she signs before and during the study. Each ICF may also include authorization allowing the institution, investigator, and Sponsor to use and disclose personal health information in compliance with the Health Information Portability and Accountability Act (HIPAA).

### 10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

With the subject's approval and approval by IRB/EC, de-identified biological samples will be stored at a certified, licensed central laboratory. Remaining serum from samples collected for PK/immunogenicity endpoints may be retained for assay method development, troubleshooting, or validating. Samples will not be used for genetic analyses. During the conduct of the study, a subject may choose to withdraw consent to have biological specimens stored for future research. Those samples will be destroyed. In addition, once other samples (safety labs, tape strips) have been analyzed, specimens will be destroyed. If no analyses have been completed within 5 years following EOS, samples will be destroyed.

### 10.1.5 MEDICAL MONITOR

Medical monitoring will be conducted to ensure the early recognition, identification and reporting of issues impacting on subjects' health and well-being throughout the study. Details of medical monitoring with contact information of the Medical Monitors will be documented in a Medical Monitoring Plan.

### 10.1.6 SAFETY OVERSIGHT

No Data and Safety Monitoring Board is required as part of this study.

### 10.1.7 CLINICAL MONITORING

All aspects of the study will be monitored by the Sponsor or authorized representatives of the Sponsor according to GCP and Standard Operating Procedures (SOPs) for compliance with applicable government regulations (ie, Informed Consent Regulations [US 21CFR, Part 50] and IRB regulations [US 21CFR, Part 56.103]).

Access to all records, both during the study and after study completion, should be made available to the Sponsor at any time for review and audit to ensure the integrity of the data. The investigator must notify Sponsor immediately if the responsible IRB/EC has been disqualified or if proceedings leading to disqualification have begun.

The investigator must conduct the protocol in accordance with applicable GCP regulations and guidelines; applicable informed consent regulations (US 21CFR, Part 50); and in compliance with the Declaration of Helsinki. Every attempt must be made to follow the protocol and to obtain and record all data requested for each subject at the specified times. If data are not recorded per protocol, the reasons must be clearly documented on the eCRF/records.

Before study initiation, at a study center initiation visit or at a meeting with the investigator(s), a representative from the Sponsor will review the protocol and study eCRFs with the investigator(s) and their staff. During the study, the study monitor will visit the study center regularly to check the completeness of subject records, the accuracy of entries on the eCRFs, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that consent is being sought and obtained in compliance with applicable regulations, and that the study drug is being stored, dispensed and accounted for according to specifications.

The investigator and key study personnel must be available to assist the monitor during these visits. The investigator must give the monitor access to relevant hospital or clinical records, to confirm their consistency with the eCRF entries. No information in these records about the identity of the subjects will leave the study center.

Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of primary efficacy and safety variables. Additional checks of the consistency of the source data with the eCRFs will be performed according to the study-specific Monitoring Plan.

The investigator must promptly complete the eCRFs after the subject's visit. The monitor is responsible for reviewing them and clarifying and resolving any data queries. A copy of the eCRFs will be retained by the investigator who must ensure that it is stored in a secure place with other study documents, such as the protocol, the IB, and any protocol amendments.

The investigator must provide the Sponsor and the responsible IRB/EC with a study summary shortly after study completion, or as designated by the Sponsor.

### 10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system, and data QC checks, which will be run on the database, will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical study is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements (eg, GLP, Good Manufacturing Practices [GMP]).

The investigational site will provide direct access to all study-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by IRB/EC and local and regulatory authorities.

### 10.1.9 DATA HANDLING AND RECORD KEEPING

#### 10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

All protocol-specified data will be recorded in site source documents. Study data will be entered within the clinical database eCRFs from the original source documents. Upon each subject's completion of the study, the investigator is required to sign and affirm the data entered in the subject CRF along with a statement attesting that all pages of the subject's case report have been reviewed. All investigator data attestation signatures will be made through the 21 CFR Part 11 compliant EDC system. Signature stamps and "per signatures" are not acceptable.

It is the Sponsor's policy that study data be verifiable with the source data which necessitates access to all original recordings, laboratory reports, and other records for each subject. The investigator must therefore agree to allow access to subjects' records, and source data must be made available for all study data. Subjects (or their legal representatives) must also allow access to their medical records. Subjects will be informed of the importance of increased record access and permission granted by signature on the informed consent document prior to Screening.

Checks will be performed to ensure quality, consistency, and completeness of the data. Instances of missing or uninterpretable data will be resolved with the investigator or study coordinator. Data queries, documented within the clinical database, will be accessible to the research facility through the EDC system. Study center personnel will be responsible for providing resolutions to the data queries and for correcting the eCRFs, as appropriate.

The investigator must keep written or electronic source documents for every subject participating in the clinical study for the appropriate document retention period. The subject file that identifies the study in which the subject is participating must include the subject's available demographic and medical information, including:

- Name
- Contact information
- Year of birth
- Sex
- Fitzpatrick skin type
- Medical history
- Concomitant therapies/medication
- Study visit dates
- Performed examinations, evaluations, and clinical findings
- Investigational product administration
- AEs, SAEs, or pregnancy (as applicable)

Additionally, any other documents with source data, especially original printouts of data that were generated by technical equipment must be included in the subject's source document (eg, laboratory value listings). All these documents must have at least the subject's study number, and the date of the evaluation.

The data recorded during the course of the study will be documented in the eCRF and/or the study-specific forms. Before or at study termination, all data must be forwarded to the Sponsor. The data will then be recorded, evaluated, and stored in anonymous or coded form in accordance with data-protection regulations.

Subjects will authorize the use of their protected health information during the informed consent process in accordance with the applicable privacy requirements. Subjects who deny permission to use and disclose protected health information will not be eligible to participate in the study.

The investigator will ensure that the study documents forwarded to the Sponsor, and any other documents, contain no mention of subject names. Any amendments and corrections necessary will be undertaken in both the source documents and eCRFs (as appropriate), and countersigned by the investigator, or documented designee, stating the date of the amendment/correction. Errors must remain legible and may not be deleted with correction aids. The investigator must state his/her reason for the correction of any data. In the case of missing data/remarks, the entry spaces provided in the eCRF should be cancelled out so as to avoid unnecessary follow-up inquiries.

Electronic CRFs will be kept by the Sponsor or an authorized designee in a secured area. Clinical data will be recorded in a computer format for subsequent statistical analyses. Data files will be stored on electronic media with a final master data file kept by the Sponsor after descriptive and statistical analyses and reports have been generated and are complete.

It is the responsibility of the investigator to ensure that the study center file is maintained in accordance with the ICH Guidance for Industry E6(R2) GCP: Consolidated Guidance, Section 8 – Essential Documents for the Conduct of a Clinical Trial.

#### 10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study treatment. These documents should be retained for a longer period, however, if required by local regulations or as specified in the study agreement, whichever retention period is longer.

If the investigator withdraws from the study (eg, relocation, retirement), all study-related records should be transferred to a mutually agreed-upon designee. Notice of such transfer will be provided to the Sponsor in writing. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the investigator when these documents no longer need to be retained.

### 10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical study protocol or ICH GCP requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. Protocol deviations related to COVID-19 pandemic will be identified and documented accordingly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, Section 5.1.1
- 5.20 Noncompliance, Sections 5.20.1, and 5.20.2.

It is the responsibility of the investigator to use continuous vigilance to identify and report deviations as soon as possible. All deviations must be addressed in study source documents, and applicable deviations must be sent to the reviewing IRB/EC per their policies. The investigator is responsible for knowing and adhering to the reviewing IRB/EC requirements. Further details about the handling of protocol deviations will be included in the Protocol Deviation Plan, Data Management Plan, Medical Monitoring Plan, blind data review documentation, and SAP.

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of the subject requires immediate intervention, based on the judgment of the investigator (or a designee, appropriately trained professional designated by the investigator). In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the investigator or designee must contact the Medical Monitor and the Sponsor at the earliest possible time by telephone. This will allow an early joint decision regarding the subject's continuation in the study. This decision will be documented by the investigator and the Medical Monitor. Please refer to Section 4.2 for allowable, as necessary, modifications to the protocol due to COVID-19 restrictions.

The monitor must ensure that a prompt action is taken to secure compliance. If a noncompliance that significantly affects or has the potential to significantly affect human subject protection or reliability of study results is discovered, the CRO and the Sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions.

#### 10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations: It is understood by the investigator that the information generated in this study will be used by the Sponsor in connection with the development of the product. To allow for the use of information derived from the study, it is understood that the investigator is obliged to provide the Sponsor with complete test results, all study data, and access to all study records.

Any results of medical investigations with Sponsor's products and/or publications/lectures/manuscripts based thereon shall be exchanged and discussed by the investigator and Sponsor representative(s), 30 days before submission for publication or presentation. Due regard shall be given to Sponsor's legitimate interests for example, manuscript authorship, obtaining optimal patent protection, coordinating and maintaining the proprietary nature of submissions to health authorities, coordinating with other ongoing studies in the same field, and protecting confidential data and information. The Sponsor shall be furnished with a copy of any proposed publication. Comments shall be rendered without undue delay.

In cases of publications or presentations of material arising from multicenter clinical investigations, the Sponsor is to serve as coordinator and referee. Individual investigators who are part of a multicenter investigation may not publish or present data that are considered common to a multicenter investigation without the consent of the other participating investigators and the prior review of the Sponsor.

Results from investigations shall not be made available to any third party by the investigating team outside the publication procedure as outlined previously. The Sponsor will not quote from publications by investigators in its scientific information and/or promotional material without full acknowledgment of the source (ie, author and reference).

#### 10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, financial interest, or any aspect of this study will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this study. The Sponsor has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

### 10.2 ADDITIONAL CONSIDERATIONS

#### 10.2.1 ETHICS AND RESPONSIBILITY

This study must be conducted in compliance with the protocol, the ICH Guidance for Industry E6(R2) GCP: Consolidated Guidance, the Declaration of Helsinki, IRB/EC requirements, and all applicable national and local regulatory requirements. Investigators must submit all essential regulatory documentation, as required by local and national regulations (including approval of the protocol and ICF by a Health and Human Services [HHS]-registered IRB/EC) to the Sponsor before investigational product will be shipped to the respective study centers.

#### 10.2.2 AMENDMENT POLICY

Only the Sponsor (or designee) may modify the protocol. Amendments must be approved by all applicable national and local committees including, but not limited to, the government regulatory

authorities and/or regional IRB/EC before implementation. The only exception is when an investigator considers that a subject may be harmed, and immediate action is necessary. Under these circumstances, approval of the chairman of the IRB/EC, or an authorized designee, must be sought immediately. The investigator should inform the Sponsor, and the full IRB/EC, no later than 5 working days after the emergency occurs. Protocol-specified safety reporting requirements must be adhered to, independent of any other variables.

### 10.2.3 INSURANCE

Sponsor will provide insurance in accordance with local guidelines and requirements for the subjects in this study. The terms of the insurance will be kept in the study files.

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# 12 APPENDICES

## Appendix 1: Contraceptive Guidance and Collection of Pregnancy Information

**Definitions:**

***Woman of childbearing potential (WOCBP)***

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study treatment, additional evaluation should be considered.

***Women in the following categories are not considered WOCBP (not of childbearing potential)***

1. Premenarchal
2. Surgically sterilized based on meeting at least 1 of the following:
   a) Documented hysterectomy.
   b) Documented bilateral salpingectomy,
   c) Documented bilateral oophorectomy.
   Note: For individuals with permanent infertility due to an alternate medical cause other than the above (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.
   Note: Documentation can come from the study center personnel's review of the subject's medical records, medical examination, or medical history interview.
3. Postmenopausal female:
   a) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range will be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   b) Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

**Contraception Guidance:**

***Male subjects***

Male subjects with female partners of childbearing potential are eligible to participate if they meet or agree to ONE of the following (during the protocol-defined time frame in Section 5.1):

- Documented vasectomy with confirmed absence of sperm.
- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of < 1% per year when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

In addition, male subjects must refrain from donating sperm for the duration of the study and for 220 days (which includes the duration of relevant exposure plus the duration of sperm cycle) after the last dose of study treatment.
Male subjects with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration for the

duration of the study and for 220 days (which includes the duration of relevant exposure plus the duration of sperm cycle) after the last dose of study treatment.

***Female subjects***

Female subjects of childbearing potential are eligible to participate if they agree to use highly effective methods of contraception consistently and correctly as described in the table below and during the protocol-defined time frame in Section 5.1, and refrain from donating oocytes for assisted reproduction during this period. For WOCBP, hormonal contraceptives must be used without schedule changes and on a stable regimen during the study treatment. Starting hormonal contraceptives during the study is not permitted.

**Highly Effective Contraceptive Methods:**

| **Highly Effective Contraceptive Methods That Are User Dependent** [a] |
|---|
| *Failure rate of <1% per year when used consistently and correctly.* |
| Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation<br>• Oral<br>• Intravaginal<br>• Transdermal |
| Progestogen-only hormonal contraception associated with inhibition of ovulation<br>• Oral<br>• Injectable |
| **Highly Effective Methods That Are User Independent** [a] |
| Implantable progestogen-only hormonal contraception associated with inhibition of ovulation<br>• Intrauterine device (IUD)<br>• Intrauterine hormone-releasing system (IUS)<br>• Implants inserted beneath the skin<br>• Tubal ligation or tubal occlusion |
| **Vasectomized Partner**<br>*A vasectomized partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.* |
| **Sexual Abstinence**<br>*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.* |
| NOTES:<br>[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. |

**Pregnancy Testing:**

Women of childbearing potential should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test at screening and urine pregnancy test on Day 1 (prior to study treatment administration).

Additional pregnancy testing should be performed as mentioned in the SoA (see Section 1.3).

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected. Positive urine pregnancy test result should be confirmed with serum test.

**Collection of Pregnancy Information**

***Male subjects with partners who become pregnant***

The investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive study treatment.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate pregnancy form and submit it to the pharmacovigilance unit within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Any SAEs associated with the pregnancy in the male subject's partner should also be reported to the pharmacovigilance unit within 24 hours of the event using the back-up paper SAE Report Form.

***Female subjects who become pregnant***

The investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the Pregnancy Report form and submitted to the pharmacovigilance unit within 24 hours of learning of a subject's pregnancy. The subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks after the delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such.

Any poststudy pregnancy-related SAE considered reasonably related to the study treatment by the investigator will be reported to the Sponsor as described in Section 8.2.1.8. While the investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating in the study will be withdrawn from the study.

# Appendix 2: Pruritus and Pain Numeric Rating Scales

**Pruritus Numeric Rating Scale:**

**On a scale from 0 ("no itch") to 10 ("worst imaginable itch"), how was your *WORST* itch in the past 24 hours? Please select one number.**

| Numeric Rating Scale |
|---|
| 0 1 2 3 4 5 6 7 8 9 10 |
| No itch ... Worst imaginable itch |

**Source:** Phan 2012, Verweyen 2019
***http://www.pruritussymposium.de/numericalratingscale.html***

**Pain Numeric Rating Scale:**

**Select the number that best describes your *WORST* pain (with regards to your rash) during the past 24 hours? Please select one number.**

| Numeric Rating Scale |
|---|
| 0 1 2 3 4 5 6 7 8 9 10 |
| No pain ... Worst imaginable pain |

**Source: modified from** Farrar 2001

# Appendix 3: Functional Assessment of Cancer Therapy - Epidermal Growth Factor Receptor Inhibitor 18

**Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

| | | Not at all | A little bit | Somewhat | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| ST4 | My skin or scalp feels irritated | 0 | 1 | 2 | 3 | 4 |
| ST5 | My skin or scalp is dry or "flaky" | 0 | 1 | 2 | 3 | 4 |
| ST6 | My skin or scalp itches | 0 | 1 | 2 | 3 | 4 |
| ST7 | My skin bleeds easily | 0 | 1 | 2 | 3 | 4 |
| ST9 | I am bothered by a change in my skin's sensitivity to the sun | 0 | 1 | 2 | 3 | 4 |
| ST32 | My skin condition interferes with my ability to sleep | 0 | 1 | 2 | 3 | 4 |
| ST22 | My skin condition affects my mood | 0 | 1 | 2 | 3 | 4 |
| ST17 | My skin condition interferes with my social life | 0 | 1 | 2 | 3 | 4 |
| ST24 | I am embarrassed by my skin condition | 0 | 1 | 2 | 3 | 4 |
| ST37 | I avoid going out in public because of how my skin looks | 0 | 1 | 2 | 3 | 4 |
| ST26 | I feel unattractive because of how my skin looks | 0 | 1 | 2 | 3 | 4 |
| ST34 | Changes in my skin condition make daily life difficult | 0 | 1 | 2 | 3 | 4 |
| ST38 | The skin side effects from treatment have interfered with household tasks | 0 | 1 | 2 | 3 | 4 |
| ST16 | My eyes are dry | 0 | 1 | 2 | 3 | 4 |
| ST15 | I am bothered by sensitivity around my fingernails or toenails | 0 | 1 | 2 | 3 | 4 |
| ST29 | Sensitivity around my fingernails makes it difficult to perform household tasks | 0 | 1 | 2 | 3 | 4 |
| B5 | I am bothered by hair loss | 0 | 1 | 2 | 3 | 4 |
| ST11 | I am bothered by increased facial hair | 0 | 1 | 2 | 3 | 4 |

English (Universal)

*https://eprovide.mapi-trust.org/instruments/functional-assessment-of-cancer-therapy-epidermal-growth-factor-receptor-inhibitors*

# Appendix 4: Patient Global Impression of Severity

Overall, how would you rate the **severity** of your rash now?

1. ☐ Clear Skin
2. ☐ Mild
3. ☐ Moderate
4. ☐ Severe

## Appendix 5: Patient Global Impression of Change

Overall, how would you rate the change in severity of your rash compared with how it was before you started taking the medication in this study?

1. ☐ Very much better
2. ☐ Much better
3. ☐ A little better
4. ☐ No change
5. ☐ A little worse
6. ☐ Much worse
7. ☐ Very much worse

# Appendix 6: Systemic Therapy Induced Diarrhea Assessment Tool

**Onset and duration**

1) In the last 7 days, did you experience any diarrhea? (If no, skip to question 3.) ¨ Yes ¨ No
   a. If yes, how would you rate your diarrhea at your worst?
      ¨ Minimal diarrhea ¨ Moderate diarrhea ¨ Severe diarrhea

**Stool frequency**

2) On average, how many times did you have diarrhea per day in the last 7 days? _____ per day
3) On average, how many times did you pass normal stool per day in the last 7 days? _____ per day

**Diarrhea-associated symptoms**

4) In the last 7 days, have you felt like you suddenly had to pass a stool? ¨ Yes ¨ No
5) In the last 7 days, did you have any abdominal discomfort? ¨ Yes ¨ No
6) In the last 7 days, were there times when you did not make it to the bathroom for a bowel movement? ¨ Yes ¨ No

**Self-Treatment of Diarrhea**

7) Please skip this question if you do not have diarrhea. This question pertains to medications that you may have used in the last 7 days to help your diarrhea. Please complete the following table.

| Medication | Did you use this medication? | Amount used in total? | Did it help your diarrhea? |
|---|---|---|---|
| Lomotil (diphenoxylate)  | ¨ Yes ¨ No | | ¨ Yes ¨ No |
| Imodium (loperamide)  | ¨ Yes ¨ No | | ¨ Yes ¨ No |

**Impact on quality of life**

8) Rank how much your bowel habits in the last 7 days have affected your ability to perform work or daily activities of living.

0 1 2 3 4 5 6 7 8 9 10

no impact extreme impact

9) Rank how much your bowel habits in the last 7 days have affected your energy level.

0 1 2 3 4 5 6 7 8 9 10

no impact extreme impact

10) Rank how much your bowel habits in the last 7 days affect your mood.

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| no impact | | | | | | | | | | extreme impact |

11) Rank how much your diarrhea has affected your family life.

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| no impact | | | | | | | | | | extreme impact |

12) Rank how much your diarrhea has affected your social life.

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| no impact | | | | | | | | | | extreme impact |

**Source:** Lui 2017
***http://creativecommons.org/licenses/by/4.0/***

# Appendix 7: Clinical Laboratory Tests

The tests detailed in Table 18 will be performed by the central laboratory. The time points are specified in the SoA (see Section 1.3).

Local laboratory tests will be allowed in the event that the central laboratory results will not be available immediately, and the investigator needs to make an immediate decision for any safety concerns. Local laboratory tests will also be allowed at Screening for TB and viral serology testing. If a local sample is collected, it is important that the sample for central analysis is obtained at the same time. Urine pregnancy dipstick will be performed at the study center prior to study treatment administration.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Investigators must document their review of each laboratory safety report.

**Table 18: Protocol-required Safety Laboratory Assessments by Central Laboratory**

| Laboratory Assessments | Parameters | |
|---|---|---|
| Hematology | Hemoglobin | Red blood cell (RBC) count |
| | Hematocrit/ Packed cell volume (PCV) | White blood cell (WBC) count with Differential: |
| | | Neutrophils |
| | Mean corpuscular hemoglobin (MCH) | Lymphocytes |
| | Mean corpuscular volume (MCV) | Monocytes |
| | Mean corpuscular hemoglobin concentration (MCHC) | Eosinophils |
| | | Basophils |
| | Platelet count | |
| Biochemistry | Alanine aminotransferase (ALT) | Creatinine |
| | Albumin | Creatinine clearance |
| | Alkaline phosphatase (ALP) | Gamma glutamyl transferase (GGT) |
| | Aspartate aminotransferase (AST) | Glucose |
| | Bicarbonate | Potassium |
| | Bilirubin (Total) | Phosphate (Inorganic) |
| | Bilirubin (Direct-only if total is elevated) | Protein (Total) |
| | | Sodium |
| | Calcium | Blood urea nitrogen (urea) |
| | Chloride | Creatine kinase (CK) |
| | Uric acid | Triglycerides |
| | Lactate dehydrogenase | high-sensitivity C-reactive protein (hsCRP) |
| | Troponin | Total cholesterol (fractions) |
| Serum pregnancy | Human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) | |
| Follicle-stimulating hormone (FSH) | In women of nonchildbearing potential only (postmenopausal women with at least 12 months of amenorrhea without an alternative medical cause) | |

| **Laboratory Assessments** | **Parameters** | |
|---|---|---|
| Urinalysis | Bilirubin<br>Blood<br>Glucose<br>Ketones<br>Leukocytes<br>Nitrites | pH<br>Protein<br>Specific gravity<br>Urobilinogen<br>Microscopy (At discretion of the investigator based on urinalysis results) |
| Viral serology | Antibodies to hepatitis B core antigens<br>Hepatitis B surface antigen<br>Hepatitis C antibody<br>Human immunodeficiency virus antibodies | |
| Tuberculosis (TB) screening | QuantiFERON-TB Gold® In-Tube, the third-generation test (If the test indeterminate it can be retested only once) | |
| NOTES: Please see SoA for laboratory tests time points.<br>All blood samples must be drawn prior to administration of the study treatment, unless otherwise specified. The date and exact time of sample collection must be recorded. | | |

# Appendix 8: Fitzpatrick Skin Type Classification

| Fitzpatrick Classification of Skin types | | | | | |
|---|---|---|---|---|---|
| **Skin Type** | **Hair** | **Complexion** | **Freckles** | **Sun Reaction** | **Tanning** |
| **I** | Red or Blond | Very Fair | +++ | Always burns | Never tans |
| **II** | Blond | Fair | ++ | Often burns | Tans lightly |
| **III** | Blond or Light Brown | Fair to medium | + to 0 | Sometimes burns | Tans progressively |
| **IV** | Brown | Olive | 0 | Rarely burns | Tans easily |
| **V** | Brown to Black | Dark | 0 | Rarely burns | Tans deeply |
| **VI** | Black | Very dark | 0 | Never burns | Tans deeply |

**Source: Attwa 2016; Fitzpatrick 1988; Wallace 2017; Zalaudek 2007**