Statistical Analysis Plan for Study M19-771

A Phase 2 Study of Galicaftor/Navocaftor/ABBV-119 or Galicaftor/Navocaftor/ABBV-576 in Subjects with Cystic Fibrosis Who Are Homozygous or Heterozygous for the F508del Mutation

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Version 3.0

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for Study M19-771 titled "A Phase 2 Study of Galicaftor/Navocaftor/ABBV-119 or Galicaftor/Navocaftor/ABBV-576 in Subjects with Cystic Fibrosis Who Are Homozygous or Heterozygous for the F508del Mutation."

Study M19-771 examines the safety, tolerability, and efficacy of Galicaftor/Navocaftor/ABBV-119 or Galicaftor/Navocaftor/ABBV-576 combination therapy in adult subjects with Cystic Fibrosis (CF) who are homozygous or heterozygous for the F508del mutation.

The analyses of pharmacokinetic endpoints, biomarker samples 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, Hypotheses and Estimands

The primary objective is to evaluate the safety, tolerability, and efficacy for Galicaftor/Navocaftor/ABBV-119 or Galicaftor/Navocaftor/ABBV-576 combination therapy in adult subjects with CF who are homozygous or heterozygous for the F508del mutation.

The statistical hypothesis for the primary efficacy objective is that the absolute change from Baseline through Day 29 in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) (Cohorts 1 and 2) or sweat chloride (SwCl) (Cohort 3) is statistically significantly greater than zero in subjects treated with Galicaftor/Navocaftor/ABBV-119

(Cohorts 1 and 2) or Galicaftor/Navocaftor/ABBV-576 (Cohorts 3) combination therapies. This hypothesis will be tested for Cohort 1 and Cohort 2, separately, at 1-sided type I error of 5%. For Cohort 3, no hypothesis testing will be performed due to early termination of the trial before the anticipated number of subjects to be enrolled for planned interim analysis.

For Cohorts 1 and 2, the estimand corresponding to the primary efficacy objective is the mean estimate of the absolute change from Baseline through Day 29 in $ppFEV_1$ for subjects with CF who are homozygous (Cohort 1) or heterozygous (Cohort 2) for the F508del mutation and received at least one dose of Galicaftor/Navocaftor/ABBV-119 combination treatment in the per-protocol population (see definition in Section 4.0). Subjects who do not have baseline and at least one post-baseline $ppFEV_1$ value from the triple combination treatment period will be excluded. Additionally, subject's post-baseline $ppFEV_1$ data that are collected with inconsistent bronchodilator or airway clearance status at Baseline or after a subject starts another CFTR modulator therapy will be excluded from the analysis.

For Cohort 3, the estimand corresponding to the primary efficacy objective is the mean estimate of the absolute change from Baseline through Day 29 in SwCl for subjects with CF who are homozygous or heterozygous for the F508del mutation and received at least one dose of Galicaftor/Navocaftor/ABBV-576 (Cohort 3) combination treatment in the per-protocol population (see definition in Section 4.0). Subjects who do not have baseline and at least one post-baseline SwCl value from the triple combination treatment period will be excluded. Subject's post-baseline SwCl data collected after a subject starts another CFTR modulator therapy will be excluded from the analysis.

2.2 Study Design Overview

This Phase 2, proof-of-concept study will enroll subjects with a confirmed clinical diagnosis of CF who carry at least one copy of the F508del mutation. Subjects will be enrolled to one of three cohorts according to their genotype and prior use of CFTR modulator therapy.

Cohort 1 will include adult CF subjects who are homozygous for the F508del mutation and are not receiving elexacaftor/tezacaftor/ivacaftor (ETI) treatment, with a single arm, open-label design. Subjects will receive the Galicaftor/Navocaftor Dual Therapy for 28 days as the run-in period, followed by Galicaftor/Navocaftor/ABBV-119 Triple Therapy for 28 days. For subjects on stable treatment of ivacaftor/tezacaftor (Symkevi), a washout period of five days will occur before the start of the Dual Therapy run-in period. After the Triple Therapy ends, the subjects may resume Symkevi after a washout period of 5 days. Approximately 20 subjects will be enrolled in this cohort.

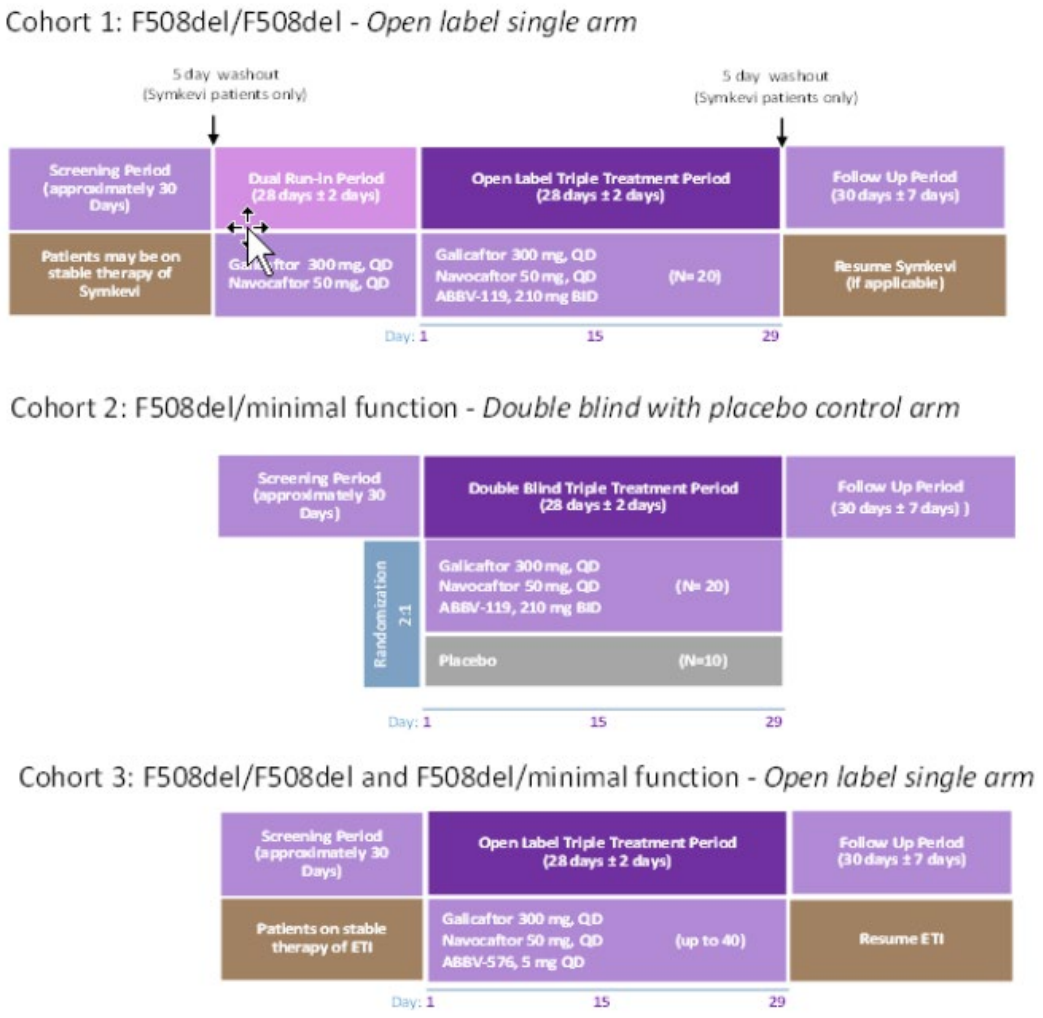
Cohort 2 will include adult CF subjects who are heterozygous for the F508del mutation and a minimal function mutation and are not receiving ETI treatment, with a double-blind, placebo-controlled, parallel-arm design. Subjects will receive Galicaftor/Navocaftor/ABBV-119 Triple Therapy, or placebo treatment for 28 days. For Cohort 2, study sites and subjects will remain blinded for the duration of the study. Approximately 30 subjects will be enrolled in this cohort and will be randomized at a 2:1 treatment to placebo ratio.

Cohort 3 will include adult CF subjects who are homozygous or heterozygous for the F508del mutation and are receiving stable treatment with ETI at the time of screening, with a single-arm, open-label design. Subjects will receive Galicaftor/Navocaftor/ABBV-576 Triple Therapy for 28 days. No washout period is planned before the start of the Triple Therapy to minimize the risk of withdrawal syndromes. Approximately 20 homozygous and up to 20 heterozygous subjects (a total of up to 40 subjects) will be enrolled in this cohort.

For all cohorts, the follow-up period after the last dose of the study drug will be 30 days.

The schematic of the study is shown in Figure 1.

Figure 1. Study Schematic



ETI = elexacaftor/tezacaftor/ivacaftor; QD = once daily

2.3 Treatment Assignment and Blinding

The treatment assignment is defined as below:

Cohort 1: 28 days of galicaftor 300 mg QD + navocaftor 50 mg QD + ABBV-119 210 mg BID preceded by 28 days of galicaftor 300 mg QD + navocaftor 50 mg QD

Cohort 2 (active): 28 days of galicaftor 300 mg QD + navocaftor 50 mg QD + ABBV-119 210 mg BID

Cohort 2 (placebo): 28 days of matching placebo for galicaftor 300 mg QD + navocaftor 50 mg QD + ABBV-119 210 mg BID

Cohort 3: 28 days of galicaftor 300 mg QD + navocaftor 50 mg QD + ABBV-576 5 mg QD

Throughout this document, Galicaftor/Navocaftor combination treatment will be referred to as the Dual Therapy, and Galicaftor/Navocaftor/ABBV-119 or Galicaftor/Navocaftor/ABBV-576 combination treatment as the Triple Therapy.

All subjects will be assigned a unique identification number by the interactive response technology (IRT) vendor at the Screening visit. For subjects who rescreen, the screening number assigned by the IRT at the initial Screening visit should be used. Cohort 1 and Cohort 3 are open-label, single arm design. In Cohort 2, which is a double-blind, placebo-controlled design, the IRT will assign a randomization number to each subject. This randomization number will encode the subject's treatment assignment according to the randomization schedule generated by the statistics department at AbbVie. The randomization in Cohort 2 will also be stratified by ppFEV$_1$ at screening ($< 70\%$ vs $\geq 70\%$).

For Cohort 2, all AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team), as well as the investigator, study site personnel, and the subjects themselves, will remain blinded to each subject's treatment assignment throughout the study.

Also, to minimize the potential for unblinding and/or bias, the AbbVie study team will not have access to the post-first-dose spirometry or SwCl results of Cohort 2 subjects until after the study database is locked for analysis. For all cohorts, site personnel and subjects will not be informed of the subjects' study-related post-first-dose SwCl results until the

end of the cohort. Subjects will not be informed of their study-related spirometry results until the end of the study.

2.4 Sample Size Determination

Sample size and power calculations are based on the primary efficacy endpoint of the within-group absolute change from baseline (Day 1) in $ppFEV_1$ (Cohorts 1 and 2) or in SwCl (Cohort 3) through Study Day 29.

For Cohort 1 (homozygote cohort, not receiving ETI at screening), a sample size of 18 subjects in Galicaftor/Navocaftor/ABBV-119 triple combination treatment will provide > 99% power to detect an estimated 8 to 12% percentage points absolute increase from Galicaftor/Navocaftor dual combination baseline (i.e., measured at the end of the Galicaftor/Navocaftor dual combination treatment run-in period) in $ppFEV_1$ at 1-sided type I error of 0.05, assuming a standard deviation of 7.5%.

For Cohort 2 (heterozygote cohort, not receiving ETI at screening), a sample size of 18 subjects in Galicaftor/Navocaftor/ABBV-119 triple combination treatment will provide > 99% power to detect an estimated 14 to 18% absolute increase from treatment naïve baseline in $ppFEV_1$ at 1-sided type I error of 0.05, assuming a standard deviation of 7.5%.

For Cohort 3 (ETI treated subjects at screening), a sample size of 18 subjects in each genotype subgroup (homozygous, heterozygous) will provide > 85% power to detect an estimated 10 mmol/L absolute decrease from ETI baseline in SwCl with standard deviation of 15 mmol/L at 1-sided type I error of 0.05. With this sample size, it provides > 90% power to detect an estimated 4 percentage points absolute increase from ETI baseline (Day 1) in $ppFEV_1$ at 1-sided type I error of 0.05, assuming a standard deviation of 5%.

The final sample size in all cohorts has been adjusted for a 10% dropout rate. The placebo group in Cohort 2 (n = 10) is mainly for safety assessment, not for formal efficacy comparisons.

3.0 Endpoints

3.1 Primary Endpoint(s)

The primary endpoint is the absolute change from baseline through Day 29 in $ppFEV_1$ for Cohorts 1 and 2, and in SwCl for Cohort 3.

3.2 Secondary Endpoint(s)

The secondary endpoints for Cohorts 1 and 2:

- Absolute change from baseline through Day 29 in SwCl
- Absolute change from baseline through Day 29 in forced vital capacity (FVC)
- Absolute change from baseline through Day 29 in forced expiratory flow at mid-lung capacity (FEF_{25-75})
- Relative changes from baseline through Day 29 in $ppFEV_1$
- Relative changes from baseline through Day 29 in FVC
- Relative changes from baseline through Day 29 in FEF_{25-75}
- Absolute change in CF Questionnaire-Revised (CFQ-R) respiratory domain score from baseline.

The secondary endpoints for Cohort 3:

- Absolute change from baseline through Day 29 in $ppFEV_1$
- Absolute change from baseline through Day 29 in FVC
- Absolute change from baseline through Day 29 in FEF_{25-75}
- Relative changes from baseline through Day 29 in $ppFEV_1$
- Relative changes from baseline through Day 29 in FVC
- Relative changes from baseline through Day 29 in FEF_{25-75}
- Absolute change in CFQ-R respiratory domain score from baseline through Day 29.

3.3 Exploratory Efficacy Endpoints

The additional exploratory endpoint is ppFEV$_1$ change over time monitored via home spirometer.

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 special interest
- Clinical laboratory tests, 12-lead electrocardiogram, vital signs, weight, physical examinations (including neurologic examination), pulse oximetry and spirometry parameters.

3.5 Exploratory Safety Endpoints

Cohort 3 will include mental health outcome measures as exploratory safety endpoints that are monitored via the Hamilton Depression Rating Scale (HDRS) and the 7-item Generalized Anxiety Disorder scale (GAD-7).

3.6 Additional Endpoint(s)

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

4.0 Analysis Populations

Since the database lock and formal analysis may be performed separately for each cohort (Section 9.1), the analysis populations defined below apply to each cohort.

The Full Analysis Set (FAS) includes all enrolled subjects (randomized subjects for Cohort 2) who received at least one dose of the study drug as Dual or Triple Therapy (or

corresponding placebo). The FAS will be used for the analyses of subject disposition, demographics, and baseline characteristics. Subjects will be grouped according to treatment as enrolled (randomized for Cohort 2).

The Per-Protocol (PP) Population includes all enrolled subjects (randomized subjects for Cohort 2) who carry the intended CFTR mutation based on central lab report and received at least one dose of the Triple Therapy or placebo. The primary efficacy endpoint will be analyzed in the PP Population. For Cohorts 1 and 2, subjects who did not have the intended genotype as confirmed by results from central lab will be excluded from the PP Population. For Cohort 3, subjects will be grouped into the intended genotype group based on the central lab test results (or screening visit genotype if central lab test results are not available). If a subject did not receive the intended treatment regimen, the subject will be grouped in the treatment group for which they received on Day 1.

The Safety Analysis Set consists of all enrolled subjects (randomized subjects for Cohort 2) who received at least one dose of study drug (Dual Therapy, Triple Therapy, or placebo). 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 one treatment, the actual treatment group will be determined by the kits dispensed on Day 1.

For analyses and summaries of the Cohort 1 Triple Therapy throughout this document, a subject will be excluded if the subject discontinued during or after the Dual Therapy and never took a dose of the triple therapy.

5.0 Subject Disposition

The number of subjects in each of the following categories will be summarized by investigator and overall, for the following group (according to assignment at randomization/enrollment): Cohort 1 total, Cohort 2 Triple Therapy, Cohort 2 placebo, Cohort 2 total, Cohort 3 homozygous, Cohort 3 heterozygous, Cohort 3 total.

- Subjects who were screened.

- Subjects who were randomized/enrolled.
- Subjects who took at least one dose of the Triple Therapy.
- Subjects who completed the Triple Therapy.
- Subjects who prematurely discontinued the Triple Therapy.
- Subjects who took at least one dose of the Dual Therapy (Cohort 1 only).
- Subjects who completed the Dual Therapy (Cohort 1 only).
- Subjects who prematurely discontinued the Dual Therapy (Cohort 1 only).
- Subjects who completed study.
- Subjects who prematurely discontinued study.
- Subjects in the FAS, PP Population, and Safety Analysis Set.
- Subjects who received treatment other than the randomized treatment.

The number and percentage of subjects, overall and by treatment arm, who prematurely discontinued the Dual Therapy or Triple Therapy will be summarized by each primary reason. Similar summaries will be provided for the premature discontinuation of study participation. The number and percentage of subjects, overall and by treatment arm, who had interruption of the Triple Therapy before discontinuation of study treatment will also be summarized. The denominator of these summaries will be FAS.

The number and percentage of subjects who were not included in the FAS, including subjects who were not randomized/enrolled and/or were screen failures will be summarized for each reason. The denominator of this summary will be all subjects who were not included in the FAS.

The number and percentage of subjects who were not included in the PP Population out of all subjects who received at least one dose of the study drug will be summarized by cohort.

6.0 Study Drug Duration and Compliance

Study drug duration, treatment compliance and temporary interruptions of study drug will be summarized for the Safety Analysis Set by the following group: Cohort 1 Dual

Therapy, Cohort 1 Triple Therapy, Cohort 2 Triple Therapy, and Cohort 2 placebo. For Cohort 3, treatment compliance will not be summarized due to the early termination of the study requested by the sponsor and resulting treatment discontinuation.

Duration of treatment is defined for each subject as last dose date minus first dose date + 1, and temporary interruptions of study drug will not be subtracted from the duration. It will be summarized using 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.

Treatment compliance is defined as the number of capsules actually taken divided by the number of tablets or capsules that should have been taken. It will be summarized using the number of subjects with available treatment compliance, mean, standard deviation, median, minimum and maximum. A listing of the treatment compliance for each subject will also be provided for Cohorts 1 and 2.

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

Demographics, baseline characteristics, medical history, and prior and concomitant medications will be summarized for the FAS Population by the following group: Cohort 1 Dual Therapy, Cohort 1 Triple Therapy, Cohort 2 Triple Therapy, Cohort 2 placebo, Cohort 2 total, Cohort 3 homozygous, Cohort 3 heterozygous, and Cohort 3 total. Demographics and baseline characteristics will also be summarized for the PP Population by the same group.

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

7.1 Demographics and Baseline Characteristics

The following demographic and baseline 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 (Europe, 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 reported at screening (Homozygous, Heterozygous)
- F508del CFTR mutation as determined by central lab genotyping (Homozygous, Heterozygous with eligible minimal function mutations, Heterozygous without eligible minimal function mutations)
- Continuous value of $ppFEV_1$ at screening visit (%)
- Continuous value of $ppFEV_1$ at baseline (%)
- Stratification factor of screening $ppFEV_1$ (< 70%, ≥ 70%)
- Screening $ppFEV_1$ category (< 40%, ≥ 40% to < 70%, ≥ 70% to < 90%, or ≥ 90%; < 70%, or ≥ 70%)
- Baseline $ppFEV_1$ category (< 40%, ≥ 40% to < 70%, ≥ 70% to < 90%, ≥ 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)
- CFQ-R respiratory domain score at baseline
- 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. 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 Handling of Potential Intercurrent Events for the Primary and Key Secondary Endpoints

Cohorts 1 and 2:

The primary efficacy endpoint of $ppFEV_1$ (defined in Section 3.1) will be analyzed using the PP Population and the following methods will be used to address the potential intercurrent events:

- If a subject starts another CFTR modulator therapy, $ppFEV_1$ data for this subject on or after the start date of the new CFTR modulator therapy will be excluded from analyses.
- Post-baseline $ppFEV_1$ data used for efficacy analyses should be consistent with baseline in terms of the timing of the last use of bronchodilator and airway clearance regimen. Otherwise, the data will be excluded from analyses.

The secondary efficacy endpoints related to spirometry evaluation (e.g., relative change in $ppFEV_1$, absolute and relative change in FVC, FEV_{25-75}, defined in Section 3.2) will be analyzed in the PP and the following methods will be used to address the potential intercurrent events:

- If a subject starts another CFTR modulator therapy, efficacy data related to spirometry for this subject on or after the start date of the new CFTR modulator therapy will be excluded from analyses.
- Post-baseline spirometry data used for efficacy analyses should be consistent with baseline in terms of the timing of the last use of bronchodilator and airway clearance regimen. Otherwise, the data will be excluded from analyses.

The secondary efficacy endpoints related to SwCl and CFQ-R (defined in Section 3.2) will be analyzed in the PP and the following methods will be used to address the potential intercurrent events:

- If a subject starts another CFTR modulator therapy, SwCl and CFQ-R for this subject on or after the start date of the new CFTR modulator therapy will be excluded from analyses.

Cohort 3:

The primary efficacy endpoint of SwCl (defined in Section 3.1) will be analyzed in the PP and the following methods will be used to address the potential intercurrent events:

- If a subject starts another CFTR modulator therapy, SwCl data for this subject on or after the start date of the new CFTR modulator therapy will be excluded from analyses.

The secondary efficacy endpoints related to spirometry evaluation (e.g., absolute and relative change in $ppFEV_1$, FVC, FEV_{25-75}, defined in Section 3.2) and CFQ-R will be analyzed in the PP and the following methods will be used to address the potential intercurrent events:

- If a subject starts another CFTR modulator therapy, efficacy data related to spirometry for this subject on or after the start date of the new CFTR modulator therapy will be excluded from analyses.

9.0 Efficacy Analyses

9.1 General Considerations

All efficacy analyses will be conducted in the PP Population separately for all Cohort 1 subjects, all Cohort 2 subjects, and Cohort 3 subjects (homozygous, heterozygous, overall). The Primary Analysis for each cohort will be conducted after all subjects in that cohort have completed the study or prematurely discontinued from the study. If the timing

of the completion of each cohort differs significantly, the database lock and formal analysis may be performed separately for each cohort.

For Cohorts 1 and 2, unless otherwise specified, continuous efficacy variables (SwCl, spirometry data, CFQ-R) will be analyzed using Mixed-Effect Model Repeat Measurement (MMRM) method. Point estimates, 90% confidence intervals (CIs) and 95% CIs of mean change from baseline within each applicable treatment group, as well as applicable comparison of the mean change from baseline between treatment groups will be provided. The observed baseline and visit means will also be summarized for each applicable treatment group among subjects who have both the baseline value and one post-baseline value. All tests for Cohorts 1 and 2 will be 1-sided at an alpha level of 0.05.

Additionally, for Cohorts 1 and 2, post-baseline spirometry values that are inconsistent with the baseline value will be excluded from the efficacy analysis. For example, if the baseline spirometry value was pre-bronchodilator, post-baseline spirometry values must also be pre-bronchodilator.

For Cohort 3, given the early termination of study trial and small number of subjects completed Day 15 and/ or Day 29 treatment, all spirometry data regardless the consistent or inconsistent use of bronchodilator and/or airway clearance regimen will be included in the efficacy summary of visit means and mean change from Day 1/Baseline (pre-dose). In addition, efficacy data (SwCl, spirometry data, CFQ-R) at each visit and change from Day 1/baseline (pre-dose) will only be summarized descriptively (N, mean, median, SD, minimum, maximum). Statistical analyses that were performed for Cohorts 1 and 2 (e.g., MMRM, sensitivity analysis excluding spirometry data with inconsistent use of bronchodilator and/or airway clearance regimen) will not be conducted for Cohort 3 data.

For all cohorts, "Baseline" refers to the last non-missing observation before the first administration of the Triple Therapy. If a subject starts another CFTR modulator treatment during the study period, all efficacy measures for this subject on or after the start date of the new CFTR modulator treatment will be excluded from analyses. Mean plots, spaghetti plots, and/or waterfall plots of $ppFEV_1$ and SwCl will be created for each

treatment group for Cohorts 1 and 2, for each genotype (homozygous, heterozygous) and both genotypes combined for Cohort 3.

9.2 Handling of Missing Data

For Cohorts 1 and 2, 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 based on the assumption of data being missing at random. No other imputation will be used in these cohorts. For Cohort 3, the change in the primary and key secondary endpoints from baseline to Day 29 will be summarized descriptively. No missing data handling technique will be employed in this cohort.

9.3 Primary Efficacy Endpoint(s) and Analyses

9.3.1 Primary Efficacy Endpoint(s)

For Cohorts 1 and 2, 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 calculated for age, gender, and height using the 2012 Global Lungs Initiative equation.[1] $ppFEV_1$ is the ratio of FEV_1 (L) to the predicted FEV_1 (L), expressed as a percentage. The null hypothesis for the primary endpoint is that the within-group absolute change from baseline through Day 29 in $ppFEV_1$ is zero.

For Cohort 3, the primary endpoint is the absolute change from baseline through Day 29 in SwCl.

9.3.2 Main Analysis of Primary Efficacy Endpoint(s)

Cohorts 1 and 2

The primary endpoint of $ppFEV_1$ will be analyzed using a MMRM model with each subject's change in $ppFEV_1$ from baseline through Day 29 as the dependent variable. For all cohorts, the model will include baseline $ppFEV_1$ and visit (Day 15, Day 29) as fixed

effect covariates. For Cohort 2, the model will also include treatment (Triple Therapy or placebo) and the interaction term between treatment and visit. Subject will be treated as the random effect in all models.

For both cohorts, the least squares (LS) estimates for within-group mean change in ppFEV$_1$ from baseline through Day 29 (with point estimate for Day 29) will be presented along with the 90% CIs, 95% CIs and the corresponding p-values for testing the null hypothesis. For Cohort 2, the estimate for the treatment effect (comparison between the Triple Therapy and placebo) will also be presented along with the 95% confidence intervals and the corresponding p-values for testing whether the treatment effect in Cohort 2 is the same between the Triple Therapy and placebo group. For all cohorts, the LS estimate for Day 15 will also be presented.

Cohort 3

The primary endpoint of SwCl at each visit and change from Day 1/baseline will be summarized descriptively (N, mean, median, SD, minimum, maximum) given that this cohort is early terminated, and the treatment discontinued.

The attributes of the estimands corresponding to the primary efficacy endpoint are summarized in Table 1.

Table 1. Summary of the Estimand Attributes of the Primary Efficacy Endpoint(s)

	Attributes of the Estimand				
Estimand Label	**Treatment**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Primary (Cohorts 1 and 2)	Cohort 1: Galicaftor / Navocaftor / ABBV-119 (Triple Therapy) 28 days with prior run-in of Galicaftor / Navocaftor 28 days in homozygous subjects Cohort 2 (active): Triple Therapy 28 days in heterozygous subjects Cohort 2 (placebo): Matching Placebo for the Triple Therapy 28 days in heterozygous subjects	Absolute change from baseline through Day 29 in $ppFEV_1$	PP Population of subjects with CF who are homozygous or heterozygous for the F508del mutation and received at least one dose of the Triple Therapy or placebo.	IE1: A subject's post-baseline corresponding spirometry data collected after the subject starts another CFTR modulator therapy will be excluded from the analyses. IE2: A subject's post-baseline corresponding spirometry data used for efficacy analyses should be consistent with baseline in terms of the timing of the last use of bronchodilator and airway clearance regimen. Otherwise, the data will be excluded from analyses.	Least squares mean estimate of change from baseline through Day 29 in $ppFEV_1$ based on MMRM model
Primary (Cohort 3)	Galicaftor / Navocaftor / ABBV-576 (Triple Therapy) 28 days in homozygous or heterozygous subjects	Absolute change from baseline through Day 29 in SwCl	PP Population of subjects with CF who are homozygous or heterozygous for the F508del mutation and received at least one dose of the Triple Therapy	A subject's post-baseline SwCl data collected after the subject starts another CFTR modulator therapy will be excluded from the analyses.	Mean change from baseline through Day 29 in SwCl

9.3.3 Sensitivity and Supplementary Analyses of the Primary Efficacy Endpoint(s)

Cohorts 1 and 2

Supplementary analysis for the primary endpoint of $ppFEV_1$ will be conducted for each cohort using all spirometry values as collected, even if the timing of bronchodilator or airway clearance regimen of certain post-baseline values were inconsistent with baseline values or if the spirometry values were after the start of other CFTR modulator therapy.

Cohort 3

No additional sensitivity analysis for the primary endpoint of SwCl will be conducted for this cohort.

9.4 Secondary Efficacy Endpoints and Analyses

9.4.1 Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are outlined below.

Cohorts 1 and 2

- Absolute change from baseline through Day 29 in SwCl
- Absolute change from baseline through Day 29 in FVC, FEF_{25-75}
- Relative change, calculated as percent change, from baseline through Day 29 in $ppFEV_1$, FVC, and FEF_{25-75}
- Absolute change in CFQ-R respiratory domain score from baseline through Day 29.

Cohort 3

- Absolute change from baseline through Day 29 in $ppFEV_1$
- Absolute change from baseline through Day 29 in FVC, FEF_{25-75}
- Relative change, calculated as percent change, from baseline through Day 29 in $ppFEV_1$, FVC, and FEF_{25-75}

- Absolute change in CFQ-R respiratory domain score from baseline through Day 29.

9.4.2 Main Analyses of Key Secondary Efficacy Endpoints

Cohorts 1 and 2

For all the key secondary efficacy endpoints, analyses will be performed similarly to the primary endpoint using MMRM models (Section 9.3.2), except that the baseline covariate needs to match the endpoint (baseline FVC, baseline FEF_{25-75}, baseline SwCl, baseline CFQ-R). The summary of results and testing will also be performed similarly.

CFQ-R has a total of 50 questions. Questions 40, 41, 42, 44, 45, 46, scored 1, 2, 3, or 4, from worst to best, will be used to calculate the respiratory domain score. The scaled score for the domain is calculated as 100 × (mean scores of all non-missing questions – 1) / 3, ranging from 0 to 100. If more than 3 questions in the domain have missing scores, the scaled score will be set as missing. Since CFQ-R will not be collected at Day 15 and only change from baseline to Day 29 score will be used for the dependent variable, no subject-level random effect will be included in the model.

Cohort 3

All the key secondary efficacy endpoints will be summarized descriptively (N, mean, median, SD, minimum, maximum) given that this cohort is early terminated, and the treatment is discontinued.

The attributes of the estimands corresponding to the key secondary efficacy endpoints are summarized in Table 2.

Table 2. Summary of the Estimand Attributes of the Key Secondary Efficacy Endpoints

	Attributes of the Estimand				
Estimand Label	**Treatment[a]**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
			Cohorts 1 and 2		
SwCl absolute change	Same as in Table 1	Absolute change from baseline through Day 29 in SwCl.	Same as in Table 1	A subject's post-baseline SwCl data collected after the subject starts another CFTR modulator therapy will be excluded from the analyses.	Least squares mean estimate of change from baseline through Day 29 in SwCl based on MMRM model.
FVC absolute change	Same as in Table 1	Absolute change from baseline through Day 29 in FVC.	Same as in Table 1	Same as in Table 1 (IE1 and IE2).	Least squares mean estimate of change from baseline through Day 29 in FVC based on MMRM model.
FEF_{25-75} absolute change	Same as in Table 1	Absolute change from baseline through Day 29 in FEF_{25-75}	Same as in Table 1	Same as in Table 1 (IE1 and IE2).	Least squares mean estimates of change from baseline through Day 29 in FEF_{25-75} based on MMRM model.
$ppFEV_1$ relative change	Same as in Table 1	Relative change from baseline through Day 29 in $ppFEV_1$	Same as in Table 1	Same as in Table 1 (IE1 and IE2).	Least squares mean estimate of percentage change from baseline through Day 29 in $ppFEV_1$ based on MMRM model.

Table 2. Summary of the Estimand Attributes of the Key Secondary Efficacy Endpoints (Continued)

	Attributes of the Estimand				
Estimand Label	**Treatment[a]**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
			Cohorts 1 and 2 (continued)		
FVC relative change	Same as in Table 1	Relative change from baseline through Day 29 in FVC	Same as in Table 1	Same as in Table 1 (IE1 and IE2).	Least squares mean estimate of percentage change from baseline through Day 29 in FVC based on MMRM model.
FEF_{25-75} relative change	Same as in Table 1	Relative change from baseline through Day 29 in FEF_{25-75}	Same as in Table 1	Same as in Table 1 (IE1 and IE2).	Least squares mean estimate of percentage change from baseline through Day 29 in FEF_{25-75} based on MMRM model.
CFQ-R absolute change	Same as in Table 1	Absolute change from baseline in CFQ-R respiratory domain score	Same as in Table 1	A subject's post-baseline CFQ-R data collected after the subject starts another CFTR modulator therapy will be excluded from the summary.	Least squares mean estimate of change from baseline through Day 29 in CFQ-R based on MMRM model.
			Cohort 3		
$ppFEV_1$ absolute change	Same as in Table 1	Absolute change from baseline through Day 29 in $ppFEV_1$	Same as in Table 1	Same as in Table 1 (IE1).	Mean change from baseline through Day 29 in $ppFEV_1$.

Table 2. Summary of the Estimand Attributes of the Key Secondary Efficacy Endpoints (Continued)

	Attributes of the Estimand				
Estimand Label	**Treatment[a]**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
			Cohort 3 (continued)		
FVC absolute change	Same as in Table 1	Absolute change from baseline through Day 29 in FVC	Same as in Table 1	Same as in Table 1 (IE1).	Mean change from baseline through Day 29 in FVC.
FEF_{25-75} absolute change	Same as in Table 1	Absolute change from baseline through Day 29 in FEF_{25-75}	Same as in Table 1	Same as in Table 1 (IE1)	Mean change from baseline through Day 29 in FEF_{25-75}.
$ppFEV_1$ relative change	Same as in Table 1	Relative change from baseline through Day 29 in $ppFEV_1$	Same as in Table 1	Same as in Table 1 (IE1)	Mean percentage change from baseline through Day 29 in $ppFEV_1$
FVC relative change	Same as in Table 1	Relative change from baseline through Day 29 in FVC	Same as in Table 1	Same as in Table 1 (IE1)	Mean percentage change from baseline through Day 29 in FVC
FEF_{25-75} relative change	Same as in Table 1	Relative change from baseline through Day 29 in FEF_{25-75}	Same as in Table 1	Same as in Table 1 (IE1)	Mean percentage change from baseline through Day 29 in FEF_{25-75}

Table 2. Summary of the Estimand Attributes of the Key Secondary Efficacy Endpoints (Continued)

	Attributes of the Estimand				
Estimand Label	**Treatment[a]**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
			Cohort 3 (continued)		
CFQ-R absolute change	Same as in Table 1	Absolute change from baseline in CFQ-R respiratory domain score	Same as in Table 1	A subject's post-baseline CFQ-R data collected after the subject starts another CFTR modulator therapy will be excluded from the summary.	Mean change from baseline through Day 29 in CFQ-R

a. Treatments:
Cohort 1: Galicaftor / Navocaftor / ABBV-119 28 days with prior run-in of Galicaftor / Navocaftor 28 days in homozygous subjects
Cohort 2 (active): Galicaftor / Navocaftor / ABBV-119 28 days in heterozygous subjects
Cohort 2 (placebo): Matching Placebo for the Triple Therapy 28 days in heterozygous subjects
Cohort 3: Galicaftor / Navocaftor / ABBV-576 28 days in homozygous or heterozygous subjects

9.5 Additional Efficacy Analyses

The efficacy of the Dual Therapy in Cohort 1 subjects will also be analyzed using a MMRM model. Each subject's change in $ppFEV_1$ from the last data point before the first dose of the Dual Therapy through Day 1 of the Triple Therapy will be the dependent variable in the MMRM model. The fixed effect covariates in the model are the last $ppFEV_1$ before the first dose of the Dual Therapy and visit (Day -15, Day 1). Subject will be treated as the random effect. Point estimates for Day -15 and Day 1 will be presented, along with 90% CIs and 95% CIs.

Home spirometry is a different part of spirometry data than the spirometry data used for efficacy analyses. Due to discontinuation of further development of ABBV-119 and early

termination of Cohort 3 that replaced ABBV-119 with ABBV-576, the analyses on home spirometry will not be performed.

9.6 Efficacy Subgroup Analyses

Descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum and maximum) of the primary endpoint will be provided for the following subgroups to evaluate the consistency of the efficacy across subgroup levels.

- Geographic region (Europe, Rest of World)
- Screening ppFEV$_1$ as observed (< 70%, ≥ 70%)

95% CIs of the mean using the normal distribution will be provided for each subgroup level if there are at least 10 subjects in that subgroup. No p-value will be provided for subgroup analysis.

Subgroup analysis will not be conducted for Cohort 3 due to early termination of this cohort.

10.0 Safety Analyses

10.1 General Considerations

Safety data will be summarized for the Safety Analysis Set by the following group: Cohort 1 Dual Therapy, Cohort 1 Triple Therapy, Cohort 2 Triple Therapy, Cohort 2 placebo, Cohort 3 homozygous, Cohort 3 heterozygous, Cohort 3 total.

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.

For Cohort 1, any safety data collected after the first dose of Triple Therapy will be summarized in the group of Cohort 1 Triple Therapy. Data collected after the first dose of Dual Therapy and before the first dose of Triple Therapy will be summarized in the group of Cohort 1 Dual Therapy.

10.2 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.

10.2.1 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. For Cohort 1 Dual Therapy, the study drug refers to Dual Therapy during the run-in period, and the definition of TEAE is further modified to exclude any AE with an onset date that is after the first dose of Triple Therapy. For Cohort 1 Triple Therapy, the study drug refers to Triple Therapy after the run-in period.

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

Pre-treatment AEs will be summarized separately in listing format. The number and percentage subjects experiencing AEs within 5 days before the first dose of the Dual

Therapy for subjects who were on Symkevi in Cohort 1 or within 7 days after the first dose of the Triple Therapy for subjects in Cohort 3 will be summarized by PT. AEs starting more than 30 days following the last dose of study drug will be summarized separately in listing format.

10.2.2 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 10.2.5)
- All deaths

10.2.3 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 grade 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 grade 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 grade/relationship level category of "unknown" even if the subject has another occurrence of the same event with a known grade/relationship. The only exception is if the subject has another occurrence of the same AE with the highest level of grade or a relationship assessment of "Reasonable possibility." In this case, the subject will be counted under the most extreme grade/relationship category.

10.2.4 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.

10.2.5 Adverse Events of Special Interest

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

- Any rash related AESIs (by gender, hormonal contraceptive use in female, maximum grade, and overall)
- Any rash related AESIs related to study drug according to the investigator
- Any rash related AESIs leading to discontinuation of study drug
- Any rash related AESIs leading to interruption of study drug
- Any serious rash related AESIs
- Any serious rash related AESIs related to study drug according to the investigator

The hepatobiliary AESIs will be identified per a Standard MedDRA Query (SMQ) of "Drug-related hepatic disorders – comprehensive search SMQ (narrow)" and be summarized by SOC and PT. The following categories will also be summarized:

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

Tabular listings of AESIs will also be provided.

10.2.6 Other Adverse Events of Interest

Treatment-emergent AEs related to creatine kinase increase will be identified per a Standard MedDRA Query (SMQ) of "rhabdomyolysis/myopathy SMQ (narrow)" as well as the following PTs: myalgia, myositis, blood creatine phosphokinase increased, musculoskeletal pain. The identified AEs will be summarized by SOC and PT and will also be presented in a tabular listing.

For all subject with relative (percent) $ppFEV_1$ decline $\geq$ 10% from the pre-dosing value (see Section 10.5), treatment-emergent respiratory AEs of interest will be identified using the following PTs: chest discomfort, dyspnoea, respiration abnormal, asthma, bronchial hyperreactivity, bronchospasm, wheezing. The identified AEs will be presented in a tabular listing.

10.3 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. For

Cohort 1 Dual Therapy, the study drug refers to Dual Therapy during the run-in period. For Cohort 1 Triple Therapy, the study drug refers to Triple Therapy after the run-in period. Baseline will be defined relative to the first dose of study drug accordingly. 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.

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 or later version) 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 with a laboratory value meeting the criteria during treatment will be summarized. Listings will be provided for summarizing 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
- ALT and/or AST > 3 × ULN, > 5 × ULN, > 8 × ULN
- Total bilirubin (TBL) > ULN and ≤ 1.5 × ULN, > 1.5 × ULN and ≤ 2 × ULN, > 2 × ULN
- Direct bilirubin > ULN and ≤ 1.5 × ULN, > 1.5 × ULN
- Indirect bilirubin > ULN and ≤ 1.5 × ULN, > 1.5 × ULN and ≤ 2 × ULN, > 2 × ULN and ≤ 3 × ULN, > 3 × 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, TBL, and alkaline phosphatase values will be provided for each subject who met one or more of the criteria defined above.

For Cohorts 1 and 2, additional plots of Drug Induced Serious Hepatotoxicity, descriptive statistics for the time to ALT/AST elevation, and listings for subjects with increased creatine kinase outlined below will be provided.

An Evaluation of Drug Induced Serious Hepatotoxicity (eDISH) plot displaying the maximum on-treatment values of TBL (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 TBL vs. AST.

Descriptive statistics for the time to ALT/AST elevation (> 5 × ULN) as well as the duration of ALT/AST elevation will be summarized.

Listing of creatine kinase and creatinine values for subjects with increased creatine kinase or related treatment-emergent adverse events (Section 10.2.6) will be provided.

10.4 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 with 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.

10.5 Other Safety Analyses

Pulse Oximetry

For oxygen saturation values by pulse oximetry, 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.

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 for Day -28, Day -15, Day 1 and Day 15 (Day -28 and Day -15 only apply to Cohort 1 Dual Therapy). 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 for all applicable visits will be summarized.

ECG

ECG findings will be summarized for Screening, Day -15, Day 1, Day 15 and Day 29 (Day -15 and Day 1 only apply to Cohort 1 Dual Therapy). Summaries will include n (%) of patients in following categories:

- Normal
- Abnormal - Not Clinically Significant
- Abnormal - Clinically Significant
- Not evaluable
- Missing

11.0 Interim Analyses

Cohort 1: One interim analysis is planned for Cohort 1, which will take place when 10 subjects in Cohort 1 have completed or prematurely discontinued the open-label Triple Therapy. The scope of the interim analysis will include the efficacy and safety assessment of the Dual Therapy and Triple Therapy of the first 10 subjects in Cohort 1. No statistical testing will be made for the interim analysis, and no type I error adjustment will be made for the final analysis. The primary purpose of this interim analysis is to support AbbVie internal decision making for the development program.

Cohort 2: No planned interim analysis.

Cohort 3: Cohort 3 is modified to replace ABBV-119 with ABBV-576, a structurally differentiated modulator with improved safety and pharmacokinetic profiles. Interim analyses for Cohort 3 may be performed when approximately 10 and/or 15 homozygous

subjects in Cohort 3 have either completed the triple combination treatment period or prematurely discontinued study drug treatment to inform AbbVie internal program development decision. No statistical testing will be made for the interim analysis, and no type I error adjustment will be made for the final analysis.

Since both Cohorts 1 and 3 are open-label, unblinding is not applicable for these interim analyses. Cohort 1 interim analysis was performed by the internal study team and reviewed by the sponsor, which led to the discontinuation of Cohort 1 and Cohort 2. For Cohort 3, the interim monitoring of the efficacy and safety data of enrolled subjects led to the decision of early termination. Therefore, the planned interim analyses for Cohort 3 will not be performed. Instead, summary information on subjects' disposition, study safety and efficacy, will be provided when all enrolled subjects completed/discontinued study treatment.

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 study results from the Phase 1 studies for ABBV-119 (e.g., single and multiple ascending dose portions of Study M19-775, drug-drug interaction Study M20-065) before the start of Study M19-771 and will provide a recommendation on the start of Study M19-771. DMC recommendation, including the DMC approved final dose and dosing regimen for ABBV-119 will be documented in DMC meeting minutes as described in a separate DMC charter.

The DMC will also review the safety and PK data from co-administered galicaftor, navocaftor, and ABBV-576 Phase 1 studies (M21-054 and Study M20-974) before the start of Cohort 3 and provide a recommendation on the start of Cohort 3. DMC recommendation, including the DMC final approval of the start of Cohort 3 will be documented in DMC meeting minutes as described in a separate DMC charter. The DMC will also periodically review the accumulating unblinded safety data for the study, as well as monitor the integrity and interpretability of the study. The DMC will provide

recommendations to the sponsor regarding ongoing study conduct or modifications to the study as described in the DMC Charter.

The DMC charter will describe the roles and responsibilities of the DMC members, frequency and scope of the data reviews, and expectations for blinded communications. In addition, the detailed data analysis and specifications for the DMC reviews are included in a separate DMC TFL specifications document.

In order to maintain sponsor blinding, an independent statistical data analysis center (SDAC) is responsible for performing the analyses described in the DMC charter as well as additional analyses requested by the DMC and facilitating interpretation and answering questions that arise before, during or after DMC review.

12.0 Overall Type-I Error Control

Multiplicity adjustment for Type I error rate is not planned for this proof-of-concept study. The primary endpoint will be analyzed and tested independently for each cohort at 1-sided alpha level of 0.05 for Cohorts 1 and 2. No statistical testing will be performed for Cohort 3 due to cohort early termination and the fact that only a very few subjects completed the planned primary efficacy evaluation visit. Since there are no efficacy analyses for early stopping planned for the DMC review, no alpha spending is needed due to the DMC review.

13.0 Version History

Table 3. SAP Version History Summary

Version	Date	Summary
1.0	08 Sep 2021	Original version
2.0	10 Nov 2021	1. Added waterfall plots to Section 9.1 2. Added additional summaries for rash AESI to Section 10.2.5 3. Added Section 10.2.6 Other Adverse Events of Interest 4. Added additional summaries for ALT/AST, total bilirubin, direct bilirubin, indirect bilirubin, and listing for creatine kinase and creatinine to Section 10.3 5. Added the interim analysis to Section 11.0 6. Added additional thresholds for creatine kinase (CPK) to Appendix B
3.0	31 May 2023	Changes were made mainly due to the update of protocol amendment V6.0 and V7.0, which modified Cohort 3 by replacing ABBV-119 with ABBV-576 in the triple therapy, and the resulted relevant changes. 1. Cohort 3 was modified, replacing the triple therapy Galicaftor/Navocaftor/ABBV-**119** with Galicaftor/Navocaftor/ABBV-**576** 2. Figure 1 (study schematic) was updated to reflect the changes made to Cohort 3. 3. Section 2.4 (sample size determination) was updated to incorporate the modifications made to Cohort 3. 4. Section 3.0 (Endpoints) included the revisions for Cohort 3: o The primary endpoint was changed from $ppFEV_1$ to SwCl. o The secondary endpoint was changed from SwCl to $ppFEV_1$ o HDRS and GAD-7 exploratory safety endpoints related to mental health (depression, anxiety) were added. 5. Section 8.0 (handling of potential intercurrent events for the primary and secondary efficacy endpoints) was updated for Cohort 3. 6. Section 9.3 (primary efficacy endpoints and analyses) was updated for Cohort 3. Estimands summary of the efficacy endpoints in Table 1 and Table 2 relevant to Cohort 3 were updated. 7. An interim analysis for Cohort 3 was added in Section 11.0. 8. Section 11.1 (Data Monitoring Committee) included a mention of the DMC's review of ABBV-576 Phase 1 safety data and provided a recommendation on the start of Cohort 3 before initiating Cohort 3 enrollment.

14.0 References

1. Quanjer PH, Stanojevic S, Cole TJ. Multi-ethnic reference values for spirometry for the 3 - 95 year age range: the global lung function 2012 equations. 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 Important 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 Important Hematology Values

Hematology Variables	Units	Definition of Potentially Clinically Significant	
		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/Erythrocytes	%	< LLN and < baseline	> 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-2. Criteria for Potentially Clinically Important Chemistry Values

Chemistry Variables	Units	Definition of Potentially Clinically Significant	
		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		> ULN and ≤ 2.5 × ULN > 2.5 × ULN and ≤ 5 × ULN > 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-3. Criteria for Potentially Clinically Important Vital Sign Values

Vital Sign	Category	Criteria for Potential Clinically Significant Vital Signs
Systolic blood pressure	Low	Value ≤ 90 mmHg and decrease ≥ 20 mmHg from baseline
	High	Value ≥ 160 mmHg and increase ≥ 20 mmHg from baseline
Diastolic blood pressure	Low	Value ≤ 50 mmHg and decrease ≥ 10 mmHg from baseline
	High	Value ≥ 100 mmHg and increase ≥ 10 mmHg from baseline
Pulse	Low	Value < 50 bpm and decrease ≥ 15 bpm from baseline
	High	Value ≥ 116 bpm and increase ≥ 15 bpm from baseline
Weight	Low	≥ 5% decrease from baseline
	High	≥ 10% increase from baseline
Temperature	High	> 39.0
Oxygen saturation	Low	< 90%

ESC = European Society or 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.