Statistical Analysis Plan for Study M19-530

A Phase 2 Study of ABBV-3067 Alone and in Combination with ABBV-2222 in Cystic Fibrosis Subjects Who Are Homozygous for the F508del Mutation

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Version 2.0

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for ABBV-3067/ABBV-2222 Study M19-530 titled "A Phase 2 Study of ABBV-3067 Alone and in Combination with ABBV-2222 in Cystic Fibrosis Subjects Who Are Homozygous for the F508del Mutation."

Study M19-530 examines the safety, tolerability, and efficacy of ABBV-3067 given alone and in combination with ABBV-2222 in adult subjects with Cystic Fibrosis (CF) who are homozygous for the F508del mutation.

The analyses of pharmacokinetic endpoints, biomarker samples and exploratory research endpoints will not be covered in this SAP.

The SAP will not be updated in case of administrative changes or amendments to the protocol unless the changes impact the analysis.

Unless noted otherwise, all analyses will be performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC 27513) or later under the UNIX operating system.

2.0 Study Design and Objectives

2.1 Objectives and Hypotheses

The objectives of Part 1 in this study are to:

1. Evaluate the safety, tolerability, and efficacy of ABBV-3067 given alone and in combination with varied dose levels of ABBV-2222 in adult subjects with CF who are homozygous for the F508del mutation.
2. Select a dose of ABBV-2222 to use in Part 2 based on safety, tolerability, efficacy, and pharmacokinetic data.

The objectives of Part 2 in this study are to:

1. Evaluate the safety, tolerability, and efficacy of ABBV-2222 (fixed dose from Part 1) combined with varied dose levels of ABBV-3067 in CF subjects who are homozygous for the F508del mutation.
2. Select a dose of ABBV-3067 to carry forward to future combination studies.

2.2 Study Design Overview

This is a Phase 2, double-blind, placebo-controlled, parallel-arm, multicenter study to evaluate the safety, efficacy and pharmacokinetics of different dose levels of ABBV-3067 given alone and in combination with different dose levels of ABBV-2222 for 28 days in subjects aged 18 years and older with CF who are homozygous for F508del CFTR mutation.

This study consists of 2 parts (Part 1 and Part 2) and will initially enroll CF subjects to Part 1. Part 2 of the study will initiate after all subjects enrolled in Part 1 complete the 30-day safety follow-up period or prematurely discontinue from the study. Each part of the study is comprised of an approximately 30-day screening period, a 28-day double-blind (DB) Treatment Period and a 30-day Follow-up Visit.

Part 1

In Part 1, approximately 117 eligible subjects with CF will be randomized in a 1:1:1:2:2:2:2:2 ratio to 8 treatment arms in a dose range-finding manner to enable a dose selection for ABBV-2222 for Part 2:

A: ABBV-3067 50 mg + Placebo for ABBV-2222

B: ABBV-3067 150 mg + Placebo for ABBV-2222

C: ABBV-3067 150 mg + ABBV-2222 10 mg

D: ABBV-3067 150 mg + ABBV-2222 30 mg

E: ABBV-3067 150 mg + ABBV-2222 100 mg

F: ABBV-3067 150 mg + ABBV-2222 200 mg

G: ABBV-3067 150 mg + ABBV-2222 300 mg

H: Placebo for ABBV-3067 + Placebo for ABBV-2222

Study drug will be administered from Baseline/Day 1 to Day 28. The last visit in the DB Treatment Period is planned at Day 29, when all scheduled efficacy, safety and pharmacokinetics assessments will be performed.

Part 2

In Part 2, approximately 72 eligible subjects with CF will be randomized in a 1:2:2:2:1 ratio to 5 treatment arms in a dose-ranging manner to enable selection of the ABBV-3067 dose for future combination studies:

I: ABBV-3067 5 mg + ABBV-2222*

J: ABBV-3067 15 mg + ABBV-2222*

K: ABBV-3067 50 mg + ABBV-2222*

L: ABBV-3067 150 mg + ABBV-2222*

M: Placebo for ABBV-3067 + Placebo for ABBV-2222

* A fixed dose for ABBV-2222 is to be determined based on Part 1 data.

Study drug will be administered from Baseline/Day 1 to Day 28. The last visit in the DB Treatment Period is planned at Day 29, when all scheduled efficacy, safety and pharmacokinetics assessments will be performed.

For both parts of the study, a follow-up visit will occur 30 days after the last dose of study drug to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs and use of any concomitant medications.

Schematics of the 2 parts of the study are shown in Figure 1 and Figure 2.

Figure 1. Part 1 Study Schematic

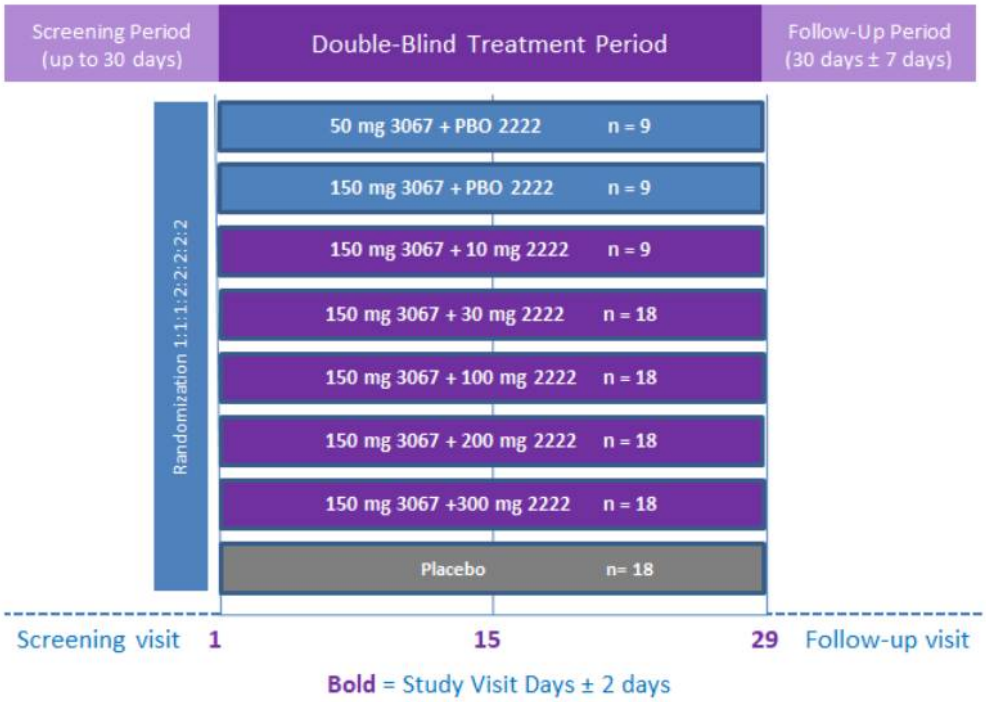
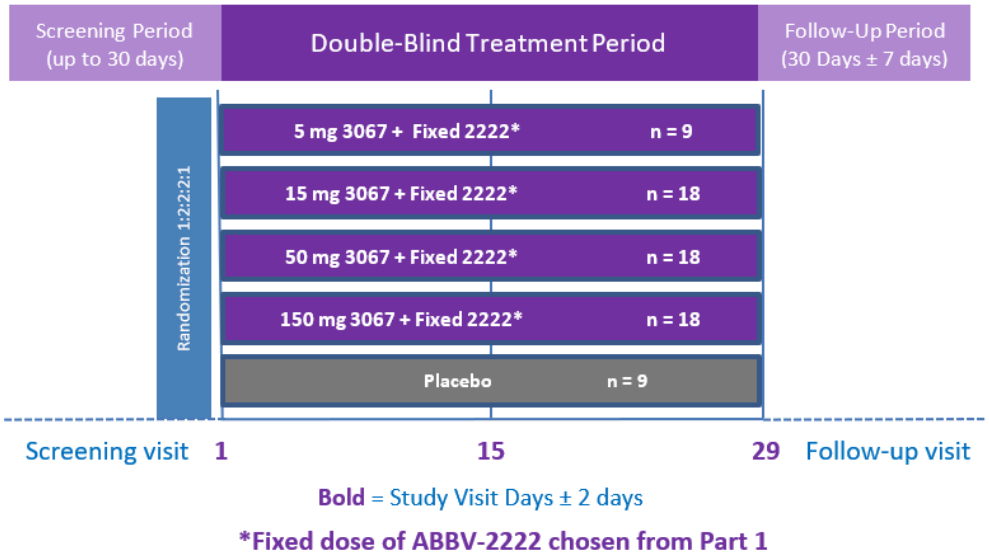


Figure 2. Part 2 Study Schematic



2222 = ABBV-2222; 3067 = ABBV-3067; PBO = placebo

2.3 Treatment Assignment and Blinding

All subjects will be assigned a unique identification number by the IRT at the Screening visit. For subjects who rescreen, the screening number assigned by the IRT at the initial Screening visit should be used. The IRT will assign a randomization number that will encode the subject's treatment assignment according to the randomization schedule generated by the statistics department at AbbVie.

In Part 1, subjects meeting eligibility criteria will be randomized at the Baseline visit to Treatment A through H in a 1:1:1:2:2:2:2:2 ratio. In Part 2, subjects meeting eligibility criteria will be randomized at the Baseline visit to Treatment I through M in a 1:2:2:2:1 ratio. Description of treatment arms are in Section 2.2. In both Part 1 and Part 2, randomization will be stratified by the percent predicted forced expiratory volume in 1 second at Screening visit ($ppFEV_1 < 70\%$ vs $ppFEV_1 \geq 70\%$). The calculation of percent predicted FEV_1 is described in Section 8.3.1.

To minimize the potential of unblinding, the AbbVie study team will not have access to the post-first-dose spirometry or sweat chloride results until after the study is unblinded for Part 1 or Part 2 analysis. During the blinding phases, the vendors for central reading of the spirometry data or sweat chloride data will only send the blinded files to the sponsor's database to be used for developing the statistical programs.

2.4 Sample Size Determination

The power calculations are provided for the most potentially efficacious groups with the combination treatment for both Part 1 and Part 2 for the primary efficacy endpoint. Placebo groups from both Part 1 and Part 2 will be combined in the Part 2 efficacy analysis. A sample size of 18 subjects in a group will provide 80% power to detect a 5.3% absolute increase from Baseline in $ppFEV_1$ for that group assuming a standard deviation of 7.5%. When comparing to the placebo group, a sample size of 18 subjects in both treated group and placebo group will provide 80% power (Part 1), or a sample size of 18 subjects in treated group and 27 subjects in placebo group will provide approximately 87% power (Part 2), to detect a 7.3% difference in $ppFEV_1$ change from Baseline between a treated group and the placebo group assuming the standard deviation of 7.5% for change in $ppFEV_1$ for both groups.

3.0 Endpoints

3.1 Primary Endpoint(s)

The primary endpoint is the absolute change from Baseline through Day 29 in percent predicted forced expiratory volume in 1 second ($ppFEV_1$, a measure of lung function).

3.2 Secondary Endpoint(s)

The secondary endpoints are:

1. Absolute change from Baseline through Day 29 in Sweat Chloride (a biomarker of CFTR activity)

2. Absolute change from Baseline through Day 29 in other spirometric measures (forced vital capacity [FVC], forced expiratory flow at mid-lung capacity [FEF_{25-75}])
3. Relative changes from Baseline through Day 29 in $ppFEV_1$, FVC, and FEF_{25-75}.

3.3 Other Efficacy Endpoint(s)

There are no additional efficacy endpoints for this study.

3.4 Safety Endpoint(s)

The following endpoints will be included in the safety analyses:

- Treatment emergent adverse events
- Serious adverse events
- Adverse events of safety interest
- Adverse events leading to study drug discontinuation
- Clinical laboratory tests, 12-lead electrocardiogram, vital signs, weight, pulse oximetry and spirometry parameters.

3.5 Additional Endpoint(s)

The pharmacokinetic endpoints will be analyzed separately and not be covered in this SAP.

4.0 Analysis Populations

The following population sets will be used for analyses in each part of the study.

The Full Analysis Set (FAS) includes all randomized subjects who received at least 1 dose of study drug. The FAS will be used for all efficacy and baseline analyses. Subjects will be grouped according to treatment as randomized.

The Safety Analysis Set consists of all subjects who received at least 1 dose of study drug. The Safety Analysis Set will be used for safety analyses. Subjects will be included in the analysis according to the study drug that they actually received. If a subject takes more than 1 treatment, the subject will be grouped in the treatment group for which they received the most doses.

5.0 Subject Disposition

For each part of the study, the total number of subjects who were randomized and treated will be summarized.

A summary of subject accountability will be provided where the number of subjects in each of the following categories will be summarized for each treatment group:

- Subjects randomized in the study;
- Subjects who took at least one dose of study drug;
- Subjects who completed protocol-specified treatment;
- Subjects who prematurely discontinued study drug;
- Subjects who completed study;
- Subjects in each analysis population, as applicable.

The number and percentage of subjects who discontinued study drug by reason (all reasons and primary reason) will be summarized overall and by treatment arm, as well as for the combined placebo arms from Part 1 and Part 2. Similar summaries will be provided for discontinuations from the study.

6.0 Study Drug Duration and Compliance

Study drug duration, treatment compliance and study drug temporary interruptions will be summarized on the Safety Analysis Set for each treatment arm as well as for the combined placebo arms from Part 1 and Part 2.

Duration of treatment is defined for each subject as last dose date minus first dose date + 1. Study drug temporary interruptions will not be subtracted from the duration. Duration of treatment will be summarized including the number of subjects treated, mean, standard deviation, median, minimum and maximum. In addition, the number and percentage of subjects in each treatment duration interval (1 to 7, 8 to 14, 15 to 21, 22 to 28, and > 28 days) will be summarized.

The number and percentage of subjects with reported study drug temporary interruptions will be summarized by reason as captured on the eCRF.

Treatment compliance is defined as the number of tablets or capsules actually taken divided by the number of tablets or capsules that should have been taken. Percent compliance will be summarized by treatment arm, and a listing with percent compliance for each subject will be provided.

7.0 Demographics, Baseline Characteristics, Medical History, and Prior/Concomitant Medications

Demographics, baseline or disease characteristics, medical history, and prior and concomitant medications will be summarized for the FAS overall and by treatment arm, as well as for the combined placebo arms from Part 1 and Part 2.

Categorical variables will be summarized with the number and percentage of subjects; percentages will be calculated based on the number of non-missing observations. Continuous variables will be summarized with descriptive statistics including number of non-missing observations, mean and standard deviation, median, minimum and maximum.

7.1 Demographics and Baseline Characteristics

The following demographic and characteristics parameters will be summarized.

Subject Demographics

- Sex (male, female)
- Age (years)
- Race (White, Black, American Indian/Alaska Native, Native Hawaiian or Other Pacific Islander, Asian, Multi, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Country
- Region (North America, Rest of World)
- Body weight (kg) at baseline
- Height (cm) at baseline
- BMI (kg/m^2) baseline

Disease Characteristics

- Alcohol status (Never, Current, Former)
- F508del CFTR mutation as captured on the Cystic Fibrosis History eCRF (Homozygous, Heterozygous),
- F508del CFTR mutation as determined by central lab genotyping (Homozygous, Heterozygous)
- Continuous value of $ppFEV_1$ at screening visit (%)
- Continuous value of $ppFEV_1$ at baseline (%)
- Stratification factor of screening $ppFEV_1$ ($< 70\%$, $\geq 70\%$)
- Screening $ppFEV_1$ category ($< 40\%$, $\geq 40\%$ to $< 70\%$, $\geq 70\%$ to $< 90\%$, $\geq 90\%$)
- Baseline $ppFEV_1$ category ($< 40\%$, $\geq 40\%$ to $< 70\%$, $\geq 70\%$ to $< 90\%$, $\geq 90\%$)
- Continuous value of sweat chloride at baseline (mmol/L)
- Continuous value of FEV_1 at baseline (L)
- Continuous value of FVC at baseline (L)
- Continuous value of FEF_{25-75} at baseline (L/sec)
- Prior use of CFTR modulators (Yes, No)
- For subjects with prior use of CFTR modulators only:

- prior CFTR modulator medication
- reason for discontinuation of prior CFTR modulators (Lack of efficacy, Tolerability, Other)

- Number of exacerbations requiring hospitalization and/or intravenous antibiotics in last 12 months
- Supplemental oxygen use while awake (Yes, No)
- Supplemental oxygen use while sleeping (> 2 L/minute, ≤ 2 L/minute, No)
- Microbiology history in the past year as captured on the Microbiology History eCRF

7.2 Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA coding dictionary will be noted in the statistical tables and clinical study report. The number and percentage of subjects in each medical history category (by MedDRA system organ class and preferred term) will be summarized overall and by treatment group. The system organ class (SOC) will be presented in alphabetical order, and the preferred terms (PTs) will be presented in alphabetical order within each SOC. Subjects reporting more than one condition/diagnosis will be counted only once in each row (SOC or PT).

7.3 Prior and Concomitant Medications

Prior and concomitant medications will be summarized by generic name. A prior medication is defined as any medication taken prior to the date of the first dose of study drug. A concomitant medication is defined as any medication that started prior to the date of the first dose of study drug and continued to be taken after the first dose of study drug or any medication that started on or after the date of the first dose of study drug, but not after the date of the last dose of study drug. The number and percentage of subjects taking medications will be summarized by generic drug name based on the World Health Organization (WHO) Drug Dictionary for both prior and concomitant medications.

8.0 Efficacy Analyses

8.1 General Considerations

All efficacy analyses will be conducted for the FAS. All tests will be 2-sided at an alpha level of 0.05. For each part of the study, the efficacy analysis will be performed after all ongoing subjects have completed the study part and the database has been locked.

For the primary efficacy endpoint, the null hypothesis that the within-group absolute change from baseline in ppFEV$_1$ through Day 29 is zero will be tested for each treated group at 2-sided alpha of 0.05.

Unless otherwise specified, any subject who is randomized based on a wrong stratum will be analyzed according to the actual stratum to which the subject belongs.

"Baseline" refers to the last non-missing observation before the first administration of study drug.

Unless otherwise specified, continuous variables will be analyzed using Mixed-Effect Model Repeat Measurement (MMRM) method with the model based mean and standard error being provided. The Baseline and visit means will also be presented for each treatment group among subjects who have both Baseline and at least one post Baseline visit values. Treatment groups will be compared using MMRM model as described in Section 8.2. Point estimates and 95% CIs of mean change from Baseline within each treatment group, the difference between each active treatment group and placebo, and the difference between each combination therapy arm and the ABBV-3067 150 mg monotherapy arm (Part 1 only) will be provided. Note that both placebo arms in Part 1 and Part 2 will be combined into one placebo group for the Part 2 model comparison.

Plots of the primary endpoint and certain secondary endpoints by treatment group will be used to visualize the change of endpoint values over time and the difference between treatment groups.

Use of bronchodilator medications and/or airway clearance techniques may affect lung function measurements in the short term. Therefore, post-baseline spirometric measurement that are collected inconsistently with the conditions for the baseline spirometric measurement will be excluded from the efficacy analysis. For example, if baseline spirometric measurement was collected prior to bronchodilator use, then any spirometric measurement collected post bronchodilator use at a subsequent visit will be excluded from analysis.

If a subject starts another CFTR modulator treatment during the study period, then all efficacy measures for this subject on or after the start date of the new CFTR modulator treatment will be excluded from analyses.

8.2 Handling of Missing Data

The primary endpoint and key secondary endpoints will use the same analysis method: Mixed-Effect Model Repeat Measurement (MMRM). This modeling approach handles partially missing dependent variables (change from Baseline to one of the visits is missing) based on the assumption of data being missing at random. No other imputation will be used.

8.3 Primary Efficacy Endpoint(s) and Analyses

8.3.1 Primary Efficacy Endpoint(s)

The primary endpoint is the absolute change from Baseline through Day 29 in $ppFEV_1$. The predicted values of FEV_1 (L) at all study visits will be estimated for age, gender, and height using the 2012 Global Lungs Initiative equation.[2] Percent predicted FEV_1 is the ratio of FEV_1 (L) to the predicted FEV_1 (L), expressed as a percentage. For the primary efficacy endpoint in both Part 1 and Part 2, the corresponding statistical null hypotheses are that there is no difference in the mean value of $ppFEV_1$ from baseline through Day 29 within each treatment group.

8.3.2 Handling of Missing Data for the Primary Efficacy Endpoint(s)

Missing data will be handled using MMRM method as described in Section 8.2.

8.3.3 Primary Efficacy Analysis

The primary analysis will be performed using MMRM with change from Baseline in $ppFEV_1$ as the dependent variable. The mixed model includes the categorical fixed effects of treatment, visit and treatment-by-visit interaction, as well as the continuous fixed effect of baseline $ppFEV_1$. The random effects of the model will be subject ID. Parameter estimation will use the method of restrictive maximum likelihood (REML).[1]

The point estimate for the primary endpoint from the MMRM model along with the 95% confidence interval and the corresponding p-value will be presented for the primary efficacy analysis. The pairwise comparison of the primary endpoint of $ppFEV_1$ between each active treatment group versus the placebo group will also be estimated using the same model. The Least Squares Mean of the treatment difference between each active treatment group versus the placebo group will be presented along with the 95% confidence interval and a 2-sided p-value.

8.3.4 Additional Analyses of the Primary Efficacy Endpoint(s)

Sensitivity analysis for the primary endpoint of $ppFEV_1$ will be conducted using all spirometry data as collected if there are at least 5% of the total subjects in each study part who have at least one post-Baseline inconsistent use of bronchodilator medications and/or airway clearance.

8.4 Secondary Efficacy Analyses

Efficacy analyses will be performed by treatment group at each protocol-specified visit on each of the secondary efficacy endpoints including

- absolute change from Baseline through Day 29 in Sweat Chloride (in mmol/L),

- absolute change from Baseline through Day 29 in FVC (in L), FEF_{25-75} (in L/s), and
- relative change, calculated as percent change, from Baseline through Day 29 in $ppFEV_1$, FVC, and FEF_{25-75}

The point estimate for each of the secondary efficacy endpoints from the MMRM model along with the 95% confidence intervals and the corresponding p-values will be presented. In addition, pairwise comparison of each active treatment group versus placebo group will be analyzed using MMRM method as described in Section 8.3.3.

8.5 Additional Efficacy Analyses

There are no additional efficacy analyses planned for this study.

8.6 Efficacy Subgroup Analyses

Descriptive statistics of the primary endpoint will be provided for the following subgroups to evaluate the consistency of the efficacy across subgroup levels.

- Geographic region (North America, Rest of World)
- Stratification factor of screening $ppFEV_1$ (< 70%, ≥ 70%)
- Prior use of CFTR modulators (Yes, No)

The point estimates and 95% CIs will be provided within each subgroup level. No p-value will be provided for subgroup analysis.

9.0 Safety Analyses

9.1 General Considerations

Safety data will be summarized for the Safety Analysis Set for each part of the study. Safety summaries will be presented by treatment arm, as well as for the combined placebo arms from Part 1 and Part 2.

For the safety analysis, subjects are assigned to a treatment group based on the treatment actually received, regardless of the treatment randomized. If a subject received more than one treatment, the subject will be grouped in the treatment group for which they received the most doses. All safety analyses will be based on observed data. Missing safety data will not be imputed.

9.2 Adverse Events

Adverse events (AEs) will be summarized and presented using primary MedDRA System Organ Classes (SOCs) and preferred terms (PTs) according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the AE tables and in the clinical study report. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

9.2.1 Treatment-Emergent Adverse Events

Treatment-emergent (TE) AEs are defined as any AE with an onset date that is after the first dose of study drug and no more than 30 days after the last dose of study drug. Events where the onset date is the same as the study drug start date are assumed to be treatment-emergent. All TEAEs will be summarized overall, as well as by primary MedDRA SOC and PT. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

The number and percentage of subjects experiencing TEAEs will be summarized.

Pre-treatment AEs will be summarized separately in listing format.

AEs starting more than 30 days following the last dose of study drug will be summarized separately in listing format.

9.2.2 Adverse Event Overview

An overview of TEAEs will be presented consisting of the number and percentage of subjects experiencing at least one event for each of the following AE categories:

- Any TEAE
- Any TEAE related to study drug according to the investigator
- Any TEAEs of Grade 3 or higher
- Any serious TEAE
- Any serious TEAE related to study drug according to the investigator
- Any TEAE leading to discontinuation of study drug
- TEAEs leading to interruption of study drug
- Any fatal TEAE
- AEs of special interest (AESI) (defined in Section 9.2.5)
- All deaths

9.2.3 Treatment-Emergent Adverse Events by SOC and/or PT

Treatment-emergent AEs will be summarized by SOC and PT; by maximum relationship to study drug as assessed by the investigator (e.g., reasonable possibility or no reasonable possibility) and SOC and PT; by maximum severity and SOC and PT; and by subject number and SOC and PT. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

If a subject has an AE with unknown severity or relationship to study drug, then the subject will be counted in the severity/relationship level category of "unknown" even if the subject has another occurrence of the same event with a severity present. The only exception is if the subject has another occurrence of the same AE with the highest level of severity or a relationship assessment of "Reasonable possibility." In this case, the subject will be counted under the most extreme severity/relationship category.

In addition, TEAEs will be summarized by PT and sorted by the overall descending frequency in the ABBV-3067 150 mg plus ABBV-2222 300 mg arm for Part 1 analysis and by the overall descending frequency in the ABBV-3067 150 mg plus ABBV-2222 fixed dose arm for Part 2 analysis.

9.2.4 SAEs (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation

Treatment-emergent SAEs (including deaths) and AEs leading to study drug discontinuation will be summarized by SOC and PT and in listing format.

A listing of all deaths will be generated.

9.2.5 Adverse Events of Special Interest

The rash AESIs will be identified per a Product MedDRA Query (PMQ) of "Drug Induced rash (Cystic Fibrosis Transmembrane Regulator [CFTR] Modulators Product Specific)" and be summarized by SOC and PT. For rash related AESIs, the following categories will be summarized by treatment group:

- Any rash AESIs
- Any rash AESIs related to study drug according to the investigator
- Any rash AESIs leading to discontinuation of study drug
- Any rash AESIs leading to interruption of study drug
- Any serious rash AESIs
- Any serious rash AESIs related to study drug according to the investigator

Tabular listings of AESIs will also be provided.

9.3 Analysis of Laboratory Data

Data collected from central and local laboratories, including additional laboratory testing due to an SAE, will be used in all analyses, except for Baseline where SAE-related laboratory assessments on or before the first dose of study drug will be excluded. The

clinical laboratory tests defined in the protocol operations manual (e.g., hematology and clinical chemistry) will be summarized.

Each laboratory variable will be summarized for all visits (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Mean change from baseline to each applicable post-baseline visit will be summarized for laboratory variables with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard error, and 95% confidence interval will be presented for the mean change from baseline within each treatment group.

In the DB Treatment Period, changes in selected laboratory parameters will be tabulated using shift tables for categories of low, normal, or high based on the normal ranges. A shift table from Baseline values of high or normal to post-Baseline low, or from Baseline values of low or normal to post-Baseline high will be created based on the worst post-Baseline value during treatment. Shifts from Baseline grade to the worst post-Baseline grade (CTCAE 4.03) during treatment will be summarized in a cross-tabulation of grades. Similar shift tables by normal range and grade will be provided for shifts from baseline to the final post-Baseline value.

Laboratory abnormalities for selected parameters will be evaluated based on Potentially Clinically Significant (PCS) criteria (Appendix B). For each laboratory PCS criterion, the number and percentage of subjects who have a laboratory value meeting the criteria during treatment will be summarized. A post-baseline value must be more extreme than the baseline value to be considered a PCS finding. Listings will be provided to summarize subject-level laboratory data for subjects meeting PCS criteria.

The number and percentage of subjects with laboratory values meeting the following criteria during treatment will be summarized to support the assessment of potential hepatotoxicity.

- ALT > 3 × ULN, > 5 × ULN, > 10 × ULN, > 20 × ULN
- AST > 3 × ULN, > 5 × ULN, > 10 × ULN, > 20 × ULN

- TBL > 1.5 × ULN, > 2 × ULN
- ALT and/or AST > 3 × ULN and TBL > 1.5 × ULN
- ALT and/or AST > 3 × ULN and TBL > 2 × ULN
- ALT > 3 × ULN and TBL > 1.5 × ULN
- ALT > 3 × ULN and TBL > 2 × ULN
- Alkaline phosphatase > 1.5 × ULN

Listing of ALT, AST, total bilirubin, and alkaline phosphatase values will be provided for each subject who met one or more of the criteria defined above.

An Evaluation of Drug Induced Serious Hepatotoxicity (eDISH) plot displaying the maximum on-treatment values of total bilirubin (as multiple of ULN) versus ALT (as multiple of ULN), not necessarily concurrent, will be created. A similar eDISH plot and subject listing will be presented for AST vs. total bilirubin.

9.4 Analysis of Vital Signs

Vital sign measurements include systolic blood pressure [mmHg], diastolic blood pressure [mmHg], pulse [beats per minute], body temperature [°C], oxygen saturation [%], respiratory rate [breaths/minute] and weight [kg].

Each vital sign variable will be summarized for all visits (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Mean change from baseline to each applicable post-baseline visit will be summarized for each vital sign variable, with the number of observations, baseline mean, and visit mean.

Vital sign variables will be evaluated based on potentially clinically important (PCS) criteria (Appendix B). For each vital sign PCS criterion, the number and percentage of subjects who have a vital sign value meeting the criteria during treatment will be summarized. A post-baseline value must be more extreme than the baseline value to be

considered a PCS finding. Listings will be provided to summarize subject-level vital sign data for subjects meeting PCS criteria.

9.5 Safety Subgroup Analyses

There are no safety subgroup analyses planned for this study.

9.6 Other Safety Analyses

Pulse Oximetry

For oxygen saturation values by pulse oximetry, a summary of observed values and change from baseline values will be provided at each visit by treatment group. The number and percentage of subjects with shift changes from baseline (categorized as < 95% or ≥ 95%) to the minimum value of oxygen saturation during treatment (categorized as < 90%, 90 – < 95%, or ≥ 95%) will be tabulated by treatment group.

Post-dose Spirometry

The absolute change and relative (percent) change from the pre-dosing value to the post-dosing value of $ppFEV_1$ on the same visit day will be provided by treatment group for the Day 1 and Day 15 visit. The descriptive statistics include the number of observations, mean, median, standard deviation, median, minimum and maximum.

In addition, the number and percentage of subjects with relative (percent) $ppFEV_1$ decline ≥ 10% from the pre-dosing value at the Day 1 and Day 15 visit will be summarized by treatment group.

ECG

ECG is collected at Screening, Day 15 and Day 29 visits. ECG findings will be summarized by treatment group for each visit. Summaries will include n (%) of patients in following categories:

- Normal

- Abnormal - Not Clinically Significant
- Abnormal - Clinically Significant
- Unable to Evaluate
- Missing

10.0 Other Analyses

There are no other safety analyses planned for this study.

11.0 Interim Analyses

One interim analysis is planned when all of the subjects participating in study Part 1 have completed the Follow Up Period (including those who discontinue prior to the Follow Up visit) and the database has been locked for analysis. An additional interim analysis may be conducted when all of the subjects participating study Part 2 have completed or discontinued the Treatment Period and the database has been locked for analysis.

11.1 Data Monitoring Committee

An external data monitoring committee (DMC) composed of persons independent of AbbVie and with relevant expertise in the Cystic Fibrosis field will review unblinded safety data from the ongoing study. The primary responsibility of the DMC will be to protect the safety of the subjects participating in this study.

A separate DMC charter describes the roles and responsibilities of the DMC members, frequency of data reviews, relevant data to be assessed, and general operations. In addition, the detailed data analysis and specifications for the DMC reviews are included in a separate DMC TFL specifications document.

12.0 Overall Type-I Error Control

There is no multiple testing procedure planned for this dose ranging study.

Since Part 1 subjects and Part 2 subjects are two independent study populations and there is no plan to stop the study early for any efficacy claim after Part 1 is complete, no alpha spending is needed.

13.0 Version History

Table 1. SAP Version History Summary

Version	Date	Summary
1.0	10 Feb 2020	Original version
2.0	27 Jul 2021	• Added plots for the primary endpoint and certain secondary endpoints in Section 8.1 • Clarified the missing data approach in Section 8.2 • Changed "rash related AESIs" to "rash AESIs" in Section 9.2.5 • For PCS labs in Section 9.3, changed "grade" to "value" in "post-baseline grade must be more extreme than baseline grade" • Specifically mentioned CTCAE v. 4.03 for grade shift tables in Section 9.4 • Replaced specific categories of protocol deviations with a more general text in Appendix A

14.0 References

1. SAS Institute Inc. SAS/STAT® 14.1 User's Guide, The MIXED Procedure. Cary, NC; SAS Institute Inc., 2015.
2. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3 - 95-year age range: the global function 2012 equations: Report of the Global Lung Function Initiative (GLI), ERS Task Force to establish improved lung function reference values. Eur Respir J. 2012;40(6):1324-43.

Appendix A. Protocol Deviations

The number and percentage of subjects for each category in the collected protocol deviation data will be summarized.

Appendix B. Potentially Clinically Significant Criteria for Safety Endpoints

The criteria for Potentially Clinically Significant (PCS) laboratory findings are described in Table B-1 and Table B-2, and the PCS criteria for vital sign findings are described in Table B-3.

Table B-1. Criteria for Potentially Clinically Significant Chemistry Values

Chemistry Variables	Units	Very Low	Very High
Total Bilirubin	mcmol/L		> 1.5 × ULN if baseline was normal; > 1.5 × baseline if baseline was abnormal
SGOT/AST	U/L		> 5.0 × ULN if baseline was normal; > 5.0 × baseline if baseline was abnormal
SGPT/ALT	U/L		> 5.0 × ULN if baseline was normal; > 5.0 × baseline if baseline was abnormal
Albumin	g/L	< 20	
Glucose	mmol/L	< 2.2	> 13.9
Creatinine	mcmol/L		> 1.5 × ULN or 1.5 × baseline
Sodium	mmol/L	< 130	> 155
Potassium	mmol/L	< 3.0	> 6.0
Calcium	mmol/L	< 1.75	> 3.1
CPK	U/L		> 5.0 × ULN
Total Cholesterol	mmol/L		> 10.34
GGT	U/L		> 5.0 × ULN if baseline was normal; > 5.0 × baseline if baseline was abnormal
Alkaline phosphatase	U/L		> 5.0 × ULN if baseline was normal; > 5.0 × baseline if baseline was abnormal

Note: A post-baseline value must be more extreme than the baseline value to be considered a potentially clinically significant finding.

Table B-2. Criteria for Potentially Clinically Significant Hematology and Coagulation Values

Hematology Variables	Units	Very Low	Very High
Hemoglobin	g/dL	< 8.0	
Platelets count	10^9/L	< 75.0	
WBC count	10^9/L	< 2.0	
Neutrophils	10^9/L	< 1.0	
Lymphocytes decrease	10^9/L	< 0.5	
Reticulocyte count	10^9/L		> ULN and > baseline
INR	N/A		>1.5

Note: A post-baseline value must be more extreme than the baseline value to be considered a potentially clinically significant finding.

Table B-3. Criteria for Potentially Clinically Important Vital Sign Values

Vital Sign	Category	Criteria for Potential Clinically Significant Vital Signs	Reference
Systolic blood pressure	Low	Value ≤ 90 mmHg and decrease ≥ 20 mmHg from Baseline	Vaccine Trial Guidance, Grade 1 or above
	High	Value ≥ 160 mmHg and increase ≥ 20 mmHg from Baseline	CTCAE, Grade 3 or above, 2018 ESC/ESH guidelines
Diastolic blood pressure	Low	Value ≤ 50 mmHg and decrease ≥ 10 mmHg from Baseline	
	High	Value ≥ 100 mmHg and increase ≥ 10 mmHg from Baseline	CTCAE, Grade 3 or above, 2018 ESC/ESH guidelines
Pulse	Low	Value < 50 bpm and decrease ≥ 15 bpm from Baseline	Vaccine Trial Guidance, Grade 2 or above
	High	Value ≥ 116 bpm and increase ≥ 15 bpm from Baseline	Vaccine Trial Guidance, Grade 2 or above
Weight	Low	≥ 5% decrease from baseline	CTCAE, Grade 1 or above
	High	≥ 10% increase from baseline	CTCAE, Grade 2 or above
Temperature	High	> 39.0	CTCAE, Grade 2 or above
Oxygen saturation	Low	< 90%	

ESC = European Society of Cardiology; ESH = European Society of Hypertension

Note: A post-baseline value must be more extreme than the baseline value to be considered a potentially clinically significant finding.