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# Protocol for Study M19-771

## Indication: 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: | 7.0 | DATE: | 26 August 2022 |
| SPONSOR: | AbbVie | PLANNED NUMBER OF SITES: | 35 |
| ABBVIE INVESTIGATIONAL PRODUCT: | Galicaftor/Navocaftor/ ABBV-119/ABBV-576 | EudraCT: | 2020-005805-25 |

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

Incorporating Versions 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0 and Administrative Change 1

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# 1 SYNOPSIS

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| **Background and Rationale:** | Cystic fibrosis (CF) is caused by mutations in the gene that encodes for the CF transmembrane conductance regulator (CFTR) protein, a cyclic adenosine monophosphate (cAMP)-regulated anion channel expressed primarily at the apical plasma membrane of secretory epithelia. The F508del mutation is the most common mutation globally, which is present on at least one allele in more than 80% of CF patients.<br>The F508del mutation causes significantly reduced expression and function of the CFTR protein in various tissues (e.g., lung, pancreas), which leads to CF disease manifestations. CFTR modulators are compounds designed to increase the cell surface expression and restore the function of CFTR. In the cultivated human bronchial epithelial cells (HBEs) from F508del/F508del homozygous patients, the combinations of galicaftor/navocaftor/ABBV-119 and galicaftor/navocaftor/ABBV-576 showed more significant restoration of F508del *CFTR* expression and function than the combination of galicaftor and navocaftor. This study is designed to evaluate the safety, tolerability, target engagement, and efficacy for galicaftor/navocaftor/ABBV-119 and galicaftor/navocaftor/ABBV-576 combination therapies in adult subjects with CF who are homozygous or heterozygous for the F508del mutation. |
| **Objective and Endpoints:** | **Objective:**<br>Evaluate the safety, tolerability, target engagement, and efficacy for galicaftor/navocaftor/ABBV-119 (Cohorts 1 and 2) and galicaftor/navocaftor/ABBV-576 (Cohort 3) combination therapies in adult subjects with CF who are homozygous or heterozygous for the F508del mutation in each cohort.<br>**Endpoints (Cohort 1 and 2):**<br>Primary<br>1. Absolute change from Baseline through Day 29 in percent predicted forced expiratory volume in 1 second ($ppFEV_1$)<br>Secondary<br>1. Absolute change from Baseline through Day 29 in sweat chloride (SwCl)<br>2. Absolute change from Baseline through Day 29 in other spirometric measures (forced vital capacity [FVC], forced expiratory flow at mid-lung capacity [$FEF_{25-75}$])<br>3. Relative changes from Baseline through Day 29 in $ppFEV_1$, FVC, and $FEF_{25-75}$<br>4. Absolute change in CF Questionnaire-Revised (CFQ-R) respiratory domain score from Baseline through Day 2**Endpoints (Cohort 3):** |

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| | Cohort 1 and Cohort 2 have been terminated based on the efficacy results of an interim analysis. Cohort 3 is modified to replace ABBV-119 with ABBV-576:<br>Primary<br>1. Absolute change from Baseline through Day 29 in sweat chloride (SwCl)<br>Secondary<br>1. Absolute change from Baseline through Day 29 in ppFEV$_1$<br>2. Absolute change from Baseline through Day 29 in other spirometric measures (FVC, FEF$_{25-75}$)<br>3. Relative changes from Baseline through Day 29 in ppFEV$_1$, FVC, and FEF$_{25-75}$<br>4. Absolute change in CFQ-R respiratory domain score from Baseline through Day 29 |
| **Investigator(s):** | Multicenter |
| **Study Sites:** | Approximately 35 sites in multiple countries, which may include, but not limited to, United States, United Kingdom, Germany, Netherlands, Australia, Belgium, Hungary, New Zealand, and Slovakia |
| **Study Population and Number of Subjects to be Enrolled:** | Approximately 20 subjects with a confirmed clinical diagnosis of CF, genotype homozygous for the F508del *CFTR* mutation, and not receiving elexacaftor/tezacaftor/ivacaftor (ETI) treatment in Cohort 1; approximately 30 subjects with a confirmed clinical diagnosis of CF, genotype heterozygous for F508del *CFTR* mutation and a minimal function mutation, and not receiving ETI treatment in Cohort 2. Up to 40 subjects with a confirmed clinical diagnosis of CF, genotype homozygous or heterozygous for the F508del CFTR mutation, and on stable treatment of ETI in open-label Cohort 3.<br>Cohort 1 and Cohort 2 have been terminated based on the efficacy results of an interim analysis. Cohort 3 is modified to replace ABBV-119 with ABBV-576, a structurally differentiated modulator with improved safety and pharmacokinetic profiles. |
| **Investigational Plan:** | Cohort 1: F508del homozygous CF subjects (approximately n = 20) started with the galicaftor/navocaftor dual combination therapy run-in period (28 days), then followed by galicaftor/navocaftor/ABBV-119 triple combination therapy treatment period (28 days). Subjects on stable treatment of other CFTR modulator therapy (e.g., Symkevi) will go through 2 brief washout periods of 5 days to allow for elimination of the previous modulator drugs. The first washout period will occur before the start of the dual combination run-in period, and the second washout period will occur after the triple combination treatment period. These subjects can resume their stable modulator treatment after the second washout period.<br>Cohort 2: F508del/minimal function CF subjects (approximately n = 30) was randomized to 2 parallel treatment arms at a 2:1 treatment to placebo ratio. Subjects received the galicaftor/navocaftor/ABBV-119 triple combination therapy or placebo for 28 days. |

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| | Cohort 3: F508del homozygous (approximately n = 20) and F508del/minimal function CF subjects (up to n = 20) who are receiving stable treatment of ETI will receive the galicaftor/navocaftor/ABBV-576 triple combination therapy for 28 days. These subjects can resume their stable ETI treatment after the treatment period. |
| **Key Eligibility Criteria:** | Males and females 18 years or older with a confirmed clinical diagnosis of CF, and genotype homozygous for the F508del *CFTR* mutation for Cohort 1, genotype heterozygous for the F508del *CFTR* mutation and a minimal function for Cohort 2, or either homozygous or heterozygous for the F508del mutation for Cohort 3. Subjects must be receiving stable ETI treatment for Cohort 3. For all cohorts: $ppFEV_1 \geq 40\%$ and $\leq 90\%$ of predicted normal for age, gender and height at Screening. Sweat chloride (SwCl) must be ≥ 60 mmol/L at Screening for Cohort 1 and Cohort 2; this criterion does not apply to Cohort 3. Weight must be ≥ 35 kg at Screening and Day -28 for Cohort 1 or Day 1 for Cohort 2 and Cohort 3. |
| **Study Drug and Duration of Treatment:** | For Cohort 1 and Cohort 2, galicaftor, navocaftor, and ABBV-119 will be evaluated at fixed doses of 300 mg QD, 50 mg QD and 210 mg BID, respectively; final analysis of these cohorts has not been completed. For Cohort 3, galicaftor, navocaftor, and ABBV-576 will be evaluated at fixed doses of 300 mg QD, 50 mg QD and 5 mg QD, respectively.<br>The total duration of a subject's participation in each part of this study (including all periods) is up to approximately 4 months for Cohort 1, and 3 months for Cohort 2 and Cohort 3. |
| **Date of Protocol Synopsis:** | 26 August 2022 |

# 2 INTRODUCTION

## 2.1 Background and Rationale

### Why Is This Study Being Conducted

Cystic fibrosis (CF) is caused by mutations in the gene that encodes for the CF transmembrane conductance regulator (CFTR) protein, a cyclic adenosine monophosphate (cAMP)-regulated anion channel expressed primarily at the apical plasma membrane of secretory epithelia. The F508del mutation is the most common mutation globally, which is present on at least one allele in more than 80% of CF patients. The F508del mutation causes significantly reduced expression and function of the CFTR protein in various tissues (e.g., lung, pancreas), which leads to CF disease manifestations.

CFTR modulators are compounds designed to increase the cell surface expression and restore the function of CFTR. Triple combination therapy of CFTR modulators (i.e., elexacaftor/tezacaftor/ivacaftor, or ETI) has been recently approved and marketed as Trikafta® or Kaftrio® to treat CF patients harboring at least one F508del mutation. Although ETI demonstrated significant improvement in lung function in clinical studies, there is still a need for the development of treatment options for CF patients. Therefore, additional CFTR modulators have been investigated as combination therapy to restore F508del *CFTR* expression and function, including galicaftor (ABBV-2222), navocaftor (ABBV-3067), and ABBV-119 or ABBV-576.

In the cultivated human bronchial epithelial cells (HBEs) from F508del/F508del homozygous patients, the triple combinations of galicaftor/navocaftor/ABBV-119 and galicaftor/navocaftor/ABBV-576 showed more significant restoration of F508del *CFTR* expression and function than the combination of galicaftor and navocaftor. This study is designed to evaluate the safety, tolerability, target engagement, and efficacy for galicaftor/navocaftor/ABBV-119 and galicaftor/navocaftor/ABBV-576 combination therapies in adult subjects with CF who are homozygous or heterozygous for the F508del mutation.

## 2.2 Benefits and Risks to Subjects

### Benefits

Galicaftor has been evaluated as either single-agent therapy (GLPG2222-CL-202) or part of combination therapy (GLPG2737-CL-105) in subjects with CF who are homozygous for the F508del mutation. The completed Phase 2 study (GLPG2222-CL-202) showed that 4-week treatment of galicaftor significantly reduced sweat chloride (SwCl) in CF subjects. The completed Phase 1 study (GLPG2737-CL-105) also showed that the dual combination of galicaftor and GLPG2451 (another potentiator with a similar mechanism of action as navocaftor) further reduced SwCl and increased $ppFEV_1$ in CF subjects. In the cultivated human bronchial epithelial cells (HBEs) from F508del/F508del homozygous patients, the triple combinations of galicaftor/navocaftor/ABBV-119 and galicaftor/navocaftor/ABBV-576 showed more significant restoration of F508del *CFTR* expression and function than the dual combination of galicaftor and navocaftor. Therefore, it is anticipated that the triple combination of galicaftor/navocaftor/ABBV-119 or galicaftor/navocaftor/ABBV-576 has the potential to improve F508del *CFTR* function in patients with CF who carry at least one copy of the mutation, as well as their lung function measured by $ppFEV_1$.

An interim analysis for Cohort 1 of the study was conducted after 15 subjects in Cohort 1 had completed the galicaftor/navocaftor/ABBV-119 triple combination treatment or prematurely discontinued study drug treatment (Section 7.7). The galicaftor/navocaftor dual combination treatment was safe and well tolerated and resulted in a mean decrease in SwCl concentration (-14.2 mmol/L) from baseline at the end of 28-day run-in period. The addition of ABBV-119 in the following triple combination treatment period was also well tolerated but did not result in further decrease in SwCl concentration. Therefore, Cohort 1 and Cohort 2 of the study were terminated based on the efficacy results following the interim analysis, and the design of Cohort 3 is modified to replace ABBV-119 with ABBV-576, a structurally differentiated modulator with improved safety and pharmacokinetic profiles that is hypothesized to deliver the therapeutic benefit of the triple combination therapy.

### Risks

ABBV-119 was being characterized in two healthy-volunteer Phase 1 studies, M19-775 and M20-065, when the M19-771 study was initiated in 2021. Based on preliminary pharmacokinetics (PK) and safety data from the single ascending dose (SAD) and multiple ascending dose (MAD) portions of the ongoing Study M19-775, a dose of 210 mg BID was selected for ABBV-119 in Study M19-771. An independent data monitoring committee (DMC, see Section 5.10) reviewed the complete safety and PK data from the Phase 1 study prior to initiation of Study M19-771, and confirmed that it was safe to proceed with the planned 210 mg BID dose for ABBV-119.

ABBV-576 is currently being characterized in a Phase 1 study (Study M21-054, in healthy volunteers). Based on preliminary PK and safety data from the SAD and MAD portions of the ongoing Study M21-054, a dose of 5 mg QD has been selected for ABBV-576 in Study M19-771. An independent DMC (see Section 5.10) will review the safety and PK data from ABBV-576 Phase 1 studies prior to the initiation of Cohort 3 and confirm that it is safe to proceed with the planned 5 mg QD dose for ABBV-576.

The safety results from the completed and ongoing Phase 1 studies demonstrated that ABBV-119, ABBV-576, galicaftor, and navocaftor were generally well tolerated in healthy volunteers, either as single agents or combination regimen. The following paragraphs describe the main safety issues that are potentially associated with repeated doses of the combination of ABBV-119, ABBV-576, galicaftor, and navocaftor.

### Rash

Nonserious events of generalized rash of mild to moderate severity leading to study drug discontinuation have been observed following multiple dose treatment when galicaftor and navocaftor were co-administered with and without other CFTR modulators (such as ABBV-119). Rash was considered possibly related to study drug by the investigator and resolved after treatment discontinuation.

There were also reports of mild rash occurring among subjects who received galicaftor or navocaftor given as monotherapy, but none led to study drug discontinuation.

As a result of these rash occurrences, enhanced safety monitoring and specific guidance to the investigator is described in the Operations Manual (Appendix H). Rash is considered an adverse event of special interest (AESI) (see Section 6.1).

### Hepatobiliary Events

Elevated liver function tests (LFTs) are adverse reactions associated with marketed products with a similar mechanism of action. In the MAD part of the navocaftor first-in-human (FIH) study (GLPG3067-CL-101), one healthy volunteer who received navocaftor at the highest dose 500 mg BID temporarily interrupted treatment for a total of 2 doses because of alanine transaminase (ALT) elevation ~3.8 × upper limit of normal (ULN) without concurrent bilirubin elevation.

In the Phase 1 and 2 studies for ABBV-119, 3 asymptomatic healthy volunteers (2 subjects in M20-065; 1 subject in M19-775) and 1 CF subject in Cohort 1 of M19-771 experienced ALT elevations (peak value ~4.8 - 8 × ULN) associated with milder increases in aspartate aminotransferase (AST) and gamma glutamyl transferase (GGT) with no concurrent rise in bilirubin.[1] LFT elevations were observed 14-19 days after multiple dosing with ABBV-119 (300 mg BID or 210 mg BID) given alone or in combination with galicaftor and navocaftor. The events led to drug discontinuation in 2 subjects. Transaminases levels returned to normal in the follow-up period. No severe or life-threatening outcomes have been reported.

As a result of the hepatobiliary events, enhanced safety monitoring and specific guidance to the investigator is described in Section 6.1. Hepatobiliary events are considered an AESI. A Day 21 visit was added to Cohorts 1 and 2 (Appendix D) for clinical laboratory testing and monitoring for hepatobiliary adverse events (AEs).

Taken together, the safety and efficacy data from the Phase 1 and Phase 2 programs and the specific risk management activities to address the potential risks support further development of ABBV-576, galicaftor, and navocaftor in Phase 2 studies in subjects with CF, with the DMC review and monitoring plan (Section 5.10) in place to safeguard the study subjects.

### Potential Risks based on Nonclinical Data

There is a potential risk of testicular toxicity based on adverse testicular changes that have been observed in dogs following navocaftor administration with a no-observed effect level (NOEL) at 3-fold of the observed exposure at the anticipated clinical dose (50 mg once daily [QD]). The findings were reversible after a 13-week treatment-free period. The triple combination toxicology studies with galicaftor/navocaftor/ABBV-119 resulted in new findings in the epididymis (adverse sperm granuloma) that were not reversible after a 4-week treatment-free period. The findings and associated risks have been described in the Informed Consent. Contraceptive guidance for males has been specified in Section 5.2. To participate in the study, males must not be planning to father a child or donate sperm during the study and for 90 days after the last dose of study drug. In the triple combination toxicology studies with galicaftor/navocaftor/ABBV-576, non-adverse gallbladder epithelial vacuolation occurred in the dog at doses of 300/10/3 mg/kg (galicaftor/navocaftor/ABBV-576) for 4 weeks. A similar gallbladder effect was previously observed in dogs administered ABBV-576 for 4 weeks at 100 mg/kg (current ABBV-576[2] IB, Repeat-Dose Toxicity). These changes were low grade and without correlating effects indicative of cellular or tissue injury.

No phototoxicity assessments have been conducted for ABBV-119 or ABBV-576 and the risk for phototoxicity is unknown. Study subjects must comply with requirements to limit sun exposure and avoid UV beds and to use sun and UV-light protection (i.e., use of broad-spectrum sunscreen ≥ SPF30,

protective clothing, hats and/or sunglasses) if there will be exposure to sunlight while participating in this study.

For further details, please see findings from completed studies, including safety data in the current galicaftor[3], navocaftor[4], ABBV-119[5], and ABBV-576[2] Investigator's Brochures (IBs).

### COVID-19 Pandemic-Associated Risks

Considering the coronavirus (COVID-19) pandemic, the benefit and risk to subjects participating in this study has been re-evaluated. The marketed CFTR modulator combination therapy ETI has been shown to improve pulmonary function[1,6] and reduce sputum pathogen density in patients with CF.[7] Since the combination of galicaftor/navocaftor/ABBV-119 or galicaftor/navocaftor/ABBV-576 is anticipated to have an analogous biological effect, participation in this study is not expected to increase COVID-19-associated risk among study participants.

# 3 OBJECTIVES AND ENDPOINTS

## 3.1 Objectives, Hypotheses, and Estimands

### Primary

The primary objective is to evaluate the safety, tolerability, target engagement, and efficacy for galicaftor/navocaftor/ABBV-119 and galicaftor/navocaftor/ABBV-576 combination therapies in adult subjects with CF who are homozygous or heterozygous for the F508del mutation in each cohort.

### Clinical Hypotheses

1. Galicaftor/navocaftor/ABBV-119 and galicaftor/navocaftor/ABBV-576 combination therapies are safe and well-tolerated in adults with CF.
2. Galicaftor/navocaftor/ABBV-119 combination therapy will result in significant improvement from baseline pharmacodynamic markers of CFTR function (lung function and SwCl) in CF subjects who are homozygous or heterozygous for the F508del mutation, and not receiving ETI therapy.
3. Galicaftor/navocaftor/ABBV-119 and galicaftor/navocaftor/ABBV-576 combination therapies will be able to maintain and/or improve CFTR function (lung function and SwCl) in CF subjects who have been receiving ETI therapy.

Baseline for efficacy endpoints in this protocol refers to the last non-missing observations before the first dose of galicaftor/navocaftor/ABBV-119 or galicaftor/navocaftor/ABBV-576 triple combination therapies on Study Day 1.

The statistical hypothesis for the primary efficacy objective is that the absolute change from Baseline through Day 29 in ppFEV$_1$ (Cohorts 1 and 2) or 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 (Cohort 3) combination therapies. This hypothesis will be tested

separately for each cohort and for the homozygous and heterozygous CF subjects at 1-sided type I error of 5%.

The estimand corresponding to the primary efficacy objective is the mean estimate of the absolute change from Baseline through Day 29 in $ppFEV_1$ (Cohorts 1 and 2) or SwCI (Cohort 3) for subjects with CF who are homozygous (Cohorts 1 and 3) or heterozygous (Cohorts 2 and 3) for the F508del mutation and received at least one dose of galicaftor/navocaftor/ABBV-119 or galicaftor/navocaftor/ABBV-576 combination treatment. Subjects who do not have both Baseline and at least one post-baseline $ppFEV_1$ or SwCl value from the triple combination treatment period will be excluded. 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.

## 3.2 Primary Endpoint

Cohorts 1 and 2: Absolute change from Baseline through Day 29 in percent predicted forced expiratory volume in 1 second ($ppFEV_1$).

Cohort 3: Absolute change from Baseline through Day 29 in SwCl.

## 3.3 Secondary Endpoints

Cohorts 1 and 2:

1. Absolute change from Baseline through Day 29 in SwCl
2. Absolute change from Baseline through Day 29 in forced vital capacity [FVC]
3. Absolute change from Baseline through Day 29 in forced expiratory flow at mid-lung capacity [$FEF_{25-75}$]
4. Relative changes from Baseline through Day 29 in $ppFEV_1$
5. Relative changes from Baseline through Day 29 in FVC
6. Relative changes from Baseline through Day 29 in $FEF_{25-75}$
7. Absolute change in CF Questionnaire-Revised (CFQ-R) respiratory domain score from Baseline through Day 29

Cohort 3:

8. Absolute change from Baseline through Day 29 in $ppFEV_1$
9. Absolute change from Baseline through Day 29 in FVC
10. Absolute change from Baseline through Day 29 in $FEF_{25-75}$
11. Relative changes from Baseline through Day 29 in $ppFEV_1$
12. Relative changes from Baseline through Day 29 in FVC
13. Relative changes from Baseline through Day 29 in $FEF_{25-75}$

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

## 3.4 Exploratory Efficacy Endpoint

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

## 3.5 Safety Endpoints

Safety evaluations are AE monitoring, AESIs, weight, physical examinations (including neurologic examination for Cohorts 1 and 2 only), vital sign measurements, electrocardiogram (ECG) variables, clinical laboratory testing (hematology, chemistry, and urinalysis), pulse oximetry, and spirometry as measures of safety and tolerability for the entire study duration.

## 3.6 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).

## 3.7 Pharmacokinetic Endpoints

Plasma galicaftor, navocaftor, and ABBV-119 or ABBV-576 concentrations will be obtained at the visits indicated in Appendix D. A nonlinear mixed effects modeling approach will be used to estimate the population central values and the empirical Bayesian estimates of the individual values of galicaftor, navocaftor, and ABBV-119 or ABBV-576 oral clearance (CL/F) and volume of distribution (V/F). Additional parameters may be estimated if useful in the interpretation of the data.

## 3.8 Biomarker Research Endpoints

Optional samples (whole blood) will be collected at specific time points as described in the Activity Schedule (Appendix D) to evaluate known and/or novel disease-related or drug-related biomarkers. Types of biomarkers may include nucleic acids, proteins, lipids, and/or metabolites. The objective of this research is to analyze samples for biomarkers that will help to understand CF, related conditions, and the subject's response to galicaftor/navocaftor/ABBV-119 or galicaftor/navocaftor/ABBV-576 combination therapies. Genes of interest may include those associated with PK (drug metabolizing enzymes, drug transport proteins), genes within the target pathway, or genes related to CF (e.g., *CFTR*). This research is exploratory in nature and the results may not be included with the clinical study report.

# 4 INVESTIGATIONAL PLAN

## 4.1 Overall Study Design and Plan

This is a multicenter, multi-country, Phase 2, three parallel-cohort study of galicaftor, navocaftor, and ABBV-119 or ABBV-576 combination therapy for 28 days in adult CF subjects who are homozygous or heterozygous for the F508del mutation, including subjects already on stable CFTR modulator therapy. This study is designed as a proof-of-concept study to evaluate the safety, tolerability, target engagement, and efficacy for galicaftor/navocaftor/ABBV-119 and galicaftor/navocaftor/ABBV-576 combination therapies administered at fixed doses.

This study will enroll subjects with a confirmed clinical diagnosis of CF who carry at least one copy of the F508del mutation. In Cohort 2, randomization will be stratified by ppFEV$_1$ at Screening (< 70% versus [vs.] ≥ 70%). See Section 5.1 for detailed information regarding eligibility criteria.

Cohort 1 included adult CF subjects who are homozygous for the F508del mutation and are not receiving ETI treatment, with a single arm, open-label design. Approximately 20 subjects were enrolled in this cohort. Subjects received the galicaftor/navocaftor dual combination therapy for 28 days as the run-in period, followed by galicaftor/navocaftor/ABBV-119 triple combination therapy for 28 days. Differences in endpoint values between the dual combination run-in period and the triple combination treatment period will demonstrate the contribution of ABBV-119 to the efficacy of the triple combination.

For subjects on stable treatment of other CFTR modulator therapy (i.e., ivacaftor/tezacaftor; or Symkevi), 2 brief washout periods of 5 days were included to allow for elimination of the previous modulator drugs. The 5-day washout period was based on the mean effective half-lives ($t_{1/2}$) of ivacaftor and tezacaftor, which are 13.7 h and 15.0 h, respectively.[8] The first washout period occurred before the start of the dual combination run-in period, and the second washout period occurred after the triple combination treatment period. These subjects could resume their stable modulator treatment after the second washout period.

Cohort 2 included adult CF subjects who are heterozygous for the F508del mutation and a minimal function mutation (Appendix F) and are not receiving ETI treatment, with a double-blind, placebo-controlled, parallel-arm design. Approximately 30 subjects were enrolled in this cohort and were randomized to 2 parallel treatment arms at a 2:1 treatment to placebo ratio. Subjects received galicaftor/navocaftor/ABBV-119 triple combination therapy, or placebo treatment for 28 days. Differences in endpoint values from Baseline to the end of the triple combination treatment period will demonstrate the efficacy of the triple combination.

For Cohort 2, study sites and subjects will remain blinded for the duration of the study.

Cohort 1 and Cohort 2 have been terminated based on the efficacy results of the Cohort 1 interim analysis (see Section 2.2). Cohort 3 is modified to replace ABBV-119 with ABBV-576, a structurally differentiated modulator with improved safety and pharmacokinetic profiles.

Cohort 3 will include adult CF subjects who are homozygous or heterozygous for the F508del mutation receiving stable treatment of ETI at the time of screening, with a single arm, open-label design. Up to 40 subjects will be enrolled in this cohort, including approximately 20 F508del homozygous subjects and

up to 20 F508del heterozygous subjects. Subjects will receive galicaftor/navocaftor/ABBV-576 triple combination therapy for 28 days. Differences in endpoint values from Baseline to the end of the triple combination treatment period will be used to evaluate target engagement and the efficacy of the triple combination.

For subjects on stable treatment of ETI, no washout period is planned to minimize the risk of withdrawal syndromes.[9] In order to better monitor patient safety during the first week of the treatment period when ETI elimination is taking place, a phone call on Day 4 and a study visit on Day 8 are added for safety evaluation. In addition, considering the potential impact of ETI carry-over effect on $ppFEV_1$ response by Day 29[10], the primary endpoint for Cohort 3 has been changed to SwCl (Section 3.2), a biomarker that reflects target engagement, and is less susceptible to carry-over effect as shown in Cohort 1 interim analysis results.

To ensure the safety and integrity of the study data, an independent DMC consisting of independent experts convened before the study to review the unblinded safety data from ABBV-119 or ABBV-576 Phase 1 study and provided a recommendation on study initiation (see Section 5.10). The DMC will also periodically review the accumulating unblinded safety data for the study and provide recommendations on study continuation or early termination. The DMC charter will outline the specific responsibilities and composition of the DMC and will contain the details of outputs provided for the meetings, as well as the meeting schedule.

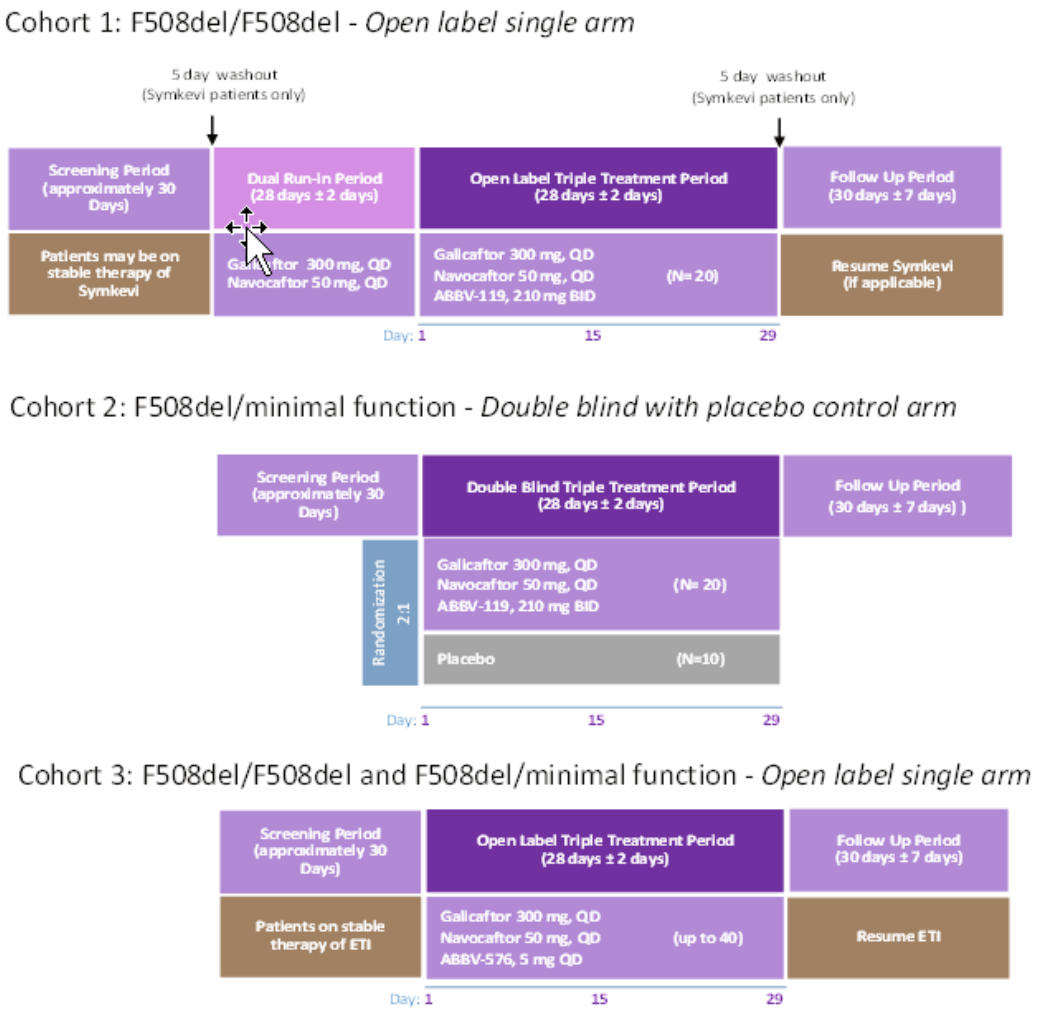
The total duration of a subject's participation in each part of this study (including all periods) is up to approximately 4 months for Cohort 1 and 3 months for Cohort 2 and Cohort 3, consisting of the following study periods:

- Screening Period: up to approximately Day –60 (Cohort 1) or approximately Day –30 (Cohort 2 and Cohort 3)
- Dual Combination Run-in Period (Cohort 1 only): 28 days (± 2 days)
  - The first dose of study drugs (as galicaftor/navocaftor dual combination) will be administered at the site on Study Day –28
  - Dose of study drugs (as galicaftor/navocaftor dual combination) on Day –15 will be administered at the site
- Triple Combination Treatment Period: 28 days (± 2 days)
  - Dose of study drugs (as galicaftor/navocaftor/ABBV-119 triple combination [or matching placebo in Cohort 2 only] or galicaftor/navocaftor/ABBV-576 triple combination) will be administered at the site on Day 1
  - Dose of study drugs (as galicaftor/navocaftor/ABBV-119 triple combination [or matching placebo in Cohort 2 only] or galicaftor/navocaftor/ABBV-576 triple combination) will be administered at the site on Day 15
  - Subjects will not dose on day of Day 29 Visit, and all study subjects can resume their ETI therapy after all of the study related procedures are completed on Day 29
- Follow-Up Period: 30 days (± 7 days) following the last dose of study drug

The schematic of the study is shown in Figure 1. Details regarding study procedures are located in the Operations Manual (Appendix H).

See Section 5 for information regarding eligibility criteria.

**Figure 1. Study Schematic**




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

## Retesting and Rescreening

Retesting of individual screening assessments that did not meet eligibility criteria is allowed once for the following parameters provided results can be obtained and it is possible to randomize the subject within the same screening period. Otherwise, subjects who do not meet one or more eligibility criterion will be considered screen failures.

- If the initial sweat collection has insufficient volume for chloride analysis, then the sweat collection may be repeated once.

- If there is clear evidence of a laboratory error (e.g., hemolyzed sample) or equipment malfunction, collection of a repeat sample for the appropriate laboratory test or assessment may be permitted.
- Exclusionary hepatic function test levels may be retested within 14 days of the original screening date.
- Spirometry may be retested once if the screening spirometry measurement failed to meet the American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria for acceptability and/or repeatability. Spirometry may also be retested once for subjects who usually have a ppFEV$_1$ within 40% to 90% of predicted value but have a first screening spirometry result just outside the eligibility range.

Subjects may be rescreened only after approval of the sponsor's study physician or delegate. If a subject is rescreened, all screening assessments will be repeated, with the exception of *CFTR* genotyping, SwCl, and follicle-stimulating hormone (FSH) (if applicable). Rescreened subjects will keep the same subject identification number. If a subject is rescreened, the screening window will begin once the first rescreening assessment has been initiated.

## 4.2 Discussion of Study Design

### Choice of Control Group

Cohort 1 and Cohort 2 of this study will mainly be conducted in countries that are not anticipated to have access to ETI throughout the study duration. Cohort 3 will mainly be conducted in countries that currently have access to ETI.

Some of these Cohort 1 and Cohort 2 countries have access to dual modulator combination therapies as standard of care for CF subjects who are homozygous for the F508del mutations. Therefore, Cohort 1 of the study will be conducted with an open-label, single arm design. Cohort 1 also includes a dual combination run-in period before the triple combination treatment period (Figure 1), where endpoint value from the dual combination run-in period can also serve as within subject control. Differences in endpoint values between the dual combination run-in period and the triple combination treatment period will demonstrate the contribution of ABBV-119 to the efficacy of the triple combination therapy (Figure 1).

Dual modulator combination therapies are not approved to treat CF subjects who are heterozygous for the F508del mutation and minimal function mutation (Appendix F). Therefore, Cohort 2 of the study will be conducted with a double-blind, placebo-controlled design. The control group consists of subjects randomly assigned to receive placebo.

In countries that currently have access to ETI as standard of care for CF subjects who are homozygous or heterozygous for the F508del mutations, Cohort 3 will be conducted with an open-label single arm design.

## Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be used. All efficacy and safety-related measurements are standard for assessing disease activity in subjects with CF. All clinical and laboratory procedures are standard and generally accepted.

## Suitability of Subject Population

This study was designed to enroll subjects with a confirmed clinical diagnosis of CF who also carry at least one copy of the F508del *CFTR* mutation because galicaftor, navocaftor, ABBV-119, and ABBV-576 are CFTR modulators designed to restore the expression and function of F508del *CFTR*. This population is the most likely to demonstrate a significant change in SwCl and $ppFEV_1$ when given a triple combination of galicaftor/navocaftor/ABBV-119 or galicaftor/navocaftor/ABBV-576.

## Selection of Doses in the Study

For Cohort 1 and Cohort 2, galicaftor, navocaftor, and ABBV-119 were evaluated at fixed doses of 300 mg (QD), 50 mg (QD) and 210 mg BID, respectively. The ABBV-119 dose and dosing regimen were selected based on the safety and PK data from the ongoing Phase 1 studies in healthy volunteers. For Cohort 3, galicaftor, navocaftor, and ABBV-576 will be evaluated at fixed doses of 300 mg (QD), 50 mg (QD) and 5 mg QD, respectively. The ABBV-576 dose and dosing regimen were selected based on the safety and PK data from the ongoing Phase 1 study in healthy volunteers.

Galicaftor has been evaluated in CF subjects who are homozygous for the F508del mutation in a Phase 2 study GLPG2222-CL-202, at dosages ranging from 50 mg to 400 mg QD. Galicaftor was generally well-tolerated in all of the regimens tested. In that 28-day study, a trend of dose-dependent decrease in SwCl was observed between 50 mg and 200 mg doses on Day 14 and Day 28, with maximum decrease in SwCl observed in the 200 mg dose group. [redacted] Considering the totality of the data from galicaftor Phase 1 and Phase 2 studies, a dose range of 10 mg to 300 mg is being evaluated in an ongoing Phase 2 dose ranging Study M19-530. The highest dose of galicaftor (300 mg QD) will be used to evaluate the galicaftor/navocaftor/ABBV-119 combination therapy in this study.

[redacted]

In addition, the completed Cohort 1 interim analysis showed that galicaftor/navocaftor dual combination treatment at the selected doses 300 mg QD/50 mg QD was safe and well tolerated and resulted in a decrease in SwCl concentration (-14.2 mmol/L) from baseline at the end of the 28-day run-in period, which further supports the doses selected for these two components of the triple combination.

[redacted]

For all of the 3 study cohorts, treatment duration of 4 weeks was selected based on efficacy endpoint responses observed in the Phase 1 and Phase 2 studies. In Phase 1 Study GLPG2737-CL-105, the reduction in SwCl and increase in ppFEV$_1$ were observed following 1 week of treatment with the dual combination of GLPG2451 and galicaftor, with the effects sustained following 2 weeks of treatment. In Phase 2 Study GLPG2222-CL-202, reduction in SwCl was similar following 2 weeks and 4 weeks of treatment with galicaftor. Therefore, it is expected that the 4-week treatment duration will be sufficient to provide an initial assessment of the responses in efficacy endpoints in this proof-of-concept study.

[redacted]

# 5 STUDY ACTIVITIES

## 5.1 Eligibility Criteria

Subjects must meet all of the following criteria to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

### Consent

- 1. Subjects or their legally authorized representative must voluntarily **sign and date an informed consent form (ICF)**, approved by an independent ethics committee (IEC)/institutional review board (IRB), before initiation of any screening or study-specific procedures.

## Demographic and Laboratory Assessments

- 2. Adult **male or female**, at least 18 years old on the day of signing the ICF.
- 3. Are willing and able to comply with procedures required in this protocol (per investigator's judgment).
- 4. Weight ≥ 35 kg at Screening and Day -28 for Cohort 1 or Day 1 for Cohort 2 and Cohort 3.
- 5. No clinically significant laboratory values at Screening that would pose undue risk for the subject or interfere with safety assessments (per the investigator).
- 6. The following laboratory values must be in the defined range at Screening:
  - Liver function test (LFT) (AST, ALT, alkaline phosphatase) < 3 × the upper limit of normal (ULN), and total bilirubin < 1.5 × ULN.
  - Estimated creatinine clearance ≥ 50 mL/minute using Cockcroft-Gault equation.
  - Hemoglobin ≥ 10 gm/dL.
  - Negative tests for human immunodeficiency virus infection (HIV-1 and HIV-2 antibodies), hepatitis B virus infection (hepatitis B virus surface antigen [HBsAg]) and active Hepatitis C virus (HCV) infection (HCV RNA).
- 7. Absence of clinically significant abnormality detected on ECG regarding rate, rhythm, or conduction (e.g., QT interval corrected for heart rate using Fridericia's formula [QTcF] should be < 450 msec for males and < 460 msec for females).

## Disease Activity

- 8. Confirmed clinical diagnosis of CF, and genotype homozygous for the F508del *CFTR* mutation for Cohort 1 and Cohort 3, heterozygous for F508del *CFTR* mutation and a minimal function mutation (see Appendix F for the list of minimal function mutations) for Cohort 2 and Cohort 3 (documented in the subject's medical record or CF patient registry).
  - Subjects may be enrolled based on prior documentation of *CFTR* genotype, but if the genotype determined at Screening from the central laboratory does not confirm study eligibility, the subject must be discontinued from the study.
  - For subjects who participated in Study M19-530, it is acceptable to use the *CFTR* genotype that the central lab provided in Study M19-530 to establish eligibility.
  - The list of minimal function mutation (Appendix F) may not include every eligible mutation, and the investigator should contact the medical monitor regarding other mutations that may also meet study eligibility criteria.
- 9. $ppFEV_1$ ≥ 40% and ≤ 90% of predicted normal for age, gender, and height (Global Lung Function Initiative [GLI] equations) at Screening.
- 10. SwCl at screening visit must be ≥ 60 mmol/L for Cohort 1 and Cohort 2, and this criterion does not apply to Cohort 3. For subjects who participated in Study M19-530, it is acceptable to use a SwCl value that the central lab provided in Study M19-530 to establish eligibility.

## Subject History

- 11. Stable pulmonary status, i.e., no respiratory infections or exacerbations requiring a change in therapy (including antimicrobials) or causing an acute decline in $ppFEV_1$ of >10% from usual $ppFEV_1$ level within 4 weeks before Day –28 in Cohort 1 or Day 1 in Cohort 2 and Cohort 3 (first dose of study drug).
- 12. Absence of co-morbidities and medical history listed below, or in the opinion of the investigator, may pose additional risk by participating in the study, or may confound the results of the study.
  - For Cohort 1 and Cohort 2, cirrhosis with or without portal hypertension (e.g., splenomegaly, esophageal varices) or history of clinically significant liver disease. For Cohort 3, cirrhosis with portal hypertension (e.g., splenomegaly, esophageal varices).
  - Past or present positive sputum culture for organisms that are often associated with a faster decline in pulmonary status (e.g., Mycobacterium abscessus, Burkholderia cenocepacia or B. dolosa, Aspergillus fumigatus infection or allergic bronchopulmonary aspergillosis [ABPA]) is allowed if, in the opinion of the investigator, clinical stability has not been adversely affected. Subjects with these organisms can remain on chronic treatment for them if applicable, as long as the medications are not prohibited in this study (see Appendix E). To assure clinical stability, treatment for these organisms should start at least 8 weeks before screening, and the subjects will be expected to continue the treatment through the final study visit.
  - History of malignancy within past 5 years (except for excised basal cell carcinoma of the skin with no recurrence or treated carcinoma in situ of the cervix with no recurrence).
  - Recent (within the past 6 months) history of drug or alcohol abuse that might preclude adherence to the protocol, in the opinion of the investigator.
  - Smoking or vaping tobacco or cannabis products within 1 year before Screening.
  - History of solid organ or hematopoietic transplantation.
  - History of known sensitivity to any component of the study drug.
  - Need for supplemental oxygen while awake, or > 2 L/minute while sleeping.
- 13. Subjects can be on stable treatment with chronic use of oral corticosteroids provided that the daily dose of prednisone (or equivalent) is ≤ 10 mg. For example, 20 mg taken every other day is permissible.
- 14. No concurrent participation in another interventional drug study. Prior participation in investigational drug studies is allowed, provided that 30 days or a washout period of at least 5 terminal half-lives of the investigational drug (whichever is longer) has elapsed before Screening.
- 15. Subjects receiving Orkambi (i.e., lumacaftor/ivacaftor) are not allowed to participate in this study. Subjects receiving Symkevi (i.e., tezacaftor/ivacaftor) at the time of screening are allowed to participate in Cohort 1. Subjects not receiving any CFTR modulator therapy at the time of screening are allowed to participate in either Cohort 1 or Cohort 2.

- 16. Only subjects on stable treatment of ETI for at least 3 months at the time of screening can participate in Cohort 3, and subjects on stable treatment of ETI cannot participate in either Cohort 1 or Cohort 2.
- 17. For Cohorts 1 and 2, no evidence of active SARS-CoV-2 infection. If a subject has signs/symptoms suggestive of SARS-CoV-2 infection, they should undergo molecular (e.g., polymerase chain reaction [PCR]) testing to rule out SARS-CoV-2 infection. Subjects who do not meet SARS-CoV-2 infection eligibility criteria must be screen failed and may only rescreen after they meet the following SARS-CoV-2 infection viral clearance criteria:
  - At least 14 days since first PCR test result have passed in asymptomatic patients or 14 days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms.
- 18. For Cohort 3, no known active SARS-CoV-2 infection. If a subject has signs/symptoms suggestive of SARS-CoV-2 infection, the subject must have a negative molecular (e.g., PCR) test or 2 negative antigen test results at least 24 hours apart. Note: SARS-CoV2 diagnostic tests should be applied following local requirements/recommendations. Subjects who do not meet SARS-CoV-2 infection eligibility criteria must be screen failed and may only rescreen for the study after they meet the following SARS-CoV-2 infection viral clearance criteria:
  - At least 10 days since first PCR test result have passed in asymptomatic patients or at least 10 days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms.
- 19. No history of diseases aggravated or triggered by ultraviolet radiation and no history of abnormal reaction photosensitivity or photoallergy to sunlight, or artificial source of intense light, especially ultraviolet light.

### Contraception

- 20. For all females of childbearing potential: a **negative serum pregnancy test** at the Screening Visit and a negative urine pregnancy test on Day –28 visit for Cohort 1 or Day 1 visit for Cohort 2 and Cohort 3, before the first dose of study drug.
- 21. Female subjects of childbearing potential must practice at least 1 protocol-specified **method of birth control** that is effective from Study Day –28 for Cohort 1 or Day 1 for Cohort 2 and Cohort 3 through at least 30 days after the last dose of study drug. Female subjects of non-childbearing potential do not need to use birth control.
- 22. Female subject who is not **pregnant, breastfeeding, or considering becoming pregnant** during the study or within 30 days after the last dose of study drug.
- 23. **If male**, and subject is **sexually active with female partner(s) of childbearing potential**, he must agree, from Study Day –28 for Cohort 1 or Day 1 for Cohort 2 and Cohort 3 through approximately 90 days after the last dose of study drug to practice protocol-specified contraception.
- 24. Male subject who is not considering **fathering a child or donating sperm** during the study or for approximately 90 days after the last dose of study drug.

### Concomitant Medications

- 25. Stable concomitant medication and airway clearance regimen for at least 4 weeks before the first dose of study drug and willing to continue the same regimen for the duration of the study.
- 26. No use of any strong inhibitor(s) or inducer(s) of CYP3A4 within 4 weeks before the first dose of study drug or during the study period (see Appendix E).
- 27. No use of drugs that are CYP2C8 substrates within 4 weeks before the first dose of study drug or during the study period (e.g., paclitaxel, torasemide, amodiaquine, cerivastatin, repaglinide).
- 28. No use of drugs that are strong CYP2C9 inducers within 4 weeks before the first dose of study drug or during the study period (e.g., enzalutamide, rifampin, carbamazepine, dabrafenib).
- 29.No use of oral cannabis products within 4 weeks before the first dose of study drug and during the study period due to potential interaction with the study drugs.

## 5.2 Contraception Recommendations

### Contraception Requirements for Females

Highly effective contraceptive measures for females of childbearing potential must be documented in the source documents (i.e., hormonal, surgical, or lifestyle decision).

Subjects must follow the following contraceptive guidelines as specified:

- Females, Non-Childbearing Potential
- Females do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria:
  1. Postmenopausal female
     - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
     - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone (FSH) level ≥ 30 IU/L.
  2. Premenopausal female with permanent sterility or permanent infertility due to one of the following:
     - Permanent sterility due to a hysterectomy, bilateral oophorectomy, bilateral salpingectomy.
     - Non-surgical permanent infertility due to Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis; investigator discretion should be applied to determining study entry for these individuals.
- Females, of Childbearing Potential
  - Females of childbearing potential must avoid pregnancy while taking study drug(s) and for at least 30 days after the last dose of study drug.

- Females must commit to one of the following methods of birth control:
  - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation plus a barrier method* initiated at least 30 days before the first dose of study drugs.
  - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation plus a barrier method* initiated at least 30 days before the first dose of study drugs.
  - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
  - Intrauterine device (IUD).
  - Intrauterine hormone-releasing system (IUS) plus a barrier method*.
  - Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
  - Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

* As there are no current clinical data available regarding potential interactions between the study drugs and hormonal contraceptives, **female subjects who use hormonal contraception should supplement this with one of the effective barrier methods described below** (preferably male condom):

- Male or female condom with or without spermicide.
- Cap, diaphragm, or sponge with spermicide.

Contraception recommendations related to use of concomitant therapies prescribed should be based on the local label.

### Contraception Requirements for Males

**Note:** Most CF males are infertile due to absence of the vas deferens. However, sperm can be harvested for *in vitro* fertilization purposes. Males must not have sperm harvested for the purpose of fertility during the study or for approximately 90 days after the last dose of study drug.

Male subjects who are sexually active with a female partner of childbearing potential, must agree **to use condoms,** from the first dose of study drugs through approximately 90 days after the last dose of study drug unless the subject meets one of the criteria below.

Contraception requirement for the male subject is **not required** for the following:

- Vasectomized male subjects or male subjects with complete bilateral absence of vas deferens are not required to use additional form of contraception providing documented azoospermia by semen analysis or demonstration of the absence of vas deferens by ultrasound.

- Male subjects who have undergone bilateral orchiectomy.

## 5.3 Prohibited Medications and Therapy

Throughout the study, strong inhibitors and inducers of CYP3A4, or strong inducers of CYP2C9, or substrates of CYP2C8 and other investigational drugs are prohibited. **Examples** of such compounds are shown in Appendix E. The use of topical treatments of CYP3A4 inhibitors/inducers or CYP2C9 inducers would not be expected to impact study drug. Consult with the AbbVie medical contact with questions regarding administration of an excluded concomitant therapy before administration.

## 5.4 Prior and Concomitant Therapy

Concomitant CF medications and other long-term medications for other conditions that are not expressly prohibited are allowed. The concomitant medication regimen must be stable for at least 4 weeks before the first dose of study drug (as specified in Section 5.1, Eligibility Criteria) and should be continued with minimal variation of dose or frequency for the study duration. Subjects who take inhaled antibiotics for suppression of chronic airway infection must be on a stable regimen for at least 8 weeks before the first study drug administration and remain on that regimen for the study duration. Examples of therapeutic regimens for pulmonary health are antibiotics; corticosteroids (inhaled or oral); inhalation of bronchodilators, hypertonic saline, mannitol or dornase alfa; ibuprofen, and airway clearance techniques.

- Inhaled antibiotics: Subjects who are on cycling inhaled antibiotics (including "on/off" cycling) must continue on the same schedule. The timing of the first dose of study drug should be synchronized as closely as possible to the first day of the inhaled antibiotic in the cycle. The timing of the first dose in a cycle also applies to subjects who are alternating 2 different inhaled antibiotics each month.
- Bronchodilators and airway clearance: Bronchodilator medications and airway clearance techniques are frequently used in CF and may affect lung function measurements in the short term. At each study visit, subjects will be asked about the medication name and timing of their last bronchodilator use (if applicable). There are several bronchodilators available, including salbutamol (albuterol), salmeterol, formoterol, arformoterol, indacaterol, vilanterol, ipratropium, tiotropium, glycopyrronium, umeclidinium, and aclidinium. In some cases, bronchodilators are combined with a second bronchodilator, an inhaled corticosteroid, or both into a single inhaler. If a subject uses a combination product, the information captured in the source documents should include the combination and not just the bronchodilator component.
- During the Screening Period, spirometry assessments may be performed before or after bronchodilator use. At all other study visits, all spirometry assessments should be performed before bronchodilator use. On Days –28, –15, 1 and 15 for Cohort 1 and Days 1 and 15 for Cohort 2 and Cohort 3, spirometry will be performed twice, before and after taking study drug. Bronchodilators should not be given between the 2 spirometry measurements.
- Pre-bronchodilator spirometry is defined as spirometry testing performed for subjects who have withheld their short-acting bronchodilators (e.g., albuterol) for more than 4 hours before the spirometry assessment; withheld their long-acting bronchodilator (e.g., salmeterol) for more

than 12 hours before the spirometry assessment; and withheld their once-daily, long-acting bronchodilator (e.g., tiotropium bromide) for more than 24 hours before the spirometry assessment.

- In the event that a subject does not withhold bronchodilator(s), spirometry assessment should be performed as follows:
  - If a subject's Day 1 spirometry is performed before bronchodilator use, but the subject does not withhold bronchodilator use at a subsequent visit, then a post-bronchodilator spirometry assessment will be obtained for that visit only, and the visit will not be rescheduled.
  - If a subject does not withhold bronchodilator use on Day 1, then Day 1 spirometry should be performed post-bronchodilator, and spirometry assessment on all subsequent visits should be performed post-bronchodilator. Each spirometry assessment will be recorded in the source documents as pre- or post-bronchodilator.

Any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded through the final post-treatment visit (30 days after the last dose of study drug). Any questions regarding concomitant or prior therapy should be raised to the AbbVie emergency contact.

Information regarding potential drug interactions with galicaftor, navocaftor, ABBV-119, or ABBV-576 is located in the galicaftor[3], navocaftor[4], ABBV-119[5], or ABBV-576[2] IBs.

Subjects must be able to safely discontinue any prohibited medications 5 half-lives or 4 weeks before first dose of study drug, whichever is longer. Subjects must be consented for the study before discontinuing any prohibited medications for the purpose of meeting study eligibility.

Cohort 1 subjects who do not tolerate the 5-day washout period before the dual run-in period will be discontinued from the study and allowed to resume their standard of care CFTR modulator therapy.

### COVID-19 Pandemic-Related Vaccination Guidance

Given the ongoing COVID-19 pandemic, selected non-live vaccines (e.g., mRNA, non-replicating viral vector, protein subunit, etc.) to prevent SARS-CoV-2 infection may be administered during screening, the treatment period, or follow up, as long as components of the vaccine are not contraindicated.

The decision to receive a locally available vaccine should be based on local guidance and an individual discussion between the treating physician and the subject.

The potential impact of study drug(s) on SARS-CoV-2 vaccination is unknown. Therefore, study drug should be administered as follows:

- The first dose of study drug(s), when possible, is preferred to be given at least ± 7 days from the SARS-CoV-2 vaccine administration.

Note: The above guidance applies to all SARS-CoV-2 vaccine doses given as part of the complete treatment course.

These recommendations may be subject to change based on the evolving knowledge around the use of SARS-CoV-2 vaccines in patients with CF and as more data are collected in real-world scenarios and clinical trials.

Any SARS-CoV-2 vaccine information must be documented on the SARS-CoV-2/COVID-19 vaccine eCRF. Refer to the Operations Manual for instructions on reporting any adverse events associated with the SARS-CoV-2/COVID-19 vaccine.

## 5.5 Withdrawal of Subjects and Discontinuation of Study

### Discontinuation of Study

A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- The investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Subject is significantly noncompliant with study procedures, which would put the subject at risk for continued participation in the trial.

### Withdrawal of Study Drug Therapy

- The medical monitor should be notified of an interruption of study drug that lasts > 72 hours for any reason and of the resumption of study drug after such interruption.
- Discontinuation of study drug therapy does not mean discontinuation from the study, and remaining study procedures should be completed as indicated in Section 5.6

**Study drug therapy must be discontinued if a subject meets any of the following criteria:**

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator or the AbbVie Therapeutic Area Medical Director.
- Life-threatening AE or a serious adverse event (SAE) that places the subject at immediate risk.
- Eligibility criteria violation after the subject started study drug and continuation of the study drug would place the subject at risk.
- Introduction of prohibited medications or dosages and continuation of the study drug would place the subject at risk.
- The subject becomes pregnant while on study drug.
- Maculopapular rash or other clinical manifestation of allergic drug reaction, for which the severity is categorized as Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0 or most recent version) Grade 3 or higher.

- Worsening pulmonary status that, in the investigator's opinion, is likely to respond to an approved and commercially available CFTR modulator therapy or that requires a significant change to the existing therapeutic regimen.
- Serious infections (e.g., requiring parenteral antimicrobial therapy and/or hospitalization).
- Arrhythmia or conduction abnormality, including, but not limited to prolonged QT interval corrected for the heart rate (HR) using Fridericia's formula (QTcF), where the severity is categorized as CTCAE (Version 5.0 or most recent version) Grade 3 or higher (QTc ≥ 501 ms on at least 2 separate ECGs) [at least 2 minutes apart] obtained within 10 minutes of the initial recording.
- If any of the following hepatic function test criteria are met, study drug must be discontinued immediately, the medical monitor must be notified, and a supplemental hepatic case report form must be completed (see Section 6.1):
  - AST and/or ALT elevations > 5 × ULN
  - AST and/or ALT elevations > 3 × ULN, **and** (total bilirubin > 2 × ULN **or** confirmed international normalized ratio [INR] > 1.5)
  - AST and/or ALT elevations > 3 × ULN, accompanied by clinical signs or symptoms suggestive for hepatic injury (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [> 5%])

A thorough investigation of potential etiologies for elevated transaminases should be conducted (e.g., trauma, acetaminophen use, viral hepatitis, alcohol ingestion), and the subject should be followed closely for clinical progression.

Subjects for whom treatment is discontinued for elevated hepatic function tests should have transaminases and bilirubin levels repeated by the central laboratory within 48 to 72 hours after the initial finding if possible, and then monitored closely until levels normalize or return to baseline. If a subject cannot return to the site for liver function testing, a local laboratory may be used. Elevations in LFTs at the local laboratory must be reported immediately to the medical monitor, and the subject must have the tests repeated and sent to the central laboratory as soon as possible (ideally within 48 to 72 hours).

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

AbbVie may terminate this study prematurely, either in its entirety or at any site. The investigator may also stop the study at his/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

### COVID-19 Pandemic-Related Acceptable Protocol Modification

During the COVID-19 pandemic, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. Acceptable mitigation strategies are identified and included in the Operations Manual in Appendix H.

The investigator should contact the sponsor medical contact before discontinuing a subject from the study for a reason other than "planned per protocol," to ensure all acceptable mitigation steps have been explored.

Refer to the Operations Manual in Appendix H for details on how to handle study activities/procedures.

## 5.6 Follow-Up After Subject Discontinuation of Study Drug or from Study

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should continue to be followed at a Premature Discontinuation visit (PD visit) and 30-day follow-up visit after the last dose of study drug to ensure that all treatment-emergent AEs/SAEs have been resolved, unless subjects have decided to discontinue study participation entirely (withdrawal of informed consent). Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early.

If a subject is discontinued from the study with an ongoing AE or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until a satisfactory clinical resolution of the AE or laboratory result is achieved.

If a subject prematurely discontinues study participation, the procedures outlined for the PD visit should be completed as soon as possible, preferably within 2 weeks.

In the event a subject withdraws consent from the clinical study, biomarker research will continue unless the subject explicitly requests analysis to be stopped. When AbbVie is informed the subject has withdrawn and no longer wishes biomarker research to continue, samples will not be analyzed, no new biomarker analysis data will be collected for the withdrawn subject or added to the existing data or database(s), and the samples will be destroyed. A subject may withdraw consent for optional biomarker research at any time and remain in the clinical study. Data generated from clinical study and/or optional biomarker research, before subject withdrawal of consent, will remain part of the study results.

## 5.7 Study Drug and Study Devices

Galicaftor, navocaftor, ABBV-119, ABBV-576, or matching placebo manufactured by AbbVie will be taken orally beginning on Day –28 for Cohort 1 and Day 1 for Cohort 2 and Cohort 3 and should be taken at approximately the same time each day. Study drug should be taken within 1 hour after a meal. If subjects forget to take their galicaftor, navocaftor, ABBV-576 or matching placebo dose at their regularly scheduled time, they should take the forgotten dose as soon as they remember as long as it is at least 10 hours before the next scheduled dose. If subjects forget to take their ABBV-119 dose at their regularly scheduled time, they should take the forgotten dose as soon as they remember as long as it is at least 4 hours before the next scheduled dose. Otherwise, they should take the next dose at the next scheduled dosing time.

The subject will be instructed to return all drug containers (even if empty) to the study site personnel at each study visit. The study site personnel will document compliance.

AbbVie will provide study drug for galicaftor, navocaftor, and ABBV-119 or ABBV-576, and their matching placebos (Cohort 2 only). Study drug provided by AbbVie should not be substituted or alternately sourced unless otherwise directed by AbbVie. If a subject is unable to come to the study site to pick up their study drug due to COVID-19-related restrictions, a direct-to-patient (DTP) study drug shipment can be made from the study site to the subject if allowed by local laws and regulations. AbbVie will submit any required notifications to the regulatory authority as applicable. Refer to the Operations Manual in Appendix H for details on DTP shipment of study drug.

Study drug will be packaged in blister cards with quantities sufficient to accommodate study design. Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Site staff will complete all blank spaces on the label before dispensing to subjects. Study drug will only be used for the conduct of this study.

Upon completion of or discontinuation from study treatment, all original study drug units (containing unused study drugs)/devices will be returned to the Sponsor (or designee) or destroyed on site. All return or destruction procedures will be according to instructions from the Sponsor and according to local regulations following completion of drug/device accountability procedures.

Information about the drug formulations to be used in this study is presented in Table 1.

## Table 1. Identity of Investigational Products

| | Investigational Product | Investigational Product | Investigational Product Placebo | Investigational Product | Investigational Product Placebo | Investigational Product | Investigational Product Placebo |
|---|---|---|---|---|---|---|---|
| Investigational Product Name | ABBV-576 5 mg capsule | ABBV-119 210 mg capsule | Placebo similar to ABBV-119 capsule | ABBV-3067 (Navocaftor) 50 mg capsule | Placebo similar to ABBV-3067 capsule | ABBV-2222 (Galicaftor) 100 mg capsule | Placebo similar to ABBV-2222 capsule |
| Active Ingredient | ABBV-576 | ABBV-119 | N/A | ABBV-3067 | N/A | ABBV-2222 | N/A |
| Mode/Route of Administration (ROA) | Oral | Oral | Oral | Oral | Oral | Oral | Oral |
| Dosage Form | Capsule | Capsule | Capsule | Capsule | Capsule | Capsule | Capsule |
| Dose and Units | 5 mg | 210 mg | 0 mg | 50 mg | 0 mg | 300 mg | 0 mg |
| Drug Preparation/ Packaging | Blister packaging to support study design | Blister packaging to support study design | Blister packaging to support study design | Blister packaging to support study design | Blister packaging to support study design | Blister packaging to support study design | Blister packaging to support study design |
| Masking | Open-Label (Cohort 3 only) | Open-Label (Cohorts 1 only) Blinded (Cohort 2 only) | Blinded (Cohort 2 only) | Open-Label (Cohorts 1 and 3) Blinded (Cohort 2 only) | Blinded (Cohort 2 only) | Open-Label (Cohorts 1 and 3) Blinded (Cohort 2 only) | Blinded (Cohort 2 only) |
| Frequency of Administration | QD | BID | BID | QD | QD | QD | QD |
| Storage Conditions | Room temperature (15° to 25°C) | Room temperature (15° to 25°C) | Room temperature (15° to 25°C) | Room temperature (15° to 25°C) | Room temperature (15° to 25°C) | Room temperature (15° to 25°C) | Room temperature (15° to 25°C) |

BID = twice daily; N/A = not applicable; QD = once daily

### Digital Health Tools Accountability

The investigator or his/her representative will verify that the digital health tools are received intact and in the correct amounts. A proof of receipt or similar document will be kept in the site files as a record of what was received.

In addition, sites will maintain records of traceability, accountability, and return including but not limited to date received/dispensed/returned, subject number, and the identification of the person dispensing/returning the digital health tools.

## 5.8 Randomization/Drug Assignment

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. For Cohort 2, IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule generated by the statistics department at AbbVie.

Cohort 1 was open-label. In Cohort 2, randomization to galicaftor/navocaftor/ABBV-119 triple vs. placebo was stratified by ppFEV$_1$ at screening (< 70% vs ≥ 70% of predicted value). Cohort 3 is open-label.

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), the investigator, study site personnel, and the subject remained blinded to each subject's treatment throughout the study. To maintain the blind, the galicaftor, navocaftor, and ABBV-119 capsules and placebo capsules provided for the study will be identical in appearance. The IRT will provide access to unblinded subject treatment information in the case of a medical emergency.

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 for 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.

## 5.9 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws and regulations regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic), the investigator is responsible for notifying independent ethics committee/institutional review board (IEC/IRB), regulatory authorities (as applicable), and AbbVie.

## 5.10 Data Monitoring Committee

To enhance the safety and integrity of the study data, an external DMC composed of clinicians and statisticians independent of AbbVie and with relevant expertise in their field reviewed the unblinded data from the Phase 1 studies for ABBV-119 (e.g., Study M19-775) before the start of Study M19-771 and provided a recommendation on the start of Study M19-771. DMC recommendation, including the DMC approved final dose and dosing regimen for ABBV-119 was documented in DMC meeting minutes.

The DMC will also review all of the safety and PK data from ABBV-576 Phase 1 studies 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.

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 a separate DMC Charter.

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.

A separate DMC charter will be prepared outside of the protocol and will further describe the roles and responsibilities of the DMC members, frequency and scope of the data reviews, and expectations for blinded communications.

# 6 SAFETY CONSIDERATIONS

## 6.1 Complaints and Adverse Events

### Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

### Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

### Medical Complaints/Adverse Events and Serious Adverse Events: Study Drug

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations" such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an AE or not. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meets protocol-specific criteria (see Section 5.4), and/or if the investigator considers them to be AEs.

The investigators will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and/or the surgery/procedure has been pre-planned before study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

If any of the following events are reported, then the following supplemental report must be completed.

| Event | Supplemental Report |
|---|---|
| **Discontinuation or interruption of study drug due to a hepatic-related AE**<br>**A hepatic-related SAE**<br>**ALT/AST > 3 × ULN with a total bilirubin > 2 × ULN**<br>**AST/ALT elevations > 5 × ULN**<br>**AST/ALT elevations > 3 × ULN, accompanied by clinical signs or symptoms suggestive for hepatic injury** | Hepatic AE eCRF |
| **Rash** | Rash Questionnaire |
| **COVID-19 infections** | COVID-19 Supplemental Signs/ Symptoms eCRF<br>COVID-19 Status Form |

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; COVID-19 = Coronavirus Disease - 2019; eCRF = electronic case report form; SAE = serious adverse event; ULN = upper limit of normal

## Clinically Significant Assessments

A laboratory value that is Grade 4 will not automatically be an SAE. A Grade 4 laboratory value will be an SAE if the clinical status of the subject indicates a life-threatening AE.

Study assessments including laboratory tests, ECGs, physical examinations, and vital signs will be assessed, and those deemed a **clinically significant** worsening from baseline will be documented as an AE. When possible, a clinical diagnosis for the study assessment will be provided, rather than the abnormal test result alone (e.g., urinary tract infection, anemia). In the absence of a diagnosis, the abnormal study assessment itself will be listed as the AE (e.g., bacteria in urine, decreased hemoglobin).

An abnormal study assessment is considered **clinically significant** if the subject has one or more of the following:

- Concomitant signs or symptoms related to the abnormal study assessment
- Further diagnostic testing or medical/surgical intervention
- A change in the dose of study drug or discontinuation from the study

Repeat testing to determine whether the result is abnormal, in the absence of any of the above criteria, does not necessarily meet clinically significant criteria. The investigator will determine whether the study assessment results are clinically significant. All study assessments deemed "clinically significant" based on the investigator's medical judgment will be managed and followed to a satisfactory clinical resolution.

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance or CRO (as appropriate) as an SAE within 24 hours of the site being made aware of the SAE (refer to Section 4.3 of the Operations Manual for reporting details and contact information [Appendix H]):

| | |
|---|---|
| **Death of Subject** | An event that results in the death of a subject. |
| **Life-Threatening** | An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form. |
| **Hospitalization or Prolongation of Hospitalization** | An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility. |
| **Congenital Anomaly** | An anomaly detected at or after birth, or any anomaly that results in fetal loss. |

| | |
|---|---|
| **Persistent or Significant Disability/Incapacity** | An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle). |
| **Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome** | An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. |

All AEs reported from the time of study drug administration until 30 days or 5 half-lives, whichever is longer, after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, study procedure-related serious and nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

The following definitions will be used for Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Reaction (SUSAR):

| | |
|---|---|
| **SAR** | Defined as all noxious and unintended responses to an IMP related to any dose administered that result in an SAE as defined above. |
| **SUSAR** | Refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the IMP was suspected by either the sponsor or the investigator, is unexpected (not listed in the applicable Reference Safety Information) and meets one of the above serious criteria. |

AbbVie will be responsible for SUSAR reporting for the Investigational Medicinal Product (IMP) in accordance with global and local requirements.

Adverse events will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects.

### Adverse Events of Special Interest

The following adverse events of special interest will be monitored during the study:

- Rash
- Hepatobiliary events

### *Rash*

*Definition and Diagnosis*

Maculopapular rash is a disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous AEs, frequently affecting the upper trunk, spreading centripetally and associated with pruritus.

Nonserious events of generalized rash of mild to moderate severity leading to study drug discontinuation have been observed following multiple dose treatment when galicaftor and navocaftor were co-administered with or without other CFTR modulators (such as ABBV-119). Rash was considered possibly related to study drug by the investigator and resolved after treatment discontinuation.

Rash is to be graded according to the CTCAE (CTCAE version 5.0 or current version).[11] Refer to the Operations Manual Section 4.2 (Appendix H) for additional guidance on the management of these events. All rash cases have to be reported within 24 hours from the time of knowledge of the event using a study-specific rash questionnaire (Operations Manual Section 7.1).

### *Hepatobiliary Events*

Elevated LFTs are adverse reactions associated with marketed products with a similar mechanism of action. Preclinical toxicology studies with ABBV-119 identified reversible hepatobiliary effects accompanied by increased serum liver enzymes and bilirubin that were dose responsive and adverse at the highest dose (150 mg/kg) (see ABBV-119[5] IB). In the MAD part of the navocaftor FIH study (GLPG3067-CL-101), one healthy volunteer who received navocaftor at the highest dose (500 mg BID) temporarily interrupted treatment for 2 doses because of ALT elevation approximately 3.8 × ULN without concurrent bilirubin elevation. Transaminase elevations have been noted in Phase 1 and 2 studies in healthy volunteers and CF subject who received multiple doses of ABBV-119, given alone or coadministered with galicaftor and navocaftor, with onset approximately 14-19 days after the start of dosing (see Section 2.2 under *Risks*; see also the navocaftor[4] IB and the ABBV-119[5] IB).

Management

Subjects with new treatment-emergent LFT elevations must be followed closely including confirmatory testing within 48 to 72 hours after the initial finding and subsequent close monitoring of LFT levels, as clinically indicated. If any of the laboratory criteria defined in Section 5.4 are met, study drug must be discontinued immediately, the medical monitor must be notified, and a supplemental hepatic case report must be completed. A thorough investigation of potential etiologies for the elevated transaminases should be conducted (e.g., trauma, acetaminophen use, viral hepatitis, alcohol ingestion), and the subject should be followed closely for clinical progression.

Subjects for whom treatment is discontinued for elevated hepatic function tests should have transaminases and bilirubin levels repeated by the central laboratory within 48 to 72 hours after the initial finding if possible, and then monitored closely until levels normalize or return to baseline.

If a subject cannot return to the site for liver function testing, a local laboratory may be used. Elevations in LFTs at the local laboratory must be reported immediately to the medical monitor, and the subject must have the tests repeated and sent to the central laboratory as soon as possible (ideally within 48 to 72 hours).

A supplemental case report form should be completed for the following:

- Discontinuation or interruption of study drug due to a hepatic-related AE
- A hepatic-related SAE
- Laboratory criteria defined in Section 5.5

### Adverse Event Severity and Relationship to Study Drug

The investigator will rate the severity of each AE according to the National Cancer Institute (NCI) CTCAE (NCI CTCAE Version 5.0 or current version).

For AEs not captured by the NCI CTCAE, the following severity grading system should be used (Note: a semicolon indicates "or" within the description of the grade):

| | |
|---|---|
| **Grade 1** | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated |
| **Grade 2** | Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a] |
| **Grade 3** | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b] |
| **Grade 4** | Life-threatening consequences; urgent intervention indicated |
| **Grade 5** | Death related to AE |

ADL = Activities of Daily Living; AE = adverse event

a. Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b. Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

| | |
|---|---|
| **Reasonable Possibility** | After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship. |
| **No Reasonable Possibility** | After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship. |

### Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.4). If a pregnancy occurs in a study subject or in the partner of a study subject, information regarding the pregnancy and the outcome will be collected.

In the event of pregnancy occurring in a subject's partner during the study, written informed consent from the partner must be obtained before collection of any such information. AbbVie will provide a separate consent form for this purpose. Pregnancy in a subject's partner(s) will be collected from the date of the first dose through 90 days following the last dose of study drug.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered an SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

## 6.2 Toxicity Management

The management of specific AEs (including AESI of rash) and laboratory parameters is described in the Operations Manual (Appendix H). Specific management for elevated hepatic function tests and hepatobiliary AESI is described in this protocol in Section 5.4 and Section 6.1.

Adverse corneal findings with neutrophilic inflammation were noted on histopathology in dogs administered ABBV-119 after 4 weeks of dosing. These occurred only at the highest dose (150 mg/kg) and were reversible after 4 weeks of recovery. No other eye findings were noted in histopathology examinations. For Cohorts 1 and 2 only: If any subject experiences an ocular AE, it is recommended to consult an ophthalmologist for examination as clinically indicated. All subjects should be assessed for alternative causes and treated as appropriate. All findings related to an AE will be captured on the appropriate eCRF page. Deidentified results of consultations should be forwarded to AbbVie as soon as they are available.

Adverse minimal to mild peripheral nerve degeneration was present in dogs administered 150 mg/kg ABBV-119 for 4 weeks. The finding was not reversible after a 4-week post-dose recovery period. A brief neurologic examination will be performed with the physical examination at time points designated in the activity schedule (for Cohorts 1 and 2 only). See Operations Manual Section 3.12 on neurologic examination for further details (Appendix H).

# 7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

## 7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be focused on primary and key secondary analyses. Complete and specific details of the statistical analysis will be described in the Statistical Analysis Plan (SAP).

The final 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 analysis may be performed separately for each cohort.

## 7.2 Definition for Analysis Populations

For each cohort, these analysis populations will be defined and used for the analysis:

- The Full Analysis Set (FAS) includes all enrolled subjects (randomized subjects for Cohort 2) who received at least 1 dose of study drug as dual or triple combination (or corresponding placebo). The FAS will be used for demographics and baseline characteristics analyses.
- A 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 1 dose of triple combination of study drug (or corresponding placebo). The PP Population will be used for all efficacy analyses as well as the summary of demographics and baseline characteristics.
- The Safety Analysis Set consists of all enrolled subjects (randomized subjects for Cohort 2) who received at least 1 dose of study drug.

## 7.3 Handling Potential Intercurrent Events for the Primary and Key Secondary Endpoints

The primary efficacy endpoint of ppFEV$_1$ (Cohorts 1 and 2) and SwCI (Cohort 3) (defined in Section 3.2) will be analyzed based on PP population to address the following potential intercurrent events:

- Enrolled subjects who do not carry the intended *CFTR* mutation based on central lab report will be excluded from the primary analysis.
- Enrolled subjects who did not receive any dose of study drug as triple combination (or corresponding placebo) will be excluded from the primary analysis.
- Subjects who did not have a baseline data measurement or did not have at least one valid post-baseline data measurement during triple combination treatment period with respect to the corresponding endpoint will be excluded from the primary analysis.
    - A valid post-baseline ppFEV$_1$ data measurement refers to ppFEV$_1$ data collected at a post-baseline visit for which spirometry data were collected pre-dose and consistently with the baseline bronchodilator or airway clearance regimen status, and subjects has not started another CFTR modulator treatment.
    - A valid post-baseline SwCI data measurement refers to SwCI data collected at a post-baseline visit for a subject who has not started another CFTR modulator treatment.

The secondary efficacy endpoints related to spirometry evaluation (e.g., relative change in $ppFEV_1$, absolute change in forced vital capacity [FVC], $FEV_{25-75}$, defined in Section 3.3) will be analyzed based on PP Population with the following potential intercurrent events being addressed:

- Enrolled subjects who do not carry the intended *CFTR* mutation based on central lab report will be excluded from the analysis.
- Enrolled subjects who did not receive any dose of study drug as triple combination (or corresponding placebo) will be excluded from the analysis.
- Subjects who did not have a baseline data or did not have at least one valid post-baseline data during triple combination treatment period with respect to the corresponding spirometry endpoint will be excluded from the analysis.
    - A valid post-baseline spirometry endpoint data refers to data collected at a post-baseline visit for which it was collected pre-dose and consistently with the baseline bronchodilator or airway clearance regimen status, and subjects has not started another CFTR modulator treatment.

The secondary efficacy endpoints related to SwCl and CFQ-R (defined in Section 3.3) will be analyzed based on PP population with the following potential intercurrent events being addressed:

- Enrolled subjects who do not carry the intended *CFTR* mutation based on central lab report will be excluded from the analysis.
- Enrolled subjects who did not receive any dose of study drug as triple combination (or corresponding placebo) will be excluded from the analysis.
- Subjects who did not have a baseline data or did not have at least one valid post-baseline data during triple combination treatment period with respect to the corresponding endpoint will be excluded from the analysis.
    - A valid post-baseline data refers to data collected at a post-baseline visit for a subject who has not started another CFTR modulator treatment.

## 7.4 Statistical Analyses for Efficacy

### Analysis of the Primary Endpoints

Analysis of the primary endpoint will be conducted on the PP population for each cohort and by CFTR genotypes (homozygote, heterozygote) based on treatment as received. If a subject takes more than one treatment, the subject will be grouped in the treatment group for which they received the most doses. The null hypothesis for the primary endpoint is that the within-group absolute change from Baseline (Day 1) through Day 29 in $ppFEV_1$ (Cohorts 1 and 2) or SwCI (Cohort 3) is zero. This null hypothesis will be tested for each cohort separately at 1-sided alpha level of 0.05.

For each cohort, the primary analysis will be performed using a mixed-effect model with repeated measures (MMRM) with change from Baseline in $ppFEV_1$ (Cohorts 1 and 2) or SwCI (Cohort 3) as the dependent variable, treatment (Cohort 2 only), visit, and treatment-by-visit interaction (Cohort 2 only) as fixed effects, subject as a random effect, and baseline $ppFEV_1$ (Cohorts 1 and 2) or baseline SwCI

(Cohort 3) as a covariate. The estimate for the within-group least squares (LS) mean change along with the 90% confidence intervals and the corresponding *P* values will be calculated as the primary analysis. Additionally, 95% CIs will also be provided for informational purpose. For Cohort 2, the between group comparison (treatment effect compared to placebo) will be estimated using the same model.

### Analysis of Secondary Endpoints

The secondary endpoints of SwCL (Cohorts 1 and 2), $ppFEV_1$ (Cohort 3), FVC, and $FEF_{25-75}$ will be analyzed based on an MMRM model similarly as the primary endpoint. Details on the secondary efficacy analyses will be provided in the SAP.

## 7.5 Statistical Analyses for Safety

All safety analyses will be performed on the safety analysis set for each cohort based on the treatment subjects actually receive. Safety will be assessed by AEs, AESIs, weight, vital signs, clinical laboratory data, 12-lead ECGs, pulse oximetry and spirometry, as well as mental health outcome measures. Details on the safety analyses will be provided in the SAP.

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA). A treatment-emergent adverse event (TEAE) is defined as an AE with an onset date on or after the first dose of study drug and within 30 days after the last dose of study drug. The number and percentage of subjects experiencing TEAEs will be tabulated using MedDRA system organ class (SOC) and preferred term as well as by severity and by relationship to the study drug as assessed by the investigator. Summaries (i.e., number and percentages) of TEAEs, SAEs, deaths, AEs leading to discontinuation, and AESIs will be provided.

For laboratory test and vital signs variables, mean change from Baseline before the first dose of study drugs and percentage of subjects with evaluations meeting criteria for predefined potentially clinically significant (PCS) values will be summarized.

## 7.6 Pharmacokinetic and Exposure-Response Analyses

Individual galicaftor, navocaftor, and ABBV-119 or ABBV-576 plasma concentrations at each study visit will be tabulated and summarized with appropriate statistical methods. For subjects receiving ivacaftor/tezacaftor at study entry, individual ivacaftor and tezacaftor plasma concentrations from the screening visit will be tabulated and summarized with appropriate statistical methods.

Data from this study may be combined with data from other studies for the population PK and exposure-response analyses. Population PK and exposure-response analyses of data only from this study may not be conducted. The following general methodology will be used for the population PK and exposure-response analyses.

The relationships between galicaftor, navocaftor, and ABBV-119 or ABBV-576 exposure and clinical observations (primary efficacy variable) will be explored. Exposure-response relationships for secondary efficacy variables or safety responses may be explored. The relationship between exposure (e.g., population PK model predicted average concentrations, area under the curve, trough concentrations, the individual model-predicted PK profiles, or some other appropriate measure of exposure) and drug effect will be explored. Several classes of models (e.g., linear, log-linear, exponential, $E_{max}$, sigmoid $E_{max}$,

etc.) will be evaluated to characterize the exposure-response relationship based on observed data. Ivacaftor and tezacaftor plasma concentrations may be evaluated as a covariate. Results of the PK and exposure response analyses may be summarized in a separate report before regulatory filing, rather than in the clinical study report.

Additional analyses will be performed if useful and appropriate.

## 7.7 Interim Analysis

One interim analysis for Cohort 1 was conducted for this study, which took place after 15 subjects in Cohort 1 completed the triple combination treatment period or prematurely discontinued study drug treatment. The scope of the interim analysis included the efficacy and safety assessment of the dual treatment and triple treatment of subjects in Cohort 1 at the time of the interim analysis. The primary purpose of this interim analysis was to inform AbbVie internal decision making.

Since Cohort 1 was open label, unblinding was not applicable for this interim analysis. The interim analysis was performed and reviewed by the sponsor.

Based on the efficacy results of this interim analysis, Cohort 1 and Cohort 2 have been terminated (see Section 2.2). 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.

Since Cohort 3 is open label, unblinding is not applicable for the interim analyses. The interim analyses will be performed and reviewed by the sponsor. The details of the interim analyses will be specified in the Statistical Analysis Plan.

## 7.8 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.

## 7.9 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 SwCI (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 one-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 percentage points 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 (homozygotes, heterozygotes) will provide >85% power to detect an estimated 10 mmol/L absolute decrease from ETI baseline in SwCI 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 for all cohorts will be adjusted considering a 10% dropout rate.

# 8 ETHICS

## 8.1 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

The protocol, ICF, recruitment materials, and all subject materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the ICF must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

## 8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, applicable laws and regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B.

In the event a significant disaster/crisis (e.g., epidemic/pandemic, natural disaster, conflict/combat) occurs leading to difficulties in performing protocol-specified procedures, AbbVie may engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local lab instead of a central lab), and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment where allowed. In all cases, these alternative measures must be allowed by local laws and regulations and permitted by IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

## 8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

# 9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s). During the COVID-19 pandemic, remote source data review and verification may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

# 10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

# 11 START AND COMPLETION OF THE STUDY

The start-of-study is defined as the date of the first site activated.

The end-of-study is defined as the date of end of study participation by the last subject in the last country where the study was conducted.

# 12 REFERENCES

1. Heijerman HGM, McKone EF, Downey DG, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. Lancet. 2019;394(10212):1940-8.

2. AbbVie. ABBV-576 Investigator's Brochure Edition 1. 2021.

3. AbbVie. Galicaftor Investigator's Brochure Edition 4. 2022.

4. AbbVie. Navocaftor Investigator's Brochure Edition 5. 2022.

5. AbbVie. ABBV-119 Investigator's Brochure Edition 4. 2022.

6. Middleton PG, Mall MA, Drevinek P, et al. Elexacaftor-Tezacaftor-Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. N Engl J Med. 2019;381(19):1809-19.

7. Nichols DP, Morgan SJ, Singh SB, et al. Elexacaftor/tezacaftor/ivacaftor markedly reduces sputum pathogen density in people with CF; a PROMISE study [abstract]. North American Cystic Fibrosis Conference, abstract 465. Pediatr Pulmonol. 2020;55(S2):S220. Available from: https://onlinelibrary.wiley.com/doi/epdf/10.1002/ppul.25089.

8. SYMDEKO® (tezacaftor/ivacaftor; ivacaftor) tablets [prescribing information]. Boston, MA; Vertex Pharmaceuticals Inc., 2020.

9. Trimble AT, Donaldson SH. Ivacaftor withdrawal syndrome in cystic fibrosis patients with the G551D mutation. J Cyst Fibros. 2018;17(2):e13-e6.

10. Moss RB, Flume PA, Elborn JS, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: a double-blind, randomised controlled trial. Lancet Respir Med. 2015;3(7):524-33.

11. US Department of Health and Human Services NIoH, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 2017 [cited 10 Feb 2020]. Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

# APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

| Abbreviation | Definition |
|---|---|
| ABPA | allergic bronchopulmonary aspergillosis |
| AE | adverse event |
| AESI | adverse events of special interest |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| ATS | American Thoracic Society |
| AUC | area under the plasma concentration curve |
| $AUC_{24,ss}$ | area under the plasma concentration-time curve from time 0 to 24 hours at steady-state |
| $AUC_{0-\tau}$ | area under the concentration vs. time curve from 0 to τ |
| BID | twice daily |
| BP | blood pressure |
| cAMP | cyclic adenosine monophosphate |
| CBC | complete blood count |
| CF | cystic fibrosis |
| CFQ-R | CF Questionnaire-Revised |
| CFTR | CF transmembrane conductance regulator |
| CL/F | oral clearance |
| ClinRo | Clinician-Reported Outcome |
| $C_{max}$ | maximum observed concentration |
| COVID-19 | Coronavirus Disease – 2019 |
| CRF | case report form |
| CRO | clinical research organization |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CYP2C9 | cytochrome P450 2C9 isoform subfamily |
| DMC | data monitoring committee |
| DTP | direct-to-patient |
| $EC_{50}$ | effective concentration providing 50% of the maximal response |
| $EC_{90}$ | effective concentration providing 90% of the maximal response |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| ERS | European Respiratory Society |

| | |
|---|---|
| ETI | Elexacaftor /tezacaftor/ivacaftor |
| EU | European Union |
| EudraCT | European Clinical Trials Database |
| FAS | full analysis set |
| $FEF_{25-75}$ | forced expiratory flow at mid-lung capacity |
| FEV | forced expiratory volume |
| $FEV_1$ | forced expiratory volume in the first second of expiration |
| FIH | first-in-human |
| FSH | follicle-stimulating hormone |
| FVC | forced vital capacity |
| GAD-7 | 7-item Generalized Anxiety Disorder scale |
| GCP | Good Clinical Practice |
| GGT | gamma glutamyl transferase |
| GLI | Global Lung Function Initiative |
| HBE | human bronchial epithelial/epithelium |
| HBsAg | hepatitis B virus surface antigen |
| HCV | hepatitis C virus |
| HDRS | Hamilton Depression Rating Scale |
| HIV | human immunodeficiency virus |
| HR | heart rate |
| hsCRP | high-sensitivity C-reactive protein |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IEC | independent ethics committee |
| IEC/IRB | Independent Ethics Committee/Institutional Review Board |
| IMP | investigational medicinal product |
| INR | international normalized ratio |
| IRB | institutional review board |
| IRT | interactive response technology |
| IU | International Unit |
| IUD | intrauterine device |
| IUS | intrauterine hormone-releasing system |

| | |
|---|---|
| LFT | liver function test |
| LS | least squares |
| MAD | multiple ascending dose |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRM | mixed-effect model with repeated measures |
| N/A | not applicable |
| NCI | National Cancer Institute |
| NOEL | no-observed effect level |
| NRI | Non-Responder Imputation |
| PCR | polymerase chain reaction |
| PCS | potentially clinically significant |
| PD visit | Premature Discontinuation visit |
| PK | pharmacokinetics |
| PP | Per-Protocol |
| $ppFEV_1$ | percent predicted forced expiratory volume in 1 second |
| PT | prothrombin time |
| QA | quality assurance |
| QD | once daily |
| QTc | QT interval corrected for heart rate |
| QTcF | QT interval corrected for heart rate using Fridericia's formula |
| RNA | ribonucleic acid |
| RR | respiration rate |
| SAD | single ascending dose |
| SAE | serious adverse event |
| SAP | Statistical analysis plan |
| SAR | serious adverse reaction |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SDAC | statistical data analysis center |
| SOC | system organ class |
| SUSAR | suspected unexpected serious adverse reactions |
| SwCl | sweat chloride |
| TEAE | treatment-emergent adverse event |
| ULN | upper limit of normal |
| V/F | volume of distribution |

| | |
|---|---|
| vs. | versus |

# APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M19-771: A Phase 2 Study of Galicaftor/Navocaftor/ABBV-119 or Galicaftor/Navocaftor/ABBV-576 Combination Therapies in Subjects with Cystic Fibrosis Who Are Homozygous or Heterozygous for the F508del Mutation

Protocol Date: 26 August 2022

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) and local laws, regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate IRB/IEC, except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly (within 1 calendar day to AbbVie, the ethics committees/institutional review boards (as required) and other appropriate individuals (e.g., coordinating investigator, institution director):
    - All changes in the research activity and all unanticipated problems involving risks to human subjects or others.
    - Any departure from relevant clinical trial law or regulation, GCP, or the trial protocol that has the potential to affect the following:
        - Rights, safety, physical or mental integrity of the subjects in the clinical trial
        - Scientific value of the clinical trial, reliability or robustness of data generated
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

| Signature of Principal Investigator | Date |
|---|---|

| Name of Principal Investigator (printed or typed) | |
|---|---|

# APPENDIX C. LIST OF PROTOCOL SIGNATORIES

| Name | Title | Functional Area |
|---|---|---|
| [redacted] | Study Project Manager II | Clinical Study Leadership |
| [redacted] | Director | Medical Writing |
| [redacted] | Executive Medical Director | Specialty Development |
| [redacted] | Senior Scientific Director | Specialty Development |
| [redacted] | Associate Director, Statistics | Data and Statistical Sciences |
| [redacted] | Senior Director and Statistics Therapeutic Area Head | Data and Statistical Sciences |
| [redacted] | Senior Clinical Pharmacologist | Clinical Pharmacology and Pharmacometrics |

# APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities across the Cohort 1, Cohort 2 and Cohort 3 subject encounters. The individual activities are described in detail in the **Operations Manual**. Allowed modifications due to COVID-19 are detailed within the Operations Manual (Appendix H).

## Study Activities Table

*COHORT 1*

| Activity | Screening Period | | Dual Run-in Period | | Treatment Period | | | | Follow Up Period |
|---|---|---|---|---|---|---|---|---|---|
| | UP to approximately Day –60 | Day –33 (phone call) - 2 days only | Day –28 | Day –15 (± 2 days) | Day 1 (± 2 days) | Day 15 (± 2 days) | Day 21 (± 2 days) | Day 29 (± 2 days) or Premature Discontinuation | 30 days after last dose (± 7 days) |
| **INTERVIEWS & QUESTIONNAIRES** | | | | | | | | | |
| Informed consent | ✓ | | | | | | | | |
| Eligibility criteria | ✓ | | ✓ | | | | | | |
| Medical/surgical history | ✓ | | | | | | | | |
| Adverse event assessment | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Prior/concomitant therapy | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Name, date, and time of last dose of bronchodilator (if applicable) | ✓ | | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ |
| Date and time of last dose of Symkevi (if applicable) | ✓ | | | | | | | | |
| Date and time of study drug doses from previous 3 days | | | | ✓ | ✓ | ✓ | | ✓ | |
| Cystic Fibrosis Questionnaire – revised (CFQ-R) (if available) | ✓ | | | | ✓ | | | ✓ | ✓ |
| Reminder to start 5-day washout period (if applicable) | | ✓ | | | | | | ✓ | |
| **LOCAL LABS & EXAMS** | | | | | | | | | |
| Height | ✓ | | | | | | | | |
| Weight | ✓ | | ✓ | | ✓ | | | ✓ | ✓ |
| Vital signs (include oral temperature, RR, HR, BP) | ✓ | | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ |
| Pulse oximetry | ✓ | | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ |
| Physical examination (full) | ✓ | | | | | | | | |
| Physical examination (limited to throat, chest, heart) | | | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ |

| Activity | Screening Period | | Dual Run-in Period | | Treatment Period | | | | Follow Up Period |
|---|---|---|---|---|---|---|---|---|---|
| | UP to approximately Day –60 | Day –33 (phone call) - 2 days only | Day –28 | Day –15 (± 2 days) | Day 1 (± 2 days) | Day 15 (± 2 days) | Day 21 (± 2 days) | Day 29 (± 2 days) or Premature Discontinuation | 30 days after last dose (± 7 days) |
| Brief neurological exam | ✓ | | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ |
| Urine pregnancy test (females of childbearing potential only; to be followed by serum pregnancy test only if urine test is positive) | | | ✓ | | ✓ | | | ✓ | ✓ |
| 12-lead ECG | ✓ | | | ✓ | ✓ | ✓ | | ✓ | |
| Sweat collection (send sample to central laboratory) | ✓ | | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ |
| On site spirometry (on Days –28, –15, 1 and 15, pre dose and 3 - 5 hr post study drug administration) – numbers in parentheses indicate the number of tests | ✓ | | ✓ (2) | ✓ (2) | ✓ (2) | ✓ (2) | | ✓ | ✓ |
| Home Spirometry (if available) | To be performed twice a week through the total duration of the study | | | | | | | | |
| **CENTRAL LABS** | | | | | | | | | |
| CFTR genotyping | ✓ | | | | | | | | |
| Urine test for drugs of abuse | ✓ | | | | | | | | |
| Serology for HBsAg, HCV, HIV type 1 & 2 antibodies | ✓ | | | | | | | | |
| Serum pregnancy test (females of childbearing potential only) | ✓ | | | | | | | | |
| hsCRP, clinical chemistry, hematology (CBC), coagulation, urinalysis | ✓ | | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ |
| Clinical chemistry, PT/INR | | | | | | | ✓ | | |
| FSH (postmenopausal females ≤ age 55 years only) | ✓ | | | | | | | | |
| Blood samples for galicaftor, navocaftor, ABBV-119 (if applicable) PK samples (Days –15 and 15: pre-dose, 2 hr, 4 hr, and 6 hr post-dose; Days 1 and 29: approx. 24 hr after the last morning dose; Follow-up period: anytime during visit) – numbers in parentheses indicate the number of samples to be drawn. | | | | ✓ (4) | ✓ (1) | ✓ (4) | | ✓ (1) | ✓ (1) |
| Blood samples for ivacaftor and tezacaftor PK assay (anytime during visit) – numbers in parentheses indicate the number of samples to be drawn. | ✓ (1) | | | | | | | | |
| Optional biomarker sample: whole blood DNA | | | | | ✓ | | | | |

| Activity | Screening Period | | Dual Run-in Period | | Treatment Period | | | | Follow Up Period |
|---|---|---|---|---|---|---|---|---|---|
| | UP to approximately Day –60 | Day –33 (phone call) - 2 days only | Day –28 | Day –15 (± 2 days) | Day 1 (± 2 days) | Day 15 (± 2 days) | Day 21 (± 2 days) | Day 29 (± 2 days) or Premature Discontinuation | 30 days after last dose (± 7 days) |
| Optional biomarker sample: whole blood RNA | | | | | ✓ | | | ✓ | |
| **℞ TREATMENT** | | | | | | | | | |
| Start of washout (if applicable) | | ✓ | | | | | | ✓ | |
| Dispense study drug | | | ✓ | ✓ | ✓ | ✓ | | | |
| Study drug administered at the site after a meal | | | ✓ | ✓ | ✓ | ✓ | | | |
| Perform drug reconciliation | | | | ✓ | ✓ | ✓ | | ✓ | |

*COHORT 2*

| Activity | Screening Period | Treatment Period | | | | Follow Up Period |
|---|---|---|---|---|---|---|
| | UP to approximately Day –30 | Day 1 | Day 15 (± 2 days) | Day 21 (± 2 days) | Day 29 (± 2 days) or Premature Discontinuation | 30 days after last dose (± 7 days) |
| **INTERVIEWS & QUESTIONNAIRES** | | | | | | |
| Informed consent | ✓ | | | | | |
| Eligibility criteria | ✓ | ✓ | | | | |
| Medical/surgical history | ✓ | | | | | |
| Adverse event assessment | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Prior/concomitant therapy | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Name, date, and time of last dose of bronchodilator (if applicable) | ✓ | ✓ | ✓ | | ✓ | ✓ |
| Date and time of study drug doses from previous 3 days | | | ✓ | | ✓ | |
| Cystic Fibrosis Questionnaire – revised (CFQ-R) (if available) | ✓ | | | | ✓ | ✓ |
| **LOCAL LABS & EXAMS** | | | | | | |
| Height | ✓ | | | | | |
| Weight | ✓ | ✓ | | | ✓ | ✓ |

| Activity | Screening Period | Treatment Period | | | | Follow Up Period |
|---|---|---|---|---|---|---|
| | UP to approximately Day –30 | Day 1 | Day 15 (± 2 days) | Day 21 (± 2 days) | Day 29 (± 2 days) or Premature Discontinuation | 30 days after last dose (± 7 days) |
| Vital signs (include oral temperature, RR, HR, BP) | ✓ | ✓ | ✓ | | ✓ | ✓ |
| Pulse oximetry | ✓ | ✓ | ✓ | | ✓ | ✓ |
| Physical examination (full) | ✓ | | | | | |
| Physical examination (limited to throat, chest, heart) | | ✓ | ✓ | | ✓ | ✓ |
| Brief neurological exam | ✓ | ✓ | ✓ | | ✓ | ✓ |
| Urine pregnancy test (females of childbearing potential only; to be followed by serum pregnancy test only if urine test is positive) | | ✓ | | | ✓ | ✓ |
| 12-lead ECG | ✓ | | ✓ | | ✓ | |
| Sweat collection (send sample to central laboratory) | ✓ | ✓ | ✓ | | ✓ | ✓ |
| On site spirometry (on Days 1 and 15, pre-dose and 3 - 5 hr post study drug administration) – numbers in parentheses indicate the number of tests. | ✓ | ✓ (2) | ✓ (2) | | ✓ | ✓ |
| Home spirometry (if available) | To be performed twice a week through the total duration of the study | | | | | |
| **CENTRAL LABS** | | | | | | |
| CFTR Genotyping | ✓ | | | | | |
| Urine test for drugs of abuse | ✓ | | | | | |
| Serology for HBsAg, HCV, HIV type 1 & 2 antibodies | ✓ | | | | | |
| Serum pregnancy test (females of childbearing potential only) | ✓ | | | | | |
| hsCRP, clinical chemistry, hematology (CBC), coagulation, urinalysis | ✓ | ✓ | ✓ | | ✓ | ✓ |
| Clinical chemistry, PT/INR | | | | ✓ | | |
| FSH (postmenopausal females ≤ age 55 years only) | ✓ | | | | | |
| Blood samples for galicaftor, navocaftor, ABBV-119 PK assay (Day 15 PK samples pre-dose, 2 hr, 4 hr, and 6 hr post-dose; Day 29 approx. 24 hr after the last morning dose; Follow-up period: anytime during visit) – numbers in parentheses indicate the number of samples to be drawn. | | | ✓ (4) | | ✓ (1) | ✓ (1) |
| Optional biomarker sample: whole blood DNA | | ✓ | | | | |
| Optional Biomarker Sample: whole blood RNA | | ✓ | | | ✓ | |
| **TREATMENT** | | | | | | |
| Randomization/drug assignment | | ✓ | | | | |
| Dispense study drugs | | ✓ | ✓ | | | |
| Study drug administered at the site after a meal | | ✓ | ✓ | | | |

| Activity | Screening Period | Treatment Period | | | | Follow Up Period |
|---|---|---|---|---|---|---|
| | UP to approximately Day –30 | Day 1 | Day 15 (± 2 days) | Day 21 (± 2 days) | Day 29 (± 2 days) or Premature Discontinuation | 30 days after last dose (± 7 days) |
| Perform drug reconciliation | | | ✓ | | ✓ | |

*COHORT 3*

| Activity | Screening Period | Treatment Period | | | | | Follow Up Period |
|---|---|---|---|---|---|---|---|
| | Up to approximately Day –30 | Day 1 | Day 4 (± 2 days) Phone call | Day 8 (± 2 days) | Day 15 (± 2 days) | Day 29 (± 2 days) or Premature Discontinuation | 30 days after last dose (± 7 days) |
| **INTERVIEWS & QUESTIONNAIRES** | | | | | | | |
| Informed consent | ✓ | | | | | | |
| Eligibility criteria | ✓ | ✓ | | | | | |
| Medical/surgical history | ✓ | | | | | | |
| Adverse event assessment | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Prior/concomitant therapy | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Name, date, and time of last dose of bronchodilator (if applicable) | ✓ | ✓ | | | ✓ | ✓ | ✓ |
| Date and time of last dose of ETI | ✓ | ✓ | | | | | |
| Date and time of study drug doses from previous 3 days | | | | | ✓ | ✓ | |
| Cystic Fibrosis Questionnaire – revised (CFQ-R) (if available) | ✓ | | | | | ✓ | ✓ |
| Hamilton Depression Rating Scale (HDRS) (if available) | ✓ | | | | | ✓ | ✓ |
| 7-item Generalized Anxiety Disorder scale (GAD-7) (if available) | ✓ | | | | | ✓ | ✓ |
| **LOCAL LABS & EXAMS** | | | | | | | |
| Height | ✓ | | | | | | |
| Weight | ✓ | ✓ | | | | ✓ | ✓ |
| Vital signs (include oral temperature, RR, HR, BP) | ✓ | ✓ | | | ✓ | ✓ | ✓ |
| Pulse oximetry | ✓ | ✓ | | | ✓ | ✓ | ✓ |

| Activity | Screening Period | Treatment Period | | | | | Follow Up Period |
|---|---|---|---|---|---|---|---|
| | Up to approximately Day –30 | Day 1 | Day 4 (± 2 days) Phone call | Day 8 (± 2 days) | Day 15 (± 2 days) | Day 29 (± 2 days) or Premature Discontinuation | 30 days after last dose (± 7 days) |
| Physical examination (full) | ✓ | | | | | | |
| Physical examination (limited to throat, chest, heart) | | ✓ | | | ✓ | ✓ | ✓ |
| Urine pregnancy test (females of childbearing potential only; to be followed by serum pregnancy test only if urine test is positive) | | ✓ | | | | ✓ | ✓ |
| 12-lead ECG | ✓ | | | | ✓ | ✓ | |
| Sweat collection (send sample to central laboratory) | ✓ | ✓ | | | ✓ | ✓ | ✓ |
| On site spirometry (on Days 1 and 15, pre dose and 3 - 5 hr post study drug administration) – numbers in parentheses indicate the number of tests | ✓ | ✓ (2) | | | ✓ (2) | ✓ | ✓ |
| Home Spirometry (if available) | To be performed twice a week through the total duration of the study | | | | | | |
| **CENTRAL LABS** | | | | | | | |
| CFTR genotyping | ✓ | | | | | | |
| Urine test for drugs of abuse | ✓ | | | | | | |
| Serology for HBsAg, HCV, HIV type 1 & 2 antibodies | ✓ | | | | | | |
| Serum pregnancy test (females of childbearing potential only) | ✓ | | | | | | |
| hsCRP, clinical chemistry, hematology (CBC), coagulation, urinalysis | ✓ | ✓ | | | ✓ | ✓ | ✓ |
| Clinical chemistry, PT/INR | | | | ✓ | | | |
| FSH (postmenopausal females ≤ age 55 years only) | ✓ | | | | | | |
| Blood samples for galicaftor, navocaftor, ABBV-576 PK samples (Days 15: pre-dose, 2 hr, 4 hr, and 6 hr post-dose; Days 29: approx. 24 hr after the last morning dose; Follow-up period: anytime during visit) – numbers in parentheses indicate the number of samples to be drawn. | | | | | ✓ (4) | ✓ (1) | ✓ (1) |
| Blood samples for ivacaftor, tezacaftor and elexacaftor PK assay (anytime during visit) – numbers in parentheses indicate the number of samples to be drawn. | ✓ (1) | | | | | | |
| Optional biomarker sample: whole blood DNA | | ✓ | | | | | |
| Optional biomarker sample: whole blood RNA | | ✓ | | | | ✓ | |
| **TREATMENT** | | | | | | | |
| Dispense study drug | | ✓ | | | ✓ | | |
| Study drug administered at the site after a meal | | ✓ | | | ✓ | | |

| Activity | Screening Period | Treatment Period | | | | | Follow Up Period |
|---|---|---|---|---|---|---|---|
| | Up to approximately Day –30 | Day 1 | Day 4 (± 2 days) Phone call | Day 8 (± 2 days) | Day 15 (± 2 days) | Day 29 (± 2 days) or Premature Discontinuation | 30 days after last dose (± 7 days) |
| Perform drug reconciliation | | | | | ✓ | ✓ | |

# APPENDIX E. EXAMPLES OF PROHIBITED MEDICATIONS AND THERAPY

| | |
|---|---|
| **Strong CYP3A4 inhibitors**, such as | Clarithromycin<br>Cobicistat<br>Conivaptan<br>Itraconazole<br>Ketoconazole<br>Nefazodone<br>Ritonavir<br>Posaconazole<br>Telaprevir<br>Telithromycin<br>Voriconazole<br>Grapefruit or grapefruit juice<br>Seville oranges (commonly used in marmalade) |
| **Strong CYP3A4 inducers**, such as | Carbamazepine<br>Enzalutamide<br>Fosphenytoine<br>Lumacaftor<br>Mitotane<br>Phenobarbital<br>Phenytoin<br>Primidone<br>Rifabutin<br>Rifampin<br>Rifapentine<br>St. John's Wort |
| **Strong CYP2C9 inducers**, such as | Enzalutamide<br>Rifampin<br>Carbamazepine<br>Dabrafenib |
| **Substrates of CYP2C8**, such as | Paclitaxel<br>Torasemide<br>Amiodiaqine<br>Cerivastatin<br>Repaglinide<br>Montelukast |

CYP = cytochrome P450

Note: This should not be considered an exhaustive list.

# APPENDIX F. CFTR MINIMAL FUNCTION MUTATIONS ELIGIBLE FOR COHORT 2 AND COHORT 3

| | | | | |
|---|---|---|---|---|
| 1078delT | 2721del11 | 4374+1G→T | G542X | S489X |
| 1119delA | 2732insA | 442delA | G550X | S4X |
| 1138insG | 2790-1G→C | 444delA | G673X | S912X |
| 1154insTC | 2869insG | 457TAT→G | G85E | V520F |
| 1161delC | 2896insAG | 541delC | I507del | W1089X |
| 1213delT | 2942insT | 574delA | K710X | W1098X |
| 1248+1G→A | 2957delT | 602del14 | L1065P | W1145X |
| 1249-1G→A | 296+1G→A | 621+1G→T | L1077P | W1204X |
| 124del23bp | 296+1G→T | 663delT | L1254X | W1282X |
| 1259insA | 2991del32 | 711+1G→T | L218X | W19X |
| 1288insTA | 3007delG | 711+5G→A | L467P | W216X |
| 1341+1G→A | 3028delA | 712-1G→T | L732X | W401X |
| 1343delG | 3040G→C (G970R) | 849delG | L88X | W496X |
| 1461ins4 | 306delTAGA | 852del22 | M1101K | W57X |
| 1471delA | 306insA | 935delA | N1303K | W846X |
| 1497delGG | 3120+1G→A | 991del5 | Q1042X | W882X |
| 1525-1G→A | 3120G→A | A46D | Q1313X | Y1092X |
| 1525-2A→G | 3121-1G→A | A559T | Q1330X | Y122X |
| 1548delG | 3121-2A→G | A561E | Q1382X | Y275X |
| 1609del CA | 3121-977_3499+248del2515 | C276X | Q1411X | Y569D |
| 1677delTA | 3171delC | C524X | Q220X | Y849X |
| 1717-1G→A | 3171insC | CFTR50kbdel | Q290X | Y913X |
| 1717-8G→A | 3271delGG | CFTRdele1 | Q2X | |
| 1782delA | 3349insT | CFTRdele11 | Q39X | |
| 1811+1.6kbA→G | 3500-2A→G | CFTRdele13,14a | Q414X | |
| 1811+1643G→T | 3600+2insT | CFTRdele14b-17b | Q493X | |
| 1811+1G→C | 365-366insT | CFTRdele16-17b | Q525X | |
| 1812-1G→A | 3659delC | CFTRdele17a,17b | Q552X | |
| 1824delA | 3667ins4 | CFTRdele17a-18 | Q685X | |
| 182delT | 3737delA | CFTRdele19 | Q715X | |
| 1833delT | 3791delC | CFTRdele19-21 | Q890X | |
| 185+1G→T | 3821delT | CFTRdele2 | Q98X | |
| 1898+1G→A | 3850-1G→A | CFTRdele2,3 | R1066C | |
| 1898+1G→C | 3876delA | CFTRdele21 | R1102X | |
| 1924del7 | 3878delG | CFTRdele22,23 | R1158X | |
| 2043delG | 3905insT | CFTRdele22-24 | R1162X | |
| 2055del9→A | 394delTT | CFTRdele2-4 | R347P | |

| | | | | |
|---|---|---|---|---|
| 2105-2117del13insAGAAA<br>2143delT<br>2183AA→Ga<br>2184delA<br>2184insA<br>2307insA<br>2347delG<br>2372del8<br>2585delT<br>2594delGT<br>2622+1G→A<br>2711delT | 4005+1G→A<br>4010del4<br>4016insT<br>4021dupT<br>4022insT<br>4040delA<br>405+1G→A<br>405+3A→C<br>406-1G→A<br>4209TGTT→AA<br>4279insA<br>4326delTC | CFTRdele3-10,14b-16<br>CFTRdele4-7<br>CFTRdele4-11<br>CFTRdup6b-10<br>E1104X<br>E1371X<br>E193X<br>E585X<br>E60X<br>E822X<br>E92X<br>G27X<br>G330X | R553X<br>R560S<br>R560T<br>R709X<br>R75X<br>R764X<br>R785X<br>R792X<br>R851X<br>S1196X<br>S1255X<br>S434X<br>S466X | |

CFTR = CF transmembrane conductance regulator; SwCl = sweat chloride

Note: The minimal function mutation is defined as a mutation that is predicted to result in CFTR protein with minimal function. This list is based on the mutation class (e.g., nonsense mutations that do not produce the full length CFTR protein) and the evidence of clinical severity on a population basis (average SwCl > 86 mmol/L and %pancreatic insufficiency > 50%) that is reported in CFTR2 patient registry (https://cftr2.org/) as of 29 April 2022. This should not be considered an exhaustive list, and the investigator should contact the medical monitor regarding other mutations that may also meet study eligibility criteria.

# APPENDIX G. PROTOCOL SUMMARY OF CHANGES

**Previous Protocol Versions**

| Protocol | Date |
|---|---|
| Version 1.0 | 14 January 2021 |
| Admin Change 1 | 22 February 2021 |
| Version 2.0 | 24 March 2021 |
| Version 3.0 | 04 June 2021 |
| Version 4.0 | 22 October 2021 |
| Version 4.1 (Belgium only) | 22 October 2021 |
| Version 4.1.1 (Belgium only) | 09 December 2021 |
| Version 4.2 (UK only) | 16 February 2022 |
| Version 5.0 | 02 March 2022 |
| Version 5.1 (Belgium only) | 21 March 2022 |
| Version 5.2 (UK only) | 21 March 2022 |
| Version 6.0 | 30 June 2022 |

The purpose of this version is to correct minor clerical errors for consistency throughout the protocol in addition to making the following changes:

Added that Cohorts 1 and 2 were terminated based on efficacy results of an interim analysis to Section 1, Section 4.1, and Section 7.7 of the protocol. **Rationale:** To provide further details on the reason for changing the study regimen.

Added 'with and without other CFTR modulators (such as ABBV-119)' to Section 2.2 and Section 6.1 of the protocol. **Rationale:** To provide further information to clarify the safety profile of the study regimen.

Added further information on hepatobiliary events to Section 2.2 and Section 6.1 of the protocol. **Rationale:** To provide further information to clarify the safety profile of the study regimen.

Added HDRS and the GAD-7 as exploratory safety endpoints for Cohort 3 in Section 3.6 of the protocol. Further details regarding the assessment have been included in Section 3.5 and Section 3.6 of the Operations Manual, respectively (see Appendix H). The scheduled assessments are described in Appendix D of the protocol and in Section 2.1 of the Operations Manual(see Appendix H). **Rationale:** To update safety measure based on clinical reports for marketed CFTR modulator therapy.

Added 'and all study subjects can resume their ETI therapy after all of the study related procedures are completed on Day 29' to Section 4.1 of the protocol. **Rationale**: To improve clarity regarding the timing of study activities at Day 29.

Added clarification on the type of cirrhosis that must be absent for subjects to participate in the study under each cohort, to eligibility criterion number 10a (Section 5.1 of the protocol). **Rationale:** To provide further guidance to guide sites in interpreting eligibility criterion 10.

Removed withdrawal criteria related to the use of triazole antimicrobial from Section 5.5 of the protocol. **Rationale**: Criteira removed due to redundancy with the prohibited medications listed in Appendix E of the protocol.

Added 'as well as mental health outcome measures' to Section 7.5 of the protocol. **Rationale:** To incorporate exploratory measurements of mental health parameters in order to inform future trials.

Added recording of 'Date and time of last dose of ETI' to the Day 1 visit for Cohort 3 in Appendix D of the protocol and in Section 2.1 of the Operations Manual (see Appendix H). **Rationale:** To update schedule of activity based on the updated Cohort 3 design.

Added definition for minimal function mutations in Appendix F. **Rationale:** Updated criteria definition based on regulatory agency feedback.

Added amylase and lipase laboratory tests to Table 1 of the Operations Manual (Appendix H). **Rationale:** To incorporate additional safety monitoring parameters.