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Protocol for Study M19-530

Cystic Fibrosis: A Phase 2 Study of ABBV-3067 Alone and in Combination with ABBV-2222

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

PRINCIPAL INVESTIGATOR(S): Investigator information on file at AbbVie.

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1 SYNOPSIS

Title: A Phase 2 Study of ABBV-3067 Alone and in Combination with ABBV-2222 in Cystic Fibrosis Subjects Who Are Homozygous for the F508del Mutation	
Background and Rationale:	Cystic fibrosis (CF) is caused by mutations in the gene that encodes for the CF transmembrane conductance regulatory (CFTR) protein. In this study, CFTR modulators are compounds designed to increase the cell surface expression and restore the function of F508del CFTR. ABBV-2222 is a CFTR corrector that improves F508del CFTR expression and ABBV-3067 is a CFTR potentiator that restores F508del CFTR function. In the cultivated human bronchial epithelial (HBE) cells, the combination of ABBV-2222 and ABBV-3067 showed significant restoration of F508del CFTR expression and function that was greater than observed for either individual component. The clinical program to date supports further investigation of ABBV-3067 and ABBV-2222 as an oral treatment for CF.
Objectives and Endpoints:	***Objectives*** **Part 1** 1. Evaluate the safety, tolerability, and efficacy of ABBV-3067 given alone and in combination with varied dose levels of ABBV-2222 in adult subjects with CF who are homozygous for the F508del mutation. 2. Select a dose of ABBV-2222 to use in Part 2 based on safety, tolerability, efficacy, and pharmacokinetic data. **Part 2** 1. Evaluate the safety, tolerability, and efficacy of ABBV-2222 (fixed dose from Part 1) combined with varied dose levels of ABBV-3067 in CF subjects who are homozygous for the F508del mutation. 2. Select a dose of ABBV-3067 to carry forward to future combination studies. ***Efficacy Endpoints*** **Primary Endpoint** Absolute change from Baseline through Day 29 in percent predicted forced expiratory volume in 1 second ($ppFEV_1$, a measure of lung function). **Secondary Endpoints** 1. Absolute change from Baseline through Day 29 in sweat chloride (SwCl; a biomarker of CFTR activity) 2. Absolute change from Baseline through Day 29 in other spirometric measures (forced vital capacity [FVC], forced expiratory flow at mid-lung capacity [FEF_{25-75}]) 3. Relative change from Baseline through Day 29 in $ppFEV_1$, FVC, and FEF_{25-75}
Investigators	Multicenter

Study Sites:	Approximately 59 sites in Europe and North America, including but not limited to, Belgium, Canada, Czech Republic, France, Hungary, Netherlands, Serbia, Slovakia, Spain, the United Kingdom and the United States.
Study Population and Number of Subjects to be Enrolled:	Approximately 189 patients with cystic fibrosis who are ≥ 18 years of age and are homozygous for the F508del mutation.
Investigational Plan:	This is a multicenter, multi-country, Phase 2, double-blind, placebo-controlled, parallel-arm, 2-part study of ABBV-3067 given alone and in combination with ABBV-2222 for 28 days in adult CF subjects who are homozygous for F508del CFTR mutation. This study is designed to evaluate the safety and efficacy of ABBV-3067 alone and in combination with ABBV-2222, and in a sequential manner that will also allow dose selection for these compounds. In Part 1 of the study, a fixed 150 mg QD dose of ABBV-3067 will be co-administered with ABBV-2222 in a dose range-finding manner to enable a dose selection for ABBV-2222 for Part 2 and future combination studies. In addition, ABBV-3067 will be given alone (i.e., with placebo for ABBV-2222) to evaluate the safety and efficacy of ABBV-3067 at 2 dose levels. Differences in endpoint values between the dual-therapy arms and monotherapy arms, from this study and a previous Phase 2 study (Study GLPG2222-CL-202), will demonstrate the respective contribution of ABBV-2222 and ABBV-3067 to the combination. In Part 2 of the study, the dose of ABBV-2222 selected from Part 1 will be co-administered with ABBV-3067 in a dose-ranging manner to enable selection of the ABBV-3067 dose for future combination studies.
Key Eligibility Criteria:	Males and females ≥ 18 years of age with a confirmed clinical diagnosis of CF and stable pulmonary function who are homozygous for the F508del CFTR mutation and who are not receiving approved or investigational CFTR modulator therapy, with $ppFEV_1$ ≥ 40% and ≤ 90% of predicted normal for age, gender and height (Global Lung Function Initiative [GLI] equations) at Screening, and SwCl at ≥ 60 mmol/L at Screening.
Study Drug and Duration of Treatment:	ABBV-3067, ABBV-2222, and matching placebos to be administered orally once daily
Date of Protocol Synopsis:	04 February 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 regulatory (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, with approximately half of the CF patients in the United States and Europe having the mutation present on both alleles, meaning that they are homozygous for this mutation. 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 in this study are compounds designed to increase the cell surface expression and restore the function of F508del CFTR. ABBV-2222 (also known as galicaftor, or referred to as GLPG2222 or G957389) is a CFTR corrector that improves F508del CFTR expression and ABBV-3067 (also known as navocaftor, or referred to as GLPG3067 or G914167) is a CFTR potentiator that restores F508del CFTR function. Results from in vitro studies using cultivated human bronchial epithelial (HBE) cells demonstrated that the combination of ABBV-2222 and ABBV-3067 significantly restored F508del CFTR expression and function to a greater degree than observed for either individual component. ABBV-3067 and ABBV-2222 are under development as an oral treatment for CF.

Clinical Hypothesis

ABBV-3067 alone and in combination with ABBV-2222 given for 28 days is safe and well tolerated in adults with CF.

The combination of ABBV-3067 and ABBV-2222 administered together for 28 days will result in significant improvements from baseline in pharmacodynamic (PD) markers of CFTR function (lung function and sweat chloride [SwCl]) in individuals with CF who are homozygous for the F508del mutation.

The decrease in SwCl and improvement of lung function as assessed by percent predicted forced expiratory volume in 1 second (ppFEV$_1$) will be greater for the ABBV-3067/ABBV-2222 combination than for ABBV-3067 monotherapy.

2.2 Benefits and Risks to Subjects

The safety results from Phase 1 studies demonstrated that ABBV-2222 and ABBV-3067 were generally well tolerated in healthy volunteers, either as single agent or combination regimen.

ABBV-2222 treatment in vitro improved CFTR channel expression and function in HBE cells. The completed Phase 2 study (Study GLPG2222-CL-202) showed that 4-week treatment of ABBV-2222 significantly reduced SwCl in CF subjects homozygous for F508del mutation. Preliminary results from the ongoing Phase 1 study (Study GLPG2737-CL-105) also showed that the dual combination of

ABBV-2222 and GLPG2451 (another potentiator under development with a similar mechanism of action as ABBV-3067) reduced SwCl and increased $ppFEV_1$ in patients with CF who are homozygous for the F508del mutation. Therefore, it is anticipated that the combination of ABBV-2222 and ABBV-3067 has the potential to improve F508del CFTR function in patients with CF, as well as their lung function measured by $ppFEV_1$.

The following paragraphs describe the main risks that are potentially associated with repeated doses of ABBV-2222, in combination with potentiator/corrector compounds (GLPG2451, ABBV-3067, and [redacted]).

Rash

Nonserious adverse events (AEs) of rash of mild to moderate severity have been observed following multiple-dose treatment with ABBV-2222 in combination with ABBV-3067 or GLPG2451, [redacted]. 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 ABBV-2222 alone, 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 F). Rash is considered an adverse event of special interest (AESI) (see Section 6.1).

Taken together, the safety and efficacy data from the Phase 1 and Phase 2 programs support further development of ABBV-3067 and ABBV-2222 in Phase 2 studies in subjects with CF.

For further details, please see findings from completed studies, including safety data in the ABBV-3067 and ABBV-2222 Investigator's Brochures.[1-2]

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

Part 1

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

Part 2

1. Evaluate the safety, tolerability, and efficacy of ABBV-2222 (fixed dose from Part 1) combined with varied dose levels of ABBV-3067 in CF subjects who are homozygous for the F508del mutation.

2. Select a dose of ABBV-3067 to carry forward to future combination studies.

3.2 Efficacy Endpoints

Primary Endpoint

Absolute change from Baseline through Day 29 in percent predicted forced expiratory volume in 1 second (ppFEV$_1$, a measure of lung function)

Secondary Endpoints

1. Absolute change from Baseline through Day 29 in SwCl (a biomarker of CFTR activity)
2. Absolute change from Baseline through Day 29 in other spirometric measures (forced vital capacity [FVC], forced expiratory flow at mid-lung capacity [FEF$_{25-75}$])
3. Relative changes from Baseline through Day 29 in ppFEV$_1$, FVC, and FEF$_{25-75}$

3.3 Safety Endpoints

Safety endpoints will be AEs, AESIs, weight, vital signs, physical exams, clinical laboratory data, 12-lead electrocardiogram (ECG), pulse oximetry, and spirometry throughout the study.

3.4 Pharmacokinetic Endpoints

Blood samples for determination of ABBV-2222 and ABBV-3067 plasma concentrations will be collected from subjects 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 ABBV-3067 and ABBV-2222 oral clearance (CL/F) and volume of distribution (V/F). Additional parameters may be estimated if useful in the interpretation of the data. Data from this study may be combined with data from other studies for the population pharmacokinetic or exposure-response analyses.

3.5 Biomarker Research

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 ABBV-2222 and/or ABBV-3067. Genes of interest may include those associated with pharmacokinetics (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.

The samples may be retained for no longer than 20 years after study completion or per local requirements.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a multicenter, multi-country, Phase 2, double-blind, placebo-controlled, parallel-arm, 2-part study of ABBV-3067 given alone and in combination with ABBV-2222 for 28 days in adult subjects with CF who are homozygous for F508del CFTR mutation. This study is designed to evaluate the safety and efficacy of ABBV-3067 alone and in combination with ABBV-2222, and in a sequential manner that will also allow dose selection for these compounds.

This study will enroll subjects with a confirmed clinical diagnosis of CF who are homozygous for the F508del CFTR mutation. In both Part 1 and Part 2, randomization will be stratified by ppFEV$_1$ at Screening (< 70% vs ≥ 70%). See Section 5 for detailed information regarding eligibility criteria.

Study drug will be administered in the morning from Day 1 to the day before the Day 29 visit. In Part 1 of the study, a fixed 150 mg once daily (QD) dose of ABBV-3067 will be administered with ABBV-2222 in a dose range-finding manner to enable a dose selection for ABBV-2222 for Part 2 and future combination studies. In addition, ABBV-3067 will be given alone (i.e., with placebo for ABBV-2222) to evaluate the safety and efficacy of ABBV-3067 at 2 dose levels. Differences in endpoint values between the dual therapy arms and monotherapy arms, from this study and a previous Phase 2 study (Study GLPG2222-CL-202), will demonstrate the respective contributions of ABBV-3067 and ABBV-2222 to the combination.

In Part 2 of the study, the dose of ABBV-2222 selected from Part 1 will be administered with ABBV-3067 in a dose-ranging manner to enable selection of the ABBV-3067 dose for future combination studies.

Part 1

ABBV-3067 will be given alone or in combination with different dose levels of ABBV-2222 for 28 days. CF subjects (approximately n = 117) will be randomized to 8 parallel treatment arms with regimens defined below. The randomization ratio will be 1:1:1:2:2:2:2:2 for Regimens A through H in Part 1.

Regimen	ABBV-3067	ABBV-2222	Number of Subjects
A	50 mg	Placebo	9
B	150 mg	Placebo	9
C	150 mg	10 mg	9
D	150 mg	30 mg	18
E	150 mg	100 mg	18
F	150 mg	200 mg	18
G	150 mg	300 mg	18
H	Placebo	Placebo	18

Part 2

Different dose levels of ABBV-3067 will be given in combination with ABBV-2222 for 28 days. Approximately 72 subjects with CF will be randomized to 5 parallel treatment arms with regimens defined below. The randomization ratio will be 1:2:2:2:1 for Regimens I through M in Part 2.

Regimen	ABBV-3067	ABBV-2222	Number of Subjects
I	5 mg	TBD	9
J	15 mg	TBD	18
K	50 mg	TBD	18
L	150 mg	TBD	18
M	Placebo	Placebo	9

TBD = to be determined

Part 2 of the study will initiate after all subjects enrolled in Part 1 complete the 30-day safety follow-up period. The dose of ABBV-2222 in each regimen will be selected based on pharmacokinetics, safety, and efficacy data from Part 1 of the study. The sponsor may also adjust the dose of ABBV-3067 or decide not to conduct a dose regimen if it is determined to be unnecessary.

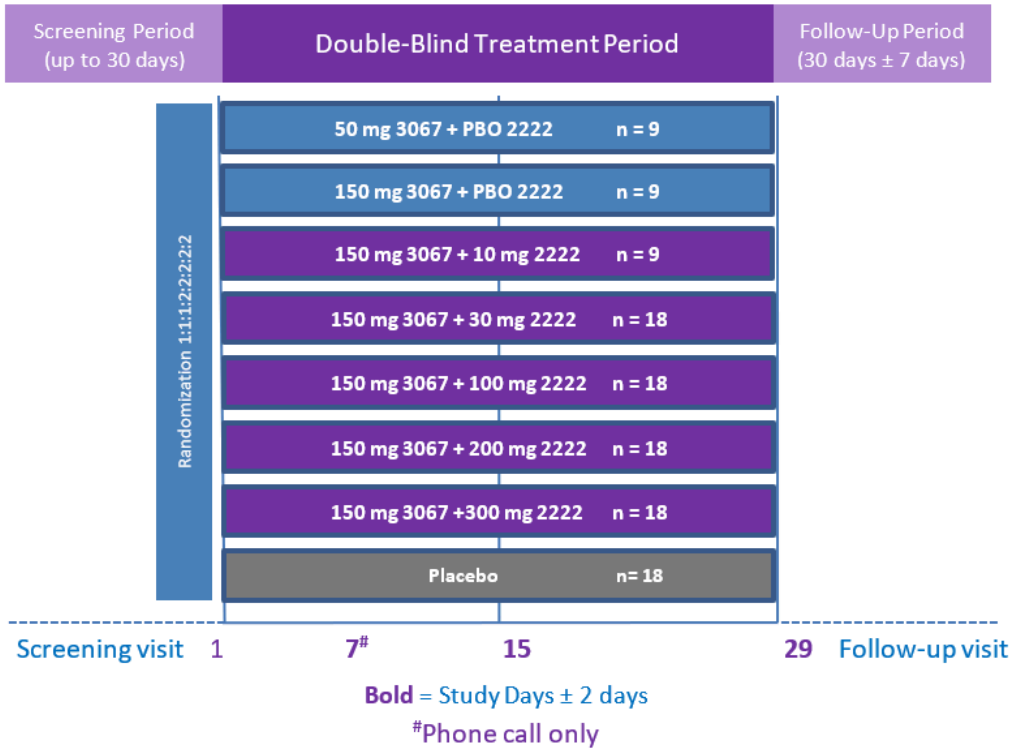
Study sites and subjects will remain blinded for the duration of the study. Interim analyses will be performed as described in Section 7.6.

To enhance the safety and integrity of the study data, a data monitoring committee (DMC) consisting of independent experts will convene periodically to review the accumulating unblinded safety data for the study and provide a recommendation 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.

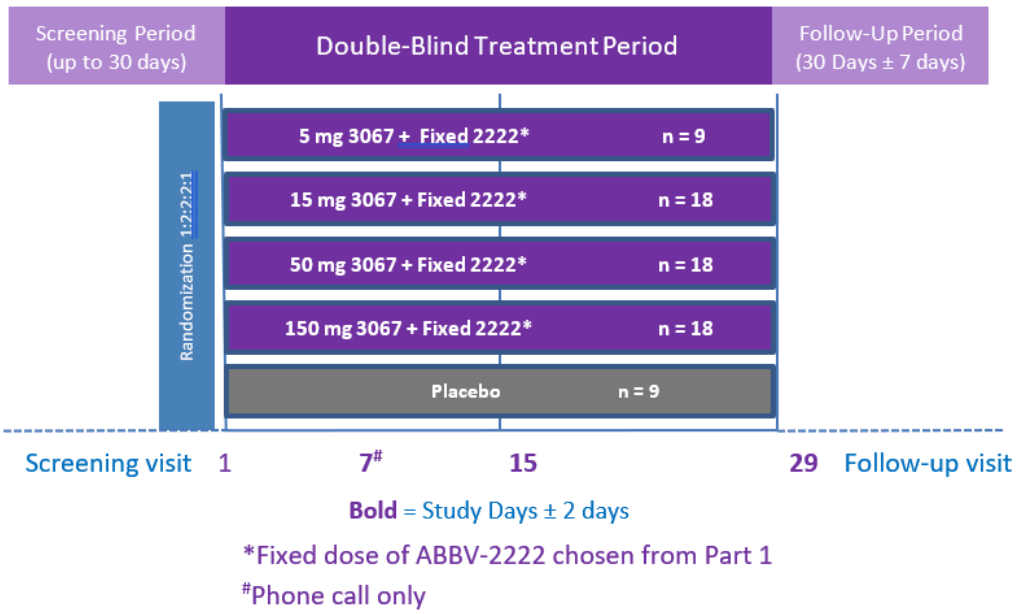
Schematics of the 2 parts of the study are shown in Figure 1 and Figure 2. Further details regarding study procedures are located in the Operations Manual (Appendix F).

Figure 1. Part 1 Schematic



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

Figure 2. Part 2 Schematic



2222 = ABBV-2222; 3067 = ABBV-3067

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 30-day screening period.

- 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 baseline ppFEV$_1$ within 40% to 90% of predicted but have a first screening spirometry result just outside the eligibility range.

Otherwise, subjects not meeting one or more of eligibility criteria will be considered screen failures. Subjects may be rescreened 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

The control group consists of subjects randomly assigned to receive placebo.

The ABBV-3067 single-agent treatment groups (i.e., Regimens A and B) also serve as control groups for the dual combination treatment groups, in order to demonstrate the contribution of ABBV-2222.

Although there are dual combination products that have been approved to treat CF subjects who are homozygous for the F508del mutation, these products are not yet considered standard of care in all countries where this study will be conducted. In countries where dual combination products are accessible as standard of care, this design will also allow the participation of CF subjects who are not on dual combination products due to concerns about safety or tolerability, lack of efficacy, or other concerns (see Eligibility Criteria #21).

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in subjects with CF. All clinical and laboratory procedures in this study are standard and generally accepted.

Suitability of Subject Population

This study was designed to enroll subjects with a confirmed clinical diagnosis of CF who are also homozygous for the F508del CFTR mutation because ABBV-2222 and ABBV-3067 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 sweat chloride and ppFEV$_1$ when given a combination of ABBV-2222 and ABBV-3067.

Selection of Doses in the Study

Part 1

ABBV-2222 has been evaluated following multiple doses in healthy volunteers (Study GLPG2222-CL-101) and patients with CF who are homozygous for F508del mutation in a Phase 2 study (Study GLPG2222-CL-202), at dosages ranging from 50 mg QD to 600 mg QD. ABBV-2222 was safe and well tolerated at all dosages tested. In Study GLPG2222-CL-202, patients with CF who were dosed with ABBV-2222 for 29 days, there was a trend of dose-dependent decrease in SwCl was observed between 50 mg and 200 mg doses on Day 15 and Day 29, with maximum decrease in SwCl observed in the 200 mg dose group. [redacted].

Considering the totality of the data from the in vitro HBE studies and Phase 1 and Phase 2 studies, a dose range of 10 mg to 300 mg would provide an opportunity to study and explore the dose range finding for ABBV-2222 in CF subjects homozygous of F508del mutation in Part 1 of the study.

[redacted].

Part 2

ABBV-2222 dose will be determined based on the analysis of Part 1 data and will be kept constant across all treatment groups in Part 2.

[redacted]

For both Part 1 and Part 2, 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 ABBV-2222, 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 ABBV-2222. Therefore, it is expected that the 4-week treatment duration of ABBV-2222 and ABBV-3067 dual combination will be sufficient to assess the responses in efficacy endpoints in this study.

The maximum dose of the ABBV-2222 administrated in this study will not exceed [redacted]. The maximum dose of ABBV-3067 administered in this study will not exceed [redacted].

Overall, ABBV-2222 exposure (maximum observed concentration [C_{max}] and area under the concentration versus time curve from 0 to τ [$AUC_{0-\tau}$]) following multiple [redacted] the highest tolerated dose in the multiple ascending dose [redacted]; and ABBV-3067 exposure following multiple doses up to [redacted] the highest tolerated dose in the multiple ascending dose [redacted].

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

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

Consent

- 1. Subjects must be able and willing to voluntarily sign and date each informed consent form (ICF), approved by an institutional review board (IRB), prior to the initiation of any Screening or study-specific procedures.
- 2. Subjects must be able to understand and adhere to protocol requirements, restrictions, and instructions (per investigator's judgment).

Demographic and Laboratory Assessments

- 3. Males and females 18 years of age or older on the day the ICF is signed.
- 4. Subjects must weigh ≥ 35 kg at Screening and Day 1
- 5. Subjects must have 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:
  - Hepatic function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase) < 3 × the upper limit of normal (ULN) and total bilirubin < 1.5 × ULN.
  - Estimated creatinine clearance ≥ 50 mL/minute using the Cockroft-Gault equation
  - Hemoglobin ≥ 10 g/dL
  - Negative serology for human immunodeficiency virus (HIV) infection (HIV-1 and/or HIV-2 antibodies), hepatitis B virus infection (hepatitis B virus surface antigen [HBsAg]), and hepatitis C virus infection (anti-HCV antibody)
- 7. Absence of clinically significant abnormality detected on electrocardiogram (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. A confirmed clinical diagnosis of CF and homozygous for the F508del CFTR mutation (documented in the subject's medical record or CF patient registry). Subjects may be randomized based on prior documentation of F508del/F508del mutation, 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 M19-771, it is acceptable to use the CFTR genotype that the central lab provided in Study M19-771 to establish eligibility.

- 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 the Screening visit must be ≥ 60 mmol/L. For subjects who participated in Study M19-771, it is acceptable to use the SwCl value that the central lab provided from the screening visit in Study M19-771 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 baseline within 4 weeks prior to Day 1 (first dose of study drug).
- 12. Absence of comorbidities and medical history items listed below, or others that, in the opinion of the investigator, may pose additional risk by participating in the study, or may confound the results of the study.
    a. Cirrhosis with portal hypertension (e.g., splenomegaly, esophageal varices)
    b. 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 (e.g., clarithromycin, rifampin, itraconazole, see table in Section 5.3). To assure clinical stability, treatment for these organisms should start at least 8 weeks prior to screening, and the subjects will be expected to continue the treatment through the final study visit.
    c. 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)
    d. Abuse of alcohol, medications, or illicit drugs within 1 year prior to Screening, per the investigator.
    e. Smoking or vaping tobacco or cannabis products within 1 year prior to Screening.
    f. History of solid organ or hematopoietic transplantation.
    g. History of known sensitivity to any component of the study drug.
    h. 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 (for non-CFTR modulator studies) or a washout period of at least 5 terminal half-lives of the investigational drug (whichever is longer) have elapsed prior to Screening. For prior participation in trials with CFTR modulators, at least 60 days must elapse between the last study dose and Screening.

Subjects who participated in Study M19-771 are allowed to participate Study M19-530 only if the subject was not withdrawn from Study M19-771 due to safety reasons.

- 15. Part 2 only: Subjects who receive treatment in Part 1 may not participate in Part 2 of the study.

Contraception

- 16. Males who are sexually active with a female partner of childbearing potential and female subjects of childbearing potential must agree to use protocol-specified effective contraceptive measures (refer to Section 5.2, Contraception Recommendations).
- 17. Negative serum pregnancy test at Screening and negative urine pregnancy test on Day 1 visit prior to the first dose of study drug (females of childbearing potential only).
- 18. Females must not be pregnant, breastfeeding, or planning to become pregnant during or within 30 days of the end of study drug treatment.
- 19. Males must not be planning to father a child or donate sperm during the study or for approximately 90 days after the last dose of study drug.

Concomitant Medications

- 20. Stable concomitant medication and airway clearance regimen (including dose and frequency) for at least 4 weeks prior to Day 1 and willing to continue the same regimen for the duration of the study.
- 21. No use of approved or investigational CFTR modulator therapy (e.g., ivacaftor, lumacaftor, tezacaftor, elexacaftor, galicaftor, navocaftor, ABBV-119) for at least 60 days prior to Screening. Individuals who take CFTR modulators as part of their therapeutic regimen should not be encouraged to stop using them in order to participate in this trial; rather, the CFTR modulators may have been discontinued due to intolerance, side effects, lack of efficacy, nonadherence, personal choice, or other reasons.
- 22. No use of any strong inhibitor(s) or inducer(s) of cytochrome P-450 (CYP) 3A4 within 4 weeks prior to the first study drug administration and during the study period (see Section 5.3).
- 23. No use of drugs that are CYP2C8 substrates within 4 weeks prior to the first study drug administration or during the study period (e.g., paclitaxel, torasemide, amodiaquine, cerivastatin, repaglinide).
- 24. No use of oral cannabis products within 4 weeks prior to the first study drug administration 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:

  - Postmenopausal, age > 55 years with no menses for 12 or more months without an alternative medical cause.
  - Postmenopausal, age ≤ 55 years with no menses for 12 or more months without an alternative medical cause ***and*** a FSH level > 40 IU/L.
  - Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

- Females, of Childbearing Potential

  - Females of childbearing potential must avoid pregnancy during study participation 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, and injectable) associated with inhibition of ovulation plus a barrier method* initiated at least 30 days prior to study Baseline Day 1.
    - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation plus a barrier method* initiated at least 30 days prior to study Baseline Day 1.
    - Intrauterine device (IUD).
    - Intrauterine hormone-releasing system (IUS) plus a barrier method.*
    - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
    - 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 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 and for approximately 90 days (1 sperm cycle) 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 Day 1 through approximately 90 days after last dose of study drug, unless the subject meets one of the criteria described below.

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

- Vasectomized male subjects (vasectomy performed 6 months or more previously) or male subjects with complete bilateral absence of vas deferens are not required to use an 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 substrates of CYP2C8 and other investigational drugs are prohibited. Examples of such compounds are shown below.

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

Note: This should not be considered an exhaustive list.

The use of topical treatments of CYP3A4 inhibitors/inducers would not be expected to impact study drug. Consult with the AbbVie medical contact with questions regarding administration of an excluded concomitant therapy prior to 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 prior to the first study drug administration (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 prior to the first study drug administration and remain on that regimen for the study duration.

Examples of therapeutic regimens for pulmonary health include 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. Since ppFEV$_1$ is the primary endpoint for this study, it is very important that the timing of these therapies is kept as consistent as possible relative to spirometry measurements at each research visit, starting with Baseline (Day 1). In order to minimize disruptions in therapeutic regimens, it is recommended that subjects who routinely use bronchodilators be counseled to use them consistently according to their usual schedule throughout the study. Further, study visits should be planned so that the timing of spirometry following bronchodilator use (if applicable) will be similar at each visit (e.g., within 2 hours of each other). Subjects should also be allowed adequate time to complete their inhaled medication/airway clearance regimen (if applicable) before coming to the study visits to maintain consistency throughout the study.

  If subjects miss their routine bronchodilator dose the morning of the Baseline (Day 1) visit, they should also withhold bronchodilators until after spirometry at subsequent visits to maintain consistency. Subjects who use bronchodilators only on an as-needed basis will be asked to refrain from using them prior to spirometry on study visit days. 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, umaclidium, 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. On study visit Days 1 and 15,

spirometry will be performed twice, before and after taking study medication. Bronchodilators should not be given between the 2 spirometry measurements.

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 medical contact. Information regarding potential drug interactions with ABBV-3067 and/or ABBV-2222 can be located in the ABBV-3067 and ABBV-2222 Investigator's Brochures.

Subjects must be able to safely discontinue any prohibited medications after at least 5 half-lives or 4 weeks prior to initial study drug administration, whichever is longer. Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

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 or the treatment period.

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

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

- life-threatening AE or a serious adverse event (SAE) that places the subject at immediate risk; or 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) Grade 3 or higher

- worsening pulmonary status that, in the opinion of the investigator, 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)
- fungal infection requiring treatment with a triazole antimicrobial (e.g., fluconazole, itraconazole, voriconazole)
- confirmed pregnancy
- arrhythmia or conduction abnormality, including but not limited to prolonged QTcF, where the severity is categorized as CTCAE (version 5.0) Grade 3 or higher (QTc ≥ 501 msec 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 is 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 > 8 × ULN
  - AST and/or ALT elevations > 5 × ULN for more than 2 weeks
  - AST and/or ALT elevations > 3 × ULN, with total bilirubin > 2 x ULN
  - 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 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 of the initial finding if possible, and then monitored closely until levels normalize or return to Baseline.

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 halt 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.

5.6 Follow-Up for Subject Withdrawal 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 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 the 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 Premature Discontinuation 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. A subject may withdraw consent for optional biomarker research at any time and remain in the clinical study. Data generated from optional biomarker research, before subject withdrawal of consent, will remain part of the study results.

5.7 Study Drug

ABBV-3067 and ABBV-2222 and their matching placebos manufactured by AbbVie will be taken orally once daily beginning on Day 1 (Baseline) and should be taken at approximately the same time in the morning each day. The study drug is to be taken within 1 hour after a meal. If subjects should forget to take their assigned study drug at their regularly scheduled dosing time, they should take the forgotten dose as soon as they remember as long as it is at least 8 hours before their 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 ABBV-3067 and ABBV-2222 and their matching placebos. Study drug provided by AbbVie should not be substituted or alternately sourced unless otherwise directed by AbbVie.

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.

Information about the drug formulations to be used in this study is presented in Table 1 for Part 1 and in Table 2 for Part 2. Additional IMPD information regarding drug formulations for Part 2 will be provided prior to the start of Part 2.

Table 1. Identity of Investigational Products in Part 1

	Investigational Product Active		Investigational Product Placebo	
Investigational product name	ABBV-3067	ABBV-2222	ABBV-3067 placebo	ABBV-2222 placebo
Active Ingredient	ABBV-3067	ABBV-2222	N/A	N/A
Mode/Route of administration	Oral	Oral	Oral	Oral
Dosage form	Film-coated tablets	Capsules	Film-coated tablets	Capsules
Strength	50 mg	10, 30, and 100 mg	0 mg	0 mg
Masking	Blinded	Blinded	Blinded	Blinded
Frequency of administration	QD	QD	QD	QD
Storage conditions	15° to 25°C	15° to 25°C	15° to 25°C	15° to 25°C
Drug packaging	Blister card	Blister card	Blister card	Blister card

N/A = not applicable; QD = once a day

Table 2. Identity of Investigational Products in Part 2

	Investigational Product Active		Investigational Product Placebo	
Investigational product name	ABBV-3067	ABBV-2222	ABBV-3067 placebo	ABBV-2222 placebo
Active Ingredient	ABBV-3067	ABBV-2222	N/A	N/A
Mode/Route of administration	Oral	Oral	Oral	Oral
Dosage form	Capsules	Capsules	Capsules	Capsules
Strength	TBD	TBD	0 mg	0 mg
Masking	Blinded	Blinded	Blinded	Blinded
Frequency of administration	QD	QD	QD	QD
Storage conditions	15° to 25°C	15° to 25°C	15° to 25°C	15° to 25°C
Drug packaging	Blister card	Blister card	Blister card	Blister card

N/A = not applicable; QD = once a day; TBD = to be determined

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. The 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.

In both Part 1 and Part 2, randomization will be stratified by the Screening visit ppFEV$_1$ (< 70% versus ≥ 70% of predicted value).

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 will remain blinded to each subject's treatment throughout the study. To maintain the blind, the active treatment and placebo formulations (Table 1 and Table 2) 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.

In addition, to minimize the potential of unblinding, the AbbVie study team will not have access to the post-first-dose spirometry or sweat chloride results until after the study is unblinded for Part 1 or Part 2 analysis. Site personnel and subjects will not be informed of the subjects' study-related post-first-dose sweat chloride results until the end of the corresponding study part (Part 1 or Part 2). Subjects will not be informed of their study-related spirometry results until the end of the corresponding study Part (Part 1 or Part 2).

A limited number of AbbVie personnel who are not directly involved in the conduct of the study may receive unblinded data prior to full enrollment of Part 1 and Part 2 to help expedite dose selection of ABBV-2222 and ABBV-3067 for further combination studies.

5.9 Protocol Deviations

The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. Protocol deviations are prohibited except when necessary to eliminate an immediate hazard to study subjects. If a protocol deviation occurs (or is identified), the investigator is responsible for notifying independent ethics committee (IEC)/IRB, regulatory authorities (as applicable), and AbbVie.

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 1 business day 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

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.

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 the surgery/procedure has been pre planned prior to 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.

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

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

Clinically Significant Assessments

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.

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.

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 clinical research organization (CRO) (as appropriate) as an SAE within 24 hours after the site became made aware of the SAE (refer to Section 4.3 of the Operations Manual for reporting details and contact information):

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

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

AbbVie will be responsible for suspected unexpected serious adverse reactions (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

Rash is an AE of special interest (AESI) and will be monitored during the study.

In prior Phase 1 studies, there were isolated instances of nonserious generalized, maculopapular rash that occurred when ABBV-3067 and ABBV-2222 were administered together. The rashes resolved after study drug discontinuation. Maculopapular rash is a disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, maculopapular rash is one of the most common cutaneous AEs, frequently affecting the upper trunk, spreading centripetally, and associated with pruritus.

Rash is to be graded according to the CTCAE (adapted) version 5.0.[3] All rash cases have to be reported within 24 hours from the time of knowledge of the event. Refer to the Operations Manual (Appendix F) for details about management of these events.

Adverse Event Severity and Relationship to Study Drug

The investigators will rate the severity of each AE according to the CTCAE version 5.0.[3]

Grading System for Adverse Events (a semicolon indicated "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

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 1 working day after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.5). 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 prior to collection of any such information. AbbVie will provide a separate consent form for this purpose. Pregnancy in a subject's partners 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 a 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 AE of special interest of rash) and laboratory parameters is described in the Operations Manual. Specific management for elevated hepatic function tests is described in this protocol in Section 5.5.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

Complete and specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the interim database lock. The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, North Carolina, USA).

7.2 Definition for Analysis Populations

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

The safety analysis set consists of all subjects who received at least 1 dose of study drug. For the safety analysis set, subjects are assigned to a treatment group based on the treatment actually received, regardless of the treatment randomized.

7.3 Statistical Analyses for Efficacy

All efficacy analyses will be conducted on the FAS based on treatment as randomized.

For the primary efficacy endpoint in both Part 1 and Part 2, the null hypothesis that the within-group absolute change from baseline in $ppFEV_1$ through Day 29 is zero will be tested for each treated group at 2-sided alpha of 0.05. The primary analysis will be performed using a mixed-effect model with repeated measures (MMRM) with change from Baseline in $ppFEV_1$ as the dependent variable; treatment group, visit, and treatment-by-visit interaction as fixed effects; subject as a random effect; and baseline $ppFEV_1$ as a covariate. The estimate for the within-group mean change along with the 95% confidence intervals and the corresponding *P* values will be calculated as the primary analysis. The treatment effect compared to placebo will be estimated using the same model.

The secondary endpoints of sweat chloride, $ppFEV_1$, FVC, and FEF_{25-75} will be analyzed based on an MMRM model similarly as the primary endpoint.

Details on the efficacy analyses are provided in the SAP.

Sample Size Estimation

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

7.4 Statistical Analyses for Safety

All safety analyses will be performed on the safety analysis set for both Part 1 and Part 2 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. Details on the safety analyses are 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 (PT), 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 and percentage of subjects with evaluations meeting criteria for predefined potentially clinically significant (PCS) values will be summarized.

7.5 Pharmacokinetic and Exposure-Response Analyses

Individual ABBV-2222 and ABBV-3067 plasma concentrations at each study 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 pharmacokinetic and exposure-response analyses. Population pharmacokinetic and exposure-response analyses of data only from this study may not be conducted. The following general methodology will be used for the population pharmacokinetic and exposure-response analyses.

[redacted]

Additional analyses will be performed if useful and appropriate.

7.6 Interim Analysis

[redacted]

8 ETHICS

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

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the informed consent form(s) 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 (ICH) guidelines, applicable 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.

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 federal, state, provincial, country-specific, and local laws and regulatory requirement(s).

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 federal, state, provincial, country-specific, and local laws and regulatory requirements.

11 COMPLETION OF THE STUDY

The end of study is defined as the date of the last subject's last visit.

12 REFERENCES

1. ABBV-2222 Investigator's Brochure, Edition 1. April 2019.
2. ABBV-3067 Investigator's Brochure, Edition 1. April 2019.
3. Common Terminology Criteria for Adverse Events, Version 4.0, DCTD, NCI, NIH, DHHS. June 14, 2010. Common Terminology Criteria for Adverse Events v4.03 (CTCAE) [cited 2019 January 11]. Available from: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.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
BID	Twice daily
cAMP	Cyclic adenosine monophosphate
CF	Cystic fibrosis
CFTR	CF transmembrane conductance regulator
CL/F	Oral clearance
C_{max}	maximum observed concentration
CRO	Clinical research organization
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P-450
DMC	Data monitoring committee
EC_{50}	Effective concentration providing 50% of the maximal response
EC_{90}	Effective concentration providing 90% of the maximal response
ECG	Electrocardiogram
ERS	European Respiratory Society
EudraCT	European Clinical Trials Database
FAS	Full analysis set
FEF_{25-75}	Forced expiratory flow at mid-lung capacity
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
GCP	Good Clinical Practice
GLI	Global Lung Function Initiative
HBE	Human bronchial epithelial/epithelium
HBsAg	Hepatitis B virus surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus

ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IMP	Investigational medicinal product
IMPD	Investigational Medicinal Product Dossier
IRB	Institutional review board
IRT	Interactive response technology
IU	International Unit
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model with repeated measures
N/A	Not applicable
PCS	Potentially clinically significant
PD	Pharmacodynamics
ppFEV$_1$	Percent predicted forced expiratory volume in 1 second
PT	Preferred term
QD	Once daily
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reactions
SwCl	Sweat chloride
TBD	To be determined
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
V/F	Volume of distribution

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M19-530: A Phase 2 Study of ABBV-3067 Alone and in Combination with ABBV-2222

Protocol Date: 04 February 2022

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation (ICH) Good Clinical Practices (GCP) and federal, state, provincial, country-specific 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 federal, state, provincial, country-specific, and local laws and regulatory requirements, current protocol and Operations Manual, and making changes to a protocol only after notifying AbbVie and the appropriate institutional review board (IRB)/independent ethics committee (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, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
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]	Principal Medical Writer	Medical Writing
[redacted]	Therapeutic Area Medical Director	General Medicine
[redacted]	Scientific Director	General Medicine
[redacted]	Director, Biostatistics	Data and Statistical Sciences
[redacted]	Senior Director and TA Head	Data and Statistical Sciences
[redacted]	Senior Director	Clinical Pharmacology and Pharmacometrics

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities across the study visits. The individual activities are described in further detail in the **Operations Manual**.

Study Activities Table

Activity	Screening Period	Treatment Period				Follow-Up Period
	UP to Day –30	Day 1	Day 7 (phone call) (± 2 days)	Day 15 (± 2 days)	Day 29 (± 2 days) or Premature Discontinuation	30-Day Follow-Up (± 7 days)
INTERVIEWS & QUESTIONNAIRES						
Informed consent	✓					
Eligibility criteria	✓	✓				
Medical/surgical history	✓					
Adverse event assessment	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓
Time of last dose of bronchodilator (if applicable)	✓	✓		✓	✓	✓
Date and time of previous 3 doses of study drug				✓	✓	
LOCAL LABS & EXAMS						
Height	✓					
Weight	✓	✓			✓	✓
Vital signs (include oral temperature, respiratory rate, heart rate, and blood pressure)	✓	✓		✓	✓	✓
Pulse oximetry	✓	✓		✓	✓	✓
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 (after at least 5 minutes of rest while supine)	✓			✓	✓	
Sweat collection (send sample to central laboratory)	✓	✓		✓	✓	✓
Spirometry (on Days 1 and 15, pre-dose [0 hr] and 3 - 5 hr following dose). Numbers in parentheses indicate the number of tests.	✓	✓ (2)		✓ (2)	✓	✓
CENTRAL LABS						
CFTR Genotyping	✓					

Activity	Screening Period	Treatment Period				Follow-Up Period
	UP to Day –30	Day 1	Day 7 (phone call) (± 2 days)	Day 15 (± 2 days)	Day 29 (± 2 days) or Premature Discontinuation	30-Day Follow-Up (± 7 days)
Urine test for drugs of abuse	✓					
Serology for HBsAg, HCV, HIV-1 and HIV-2 antibodies	✓					
Serum pregnancy test (females of childbearing potential only)	✓					
High-sensitivity C-reactive protein (hsCRP), clinical chemistry, hematology (complete blood count), urinalysis	✓	✓		✓	✓	✓
Follicle-stimulating hormone (FSH) (postmenopausal females ≤ age 55 years only)	✓					
Blood samples for ABBV-3067 and ABBV-2222 pharmacokinetic assay (Day 15 samples pre-dose [0 hour], 2, 4, and 6 hours following dose; Day 29 approx. 24 hours following last dose). Numbers in parentheses indicate the number of samples to be drawn.				✓ (4)	✓ (1)	✓ (1)
Optional biomarker sample: Whole blood		✓			✓	
℞ TREATMENT						
Randomization/drug assignment		✓				
Dispense study drugs		✓		✓		
Perform drug reconciliation				✓	✓	
Study drug administered at site after a meal		✓		✓		

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	02 May 2019
Version 2.0	28 August 2019

The purpose of this version is to make the following changes:

Modified rescreening language regarding SwCl test in Section 4.2. **Rationale:** SwCl test does not need to be repeated during rescreening as disease diagnosis biomarker.

Added eligibility criteria to specify the requirements for subjects from Study M19-771 in Section 5.1. **Rationale**: Subjects participated in Study M19-771 are allowed to participate in Study M19-530 as long as they meet the eligibility criteria.

Added Montelukast to prohibited medication list in Section 5.3. **Rationale:** Montelukast is a CYP2C8 substrate, and is a commonly used medication in CF patients.

APPENDIX F. OPERATIONS MANUAL

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Operations Manual for Clinical Study Protocol M19-530

Cystic Fibrosis: A Phase 2 Study of ABBV-3067 Alone and in Combination with ABBV-2222

SPONSOR:	AbbVie Inc.	ABBVIE INVESTIGATIONAL PRODUCT:	ABBV-3067 and ABBV-2222

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

1 CONTACTS

Sponsor/ Emergency Medical Contact	Sponsor Contact: [redacted] AbbVie Inc. Dept. R440, [redacted] 1 North Waukegan Road North Chicago, IL 60064	Office: Mobile: [redacted] Fax: Email: [redacted]
	Medical Contact: [redacted] AbbVie Inc. Dept. R440, [redacted] 1 North Waukegan Road North Chicago, IL 60064	Office: Mobile: [redacted] Fax: Email: [redacted]
	EMERGENCY 24 hour Number: **+1 (973) 784-6402**	
Safety Concerns	General Medicine Safety Team Dept. R48S, Bldg. AP31-1 1 North Waukegan Road North Chicago, IL 60064	Phone: +1 (847) 935-7577 Email: GPRD_SafetyManagement_Hormones@abbvie.com
SAE Reporting outside of RAVE	Email: PPDINDPharmacovigilance@abbvie.com	Fax: +1 (847) 938-0660
Protocol Deviations	[redacted] AbbVie Inc. Dept. R477, [redacted] 1 North Waukegan Road North Chicago, IL 60064	Phone: [redacted] Fax: Email: [redacted]
Certified Clinical Lab	Labcorp CLS 8211 SciCor Drive Indianapolis, IN 46214	Phone: +1 (866) 762-6209
Pharmacokinetic Lab	Bioanalysis AbbVie Inc. [redacted] 1 North Waukegan Rd. North Chicago, IL 60064	Phone: +1 (847) 936-1382 Fax: +1 (847) 938-9898 Email: sample.receiving@abbvie.com

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2 PROTOCOL ACTIVITIES BY VISIT

2.1 Individual Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall Treatment Period Activity Schedule.

Activities are grouped by category (Interview, Exam, etc.). Further information is provided in Section 3.

SCREENING (Up to Day –30):

INTERVIEW	• Informed consent • Eligibility criteria • Medical/surgical history	• Adverse event (AE) assessment • Prior/concomitant therapy • Time of last dose of bronchodilator (if applicable)
EXAM	• Full physical examination, including height and weight • Vital signs[a] • 12-lead electrocardiogram (ECG)[b]	• Pulse oximetry[a] • Sweat collection • Spirometry
CENTRAL LAB	• Cystic fibrosis transmembrane conductance regulatory (CFTR) genotyping • Serology for hepatitis B virus surface antigen (HBsAg), hepatitis C virus, human immunodeficiency virus (HIV) Type 1 and 2 (HIV-1 and HIV-2) antibodies • High-sensitivity C-reactive protein (hsCRP), clinical chemistry, hematology (complete blood count [CBC]), and urinalysis	• Urine test for drugs of abuse • Serum pregnancy test (for females of childbearing potential) • Follicle-stimulating hormone (FSH) (for postmenopausal females ≤ 55 years of age)

NOTES:

Section 4.1 of the protocol outlines the circumstances for which retesting of individual labs or spirometry may be performed without repeating all screening procedures. If a screen failure occurs for other reasons that may be corrected and the sponsor's study physician or delegate approves rescreening the subject, then CFTR genotyping, SwCl, and FSH (if applicable) do not need to be repeated.

a. Vital signs (Includes oral temperature, respiration rate, heart rate, blood pressure) and pulse oximetry after at least 5 minutes of rest.

b. After at least 5 minutes of rest while supine.

DAY 1:

INTERVIEW	• Eligibility criteria • AE assessment • Prior/concomitant therapy	• Time of last dose of bronchodilator (if applicable)
EXAM	• Weight • Vital signs[a] • Limited physical examination[b]	• Pulse oximetry[a] • Sweat collection • Spirometry[c]
LAB	• Urine pregnancy test	
CENTRAL LAB	• hsCRP, clinical chemistry, hematology (CBC), and urinalysis • Serum pregnancy test[d]	• Optional biomarker sample: whole blood
TREATMENT	• Randomization/drug assignment • Dispense study drug	• Study drug administered at the site after a meal

NOTES:

a. Vital signs (Includes oral temperature, respiration rate, heart rate, blood pressure) and pulse oximetry after at least 5 minutes of rest.

b. Includes throat, chest, heart, and symptom-directed exam.

c. Pre-dose (0 hour) and 3 to 5 hours following dose.

d. Only for confirmation if urine test is positive.

DAY 7 (Phone call only ± 2 days):

INTERVIEW	• AE assessment • Prior/concomitant therapy

DAY 15 (± 2 days):

INTERVIEW	• AE assessment • Prior/concomitant therapy	• Collect date and time of previous 3 doses of study drug • Time of last dose of bronchodilator (if applicable)
EXAM	• Vital signs[a] • Limited physical examination[b] • 12-lead ECG[c]	• Pulse oximetry[a] • Sweat collection • Spirometry[d]
CENTRAL LAB	• hsCRP, clinical chemistry, hematology (CBC), and urinalysis	• Blood samples for ABBV-3067 and ABBV-2222 plasma concentrations assay[e]
TREATMENT	• Dispense study drug • Perform drug reconciliation	• Study drug administered at the site after a meal

NOTES:

a. Vital signs (Includes oral temperature, respiration rate, heart rate, blood pressure, preferably before blood draw) and pulse oximetry after at least 5 minutes of rest.

b. Includes throat, chest, heart, and symptom-directed exam.

c. After at least 5 minutes of rest while supine, preferably before blood draw.

d. Pre-dose (0 hour) and 3 to 5 hours following dose.

e. Pre-dose (0 hour) and 2, 4, and 6 hours following dose.

DAY 29 (± 2 days) or
PREMATURE DISCONTINUATION:

INTERVIEW	• AE assessment • Prior/concomitant therapy	• Collect date and time of previous 3 doses of study drug • Time of last dose of bronchodilator (if applicable)
EXAM	• Weight • Vital signs[a] • Limited physical examination[b] • 12-lead ECG[c]	• Pulse oximetry[a] • Sweat collection • Spirometry
LAB	• Urine pregnancy test (for females of childbearing potential)	
CENTRAL LAB	• hsCRP, clinical chemistry, hematology (CBC), and urinalysis • Serum pregnancy test[e]	• Blood samples for ABBV-3067 and ABBV-2222 plasma concentrations assay[d] • Optional biomarker sample: whole blood
TREATMENT	• Perform drug reconciliation	

NOTES:

a. Vital signs (Includes oral temperature, respiration rate, heart rate, blood pressure, preferably before blood draw) and pulse oximetry after at least 5 minutes of rest.

b. Includes throat, chest, heart, and symptom-directed exam.

c. After at least 5 minutes of rest while supine, preferably before blood draw. If abnormal - clinically significant, it should be repeated at the follow-up visit or earlier.

d. Approximately 24 hours following last dose.

e. Only for confirmation if urine test is positive.

2.2 Individual Post-Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit.

Activities are grouped by category (Interview, Exam, etc.). Further information is presented in Section 3.

30-Day Follow-up Visit (± 7 days):

INTERVIEW	• AE assessment • Prior/concomitant therapy	• Time of last dose of bronchodilator (if applicable)
EXAM	• Weight • Vital signs[a] • Limited physical examination[b]	• Pulse oximetry[a] • Sweat collection • Spirometry
LAB	• Urine pregnancy test	
CENTRAL LAB	• hsCRP, clinical chemistry, hematology (CBC), and urinalysis	• Serum pregnancy test[c] • Blood samples for ABBV-3067 and ABBV-2222 plasma concentrations assay

NOTES:

a. Vital signs (Includes oral temperature, respiration rate, heart rate, blood pressure) and pulse oximetry after at least 5 minutes of rest.

b. Includes throat, chest, heart, and symptom-directed exam.

c. For confirmation only if urine test is positive.

3 STUDY PROCEDURES

3.1 Subject Information and Informed Consent

The investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject or any medications being discontinued by the subject in order to participate in this study, the informed consent statement must be reviewed, signed, and dated by the subject or their legally authorized representative, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the signed informed consent will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding benefits for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

Optional biomarker research samples will only be collected if the subject has voluntarily signed and dated a written consent form describing the research. The written consent may be part of the main consent form. If the subject does not consent to providing optional samples, the subject will still be allowed to participate in the study.

3.2 Medical History

A complete medical history including demographics, medical conditions, surgical history, genotype, medication use, and history of tobacco, cannabis, alcohol, and drug use will be taken at screening. The number of hospitalizations and/or number of episodes of intravenous (IV) antibiotic use for sinopulmonary signs and symptoms (i.e., exacerbations) in the 12 months prior to Screening will be recorded. The subject's medical history will be updated at the Day 1 visit. This updated medical history will serve as the baseline for clinical assessment.

3.3 Drug and Alcohol Screen

Urine specimens will be tested at the screening visit for the presence of drugs of abuse. The panel for drugs of abuse will minimally include the drugs listed below. Any positive result must be assessed for clinical significance. These analyses will be performed by the certified central laboratory chosen for the study.

- Opiates
- Barbiturates
- Amphetamines
- Cocaine
- Benzodiazepines
- Alcohol
- Phencyclidine
- Propoxyphene
- Methadone

3.4 Adverse Event Assessment

Please refer to Section 4.2.

3.5 Pharmacokinetic Sampling

Collection of Samples for Analysis

Blood samples for the analysis of ABBV-2222 and ABBV-3067 plasma concentrations will be collected from subjects on the study days and time points specified in Section 2.1.

Subjects should be instructed to not to take study drug before coming to the site on the day of the Day 15 and Day 29 visits.

At the Day 15 visit, a trough (predose) pharmacokinetic sample should be collected prior to the administration of study drug. Additional pharmacokinetic samples will be taken 2, 4, and 6 hours following the dose, as outlined in Section 2.1. Subjects should take the dose of study drug within an hour after eating a meal at the study site.

For all pharmacokinetic samples, the date and accurate time of the pharmacokinetic sample collection will be recorded on the lab requisition form.

At the Day 15 and Day 29 visits, the date and time of the previous 3 study drug doses before those visits will be recorded on the electronic case report form (eCRF).

Refer to the study specific laboratory manual for detailed instructions on sample collection, processing, and shipment.

Measurement Method

Plasma concentrations of ABBV-3067 and ABBV-2222 will be determined by the Bioanalysis Department at AbbVie using a validated method.

3.6 Biomarker Sampling

Optional whole blood samples will be collected for biomarker research as specified in Section 2. All biomarker samples should be labeled and shipped as outlined in the study-specific laboratory manual. AbbVie (or people or companies working with AbbVie) will store the samples and data in a secure storage space with adequate measures to protect confidentiality. The samples may be retained while research on ABBV-3067 and ABBV-2222 (or drugs of this class) or cystic fibrosis (CF) and related conditions continues, but for no longer than 20 years after study completion, or per local requirements.

3.7 12-Lead Electrocardiogram

A 12-lead ECG will be performed at the designated study visits as specified in Section 2. The ECG should be performed prior to blood collection and after the subject has been resting supine for at least 5 minutes.

The ECGs will be evaluated by an appropriately trained physician at the site ("local reader"). The local reader from the site will sign and date all ECG tracings and will provide his/her global interpretation as a written comment on the tracing using the following categories:

- Normal ECG
- Abnormal ECG – not clinically significant
- Abnormal ECG – clinically significant

Only the local reader's evaluation of the ECG will be collected and documented in the subject's source folder. The automatic machine reading (i.e., machine-generated measurements and interpretation that are automatically printed on the ECG tracing) will not be collected. If an ECG at the Day 29 visit is interpreted as abnormal – clinically significant, it should be repeated at the follow-up visit or earlier, per the investigator's discretion until satisfactory clinical resolution or stabilization of the finding.

3.8 Height and Weight

Height will be measured at Screening only, with shoes removed. Body weight will be measured at scheduled visits as specified in Section 2. It is recommended that the subject wear lightweight clothing and no shoes during weighing.

3.9 Vital Signs

Vital sign determinations of body temperature, respiration rate, pulse rate, and systolic and diastolic blood pressure will be obtained at visits as specified in Section 2. Blood pressure, pulse rate and respiratory rate should be measured after the subject has been sitting for at least 5 minutes.

3.10 Physical Examination

A complete physical examination (excluding genitourinary) will be performed at the Screening visit as specified in Section 2. Subsequent physical examinations will be limited to evaluations of throat, chest, and heart. At any time, a symptom-directed physical examination can be performed as deemed necessary by the investigator. The physical examination performed on Study Day 1 will serve as the baseline physical examination for the entire study. Any significant physical examination findings after the first dose will be recorded as AEs. All findings, whether related to an AE or part of each subject's medical history, will be captured on the appropriate eCRF page.

3.11 Pulse Oximetry

Pulse oximetry is an indirect measurement of oxygen saturation in blood. It will be performed beginning at Screening and as specified in Section 2. Pulse oximetry should be measured after the subject has been sitting for at least 5 minutes.

3.12 Sweat Collection

Sweat collection will be performed to evaluate sweat chloride (SwCl). Sweat chloride concentration is a biomarker of CFTR ion channel function. It is a sensitive, standardized and non-invasive measure to assess systemic CFTR modulator effects. Chloride concentration will be measured in sweat collected by an approved collection device provided to sites by a central provider and according to the 2009 guidelines issued by the Clinical and Laboratory Standards Institute.

To ensure consistency and reproducibility in this multicenter study, trained clinical study centers will collect sweat according to procedures as outlined in the lab manual. Two sweat collections, one from

each arm, will be obtained from each subject at the time points indicated in the protocol activity schedule. Sweat samples will immediately be frozen and sent to the central laboratory for testing and interpretation of results.

The clinical study center should be encouraged to select subjects for the study for which it is known that adequate quantities of sweat can be collected.

The sites will be provided with sweat collection equipment and kits, and a central laboratory will act as central readers for SwCl. Sweat collection will be measured beginning at Screening and as specified in Section 2.

To prevent the potential unblinding, site personnel and subjects will not be informed of the subjects' study-related post-first-dose sweat chloride results until the end of the corresponding study part (Part 1 or Part 2).

3.13 Spirometry

Spirometry will be performed to assess pulmonary function beginning at Screening and as specified in Section 2. At the Day 1 and Day 15 visits, spirometry must be performed pre-dose and between 3 and 5 hours following dosing.

The spirometry test must meet the criteria for acceptability and repeatability as defined in the 2005 American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines on standardization of lung function testing.[1]

Consistency is very important for subjects who take bronchodilators and perform airway clearance on a regular basis, since they may have short-term effects on FEV_1, the primary endpoint for this study. Please refer to Section 5.4 of the protocol for detailed guidance on the timing of dosing for these therapies relative to spirometry.

The following parameters will be measured as part of the spirometry assessment:

- FEV_1 (L) and percent predicted FEV_1 for age, gender, and height;
- Forced vital capacity (FVC) (L) and percent predicted FVC for age, gender, and height;
- FEV_1/FVC ratio;
- Forced expiratory flow between 25% and 75% of exhaled volume (FEF_{25-75}).

Predicted values will be estimated using the 2012 Global Lungs Initiative equation.[2]

The vendor will provide the sites with spirometers and will act as the central reader for spirometry results.

To prevent the potential unblinding, subjects will not be informed of their study-related spirometry results until the end of the corresponding study Part (Part 1 or Part 2).

3.14 Dispense Study Drug

Study drug will be dispensed to subjects beginning at Baseline (Day 1) and as specified in Section 2. The first dose of study drug will be administered after all other Baseline (Day 1) procedures are completed. At the visits specified in Section 2.1, the site personnel will review returned study drug kits, and empty study drug packaging to verify compliance.

Study drug (i.e., ABBV-3067, ABBV-2222, and respective placebos) should be dosed together and taken within approximately 1 hour after a meal. Study drugs will need to be taken at the investigative site at the Day 1 and Day 15 visits. The site will provide meals at those visits. Subjects should be instructed to take their study medications at the same time every day.

3.15 Clinical Laboratory Tests

The blood samples for serum chemistry tests will be collected prior to study drug dosing on Day 1 and Day 15. Fasting or non-fasting status will be recorded in the source documents and on the laboratory requisition. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug.

Samples will be obtained for the laboratory tests listed in Table 1 at the time points specified in Section 2.

Table 1. Clinical Laboratory Tests

Hematology[a]	Clinical Chemistry[a]	Other Tests
Hematocrit Hemoglobin Mean Corpuscular volume White blood cell count Neutrophils Lymphocytes Monocytes Eosinophils Reticulocyte count Platelet count (estimate not acceptable) Bands (if present)	hsCRP Blood urea nitrogen Creatinine Total bilirubin Direct and indirect bilirubin Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Total protein Glucose Albumin Chloride Bicarbonate Creatinine clearance (Cockcroft-Gault calculation) Gamma-glutamyl transferase (GGT) Uric acid Lactate dehydrogenase Creatine phosphokinase Cholesterol Triglycerides	Urine:[b] drugs of abuse and alcohol Urine[f] and serum human chorionic gonadotropin[b,c,d] follicle-stimulating hormone[b,c,e] Urinalysis:[a] Specific gravity Ketones pH Protein Glucose Blood Bilirubin Leukoesterase Nitrites Microscopic examination, if indicated
Coagulation[a]		**Serology[b]**
Prothrombin time (PT)/INR Activated partial thromboplastin time (aPTT)		HBsAg Anti-HCV antibody HIV-1 and HIV-2 antibodies

INR = international normalized ratio, HBsAG = Hepatitis B virus surface antigen, HCV = Hepatitis C virus, HIV = Human immunodeficiency virus, hsCRP = High-sensitivity C-reactive protein

a. Chemistries, hematology, coagulation and urinalysis labs should be performed at all visits.

b. Performed only at screening.

c. Females only.

d. Pregnancy testing is not required for females of non-childbearing potential.

e. If needed to determine postmenopausal status.

f. Local test.

A certified laboratory will be utilized to process and provide results for the clinical laboratory tests. Laboratory reference ranges will be obtained prior to the initiation of the study.

Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory and sent to the following certified laboratory addresses:

Covance CLS
8211 Scicor Drive
Indianapolis, IN 46214
USA

Covance Central Laboratory Services S.A.
Rue Moïse-Marcinhes 7
1217 Meyrin Geneva
Switzerland

ERT
1818 Market Street
Philadelphia, PA 19103
USA

ERT
Sieboldstraße 3
97230 Estenfeld
Germany

If a laboratory test value is outside the reference range and the investigator considers the laboratory result to be clinically significant, the investigator will:

- repeat the test to verify the out-of-range value using the appropriate Central lab kit;
- follow the out-of-range value to a satisfactory clinical resolution;
- if deemed appropriate, discontinue the subject from the study or require the subject to receive treatment; in this case, the laboratory result will be recorded as an AE;
- document the result and appropriate follow-up in the subject's source records and applicable eCRFs.

Pregnancy Tests (Serum and Urine)

Pregnancy testing should be performed only for women of childbearing potential.

A qualitative serum pregnancy test will be performed at Screening for all female subjects of childbearing potential. The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is positive, the subject is considered a screen failure. If the serum pregnancy test is borderline, it should be repeated ≥ 3 days later to determine eligibility.

If the repeat serum pregnancy test is:

- Positive, the subject is considered a screen failure;
- Negative, the subject can be enrolled into the trial;

- Still borderline, ≥ 3 days later, this will be considered documentation of continued lack of a positive result and the subject can be enrolled into the study (unless prohibited per local requirements) in the absence of clinical suspicion of pregnancy and other pathological causes of borderline results.

Additional urine pregnancy tests will be performed at visits indicated in the Activity Schedule (Protocol Appendix D) and Section 2. More frequent pregnancy tests can be performed throughout the study at the investigator's discretion or if required per local/country requirements.

- If the baseline urine pregnancy test is negative, then dosing with study drug may begin.
- If the baseline or post-baseline urine pregnancy test is positive, dosing with study drug must be withheld and a serum pregnancy test is required (as stated above). If the serum pregnancy test is positive, the subject should be discontinued from the study.
- Unless a woman is suspected to have become pregnant, additional pregnancy testing during the clinical trial is not necessary.

A serum pregnancy test will also be performed at the post-treatment Day 30 follow-up visit if the urine pregnancy test at this visit is positive.

Urinalysis

Dipstick urinalysis will be completed by the central laboratory at all required visits. Specified abnormal macroscopic urinalyses defined as leukocytes, nitrite, protein, ketones, or blood greater than negative, or glucose greater than normal will be followed up with a microscopic analysis at the central laboratory.

3.16 Subject Withdrawal from Study

If subjects prematurely discontinue from the study, they should be asked to return for a Premature Discontinuation visit and participate in a 30-day follow-up visit if possible.

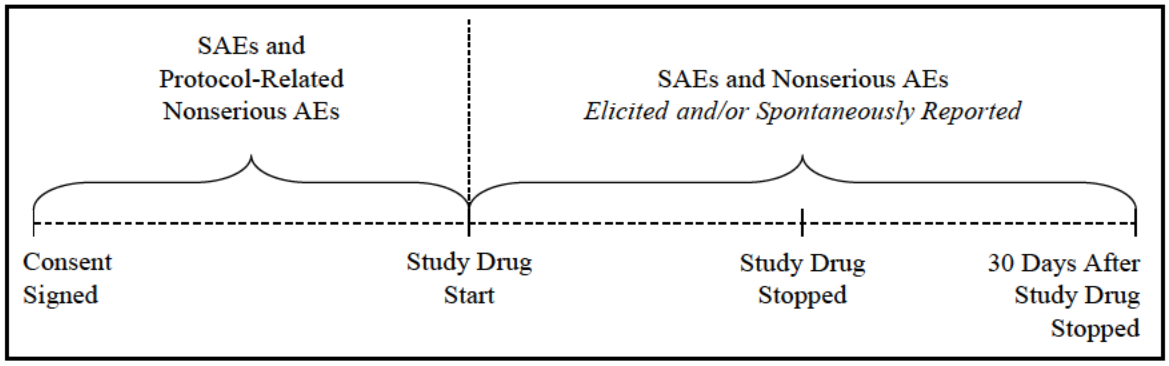
All attempts must be made to determine the date of the last study drug dose and the primary reason for discontinuation of study drug or study participation. The information will be recorded on the appropriate eCRF page. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the investigator's best clinical judgment, irrespective of whether or not the subject decides to continue participation in the study.

4 SAFETY MANUAL

4.1 Methods and Timing of Safety Assessment

All serious adverse events (SAEs) as well as protocol-related nonserious AEs (e.g., bruising at phlebotomy site, done during Screening) will be collected from the time the subject signed the study-specific informed consent until study drug administration. From the time of study drug

administration until 30 days after discontinuation of study treatment, all AEs and SAEs will be collected whether solicited or spontaneously reported by the subject.



4.2 Recording Data and Analyses of Safety Findings

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug through 30 days post-study drug dosing) will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term (PT). The tabulation of the number of subjects with treatment-emergent AEs by severity grade and relationship to study drug also will be provided. Subjects reporting more than 1 AE for a given MedDRA preferred term will be counted only once for that term using the most severe grade according to the severity grade table and the most related according to the relationship to study drug tables. Subjects reporting more than 1 type of AE within an SOC will be counted only once for that SOC.

Adverse Events of Special Interest

Isolated instances of nonserious, generalized, maculopapular rash have occurred in prior Phase 1 studies when ABBV-3067 and ABBV-2222 were administered together (see protocol Section 6.1). All rash AEs are considered adverse events of special interest (AESIs). These AEs have to be reported in real time (i.e., within 24 hours from the time of the knowledge of the event) using a study-specific rash questionnaire (Appendix B).

Maculopapular and other rash events are to be graded as follows (adapted from Common Terminology Criteria for Adverse Events [CTCAE] version 5.0):

Grade 1 Macules/papules covering < 10% body surface area (BSA) with or without symptoms (e.g., pruritis, burning, tightness).

Grade 2 Macules/papules covering 10% to 30% BSA with or without symptoms (e.g., pruritis, burning, tightness); or rash covering > 30% BSA with or without mild symptoms.

Grade 3 Macules/papules covering > 30% BSA with moderate or severe symptoms.

Note: To calculate the percent of BSA, estimate the area covered by the actual macules/papules and do not include the clear skin between them. Imagine the rash coverage as if all of the macules and papules

coalesce into a single area. A diagram showing the contribution of different body parts to BSA, helpful to calculate % BSA, can be found at: https://books.google.com/books?id=3vg8AgAAQBAJ&pg=PP118&lpg=PP118&dq=body+surface+area+calculation+rash+CTCAE+v+4&source=bl&ots=KDrEpHcWGM&sig=ACfU3U3b7vEteEqR7Z1nKhfAmgTwN2L8mw&hl=en&sa=X&ved=2ahUKEwic6KqltJPgAhVQdt8KHVJTBQYQ6AEwDHoECAAQAQ#v=onepage&q=body%20surface%20area%20calculation%20rash%20CTCAE%20v%204&f=false.

For rash Grade 3, treatment with study drug will be discontinued by the investigator (see Section 6.1 of the protocol).

The medical management of rash will be done at the discretion of the investigator. If the diagnosis is uncertain or if there is concern about a possible severe hypersensitivity reaction, the investigator may elect, at his or her discretion, to perform additional investigations to help define the rash, including but not restricted to a dermatologist or allergist consultation, a skin biopsy, or additional safety laboratories. Results of investigations (consultation reports, skin biopsies, laboratory test results, etc.) should be included with the source documents.

4.3 Reporting Adverse Events and Intercurrent Illnesses

In the event of an SAE, whether associated with study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the electronic data capture (EDC) system. SAEs that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE nonCRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

Email: PPDINDPharmacovigilance@abbvie.com
FAX to: +1 (847) 938-0660

For safety concerns, contact AbbVie's General Medicine Safety Team at:

General Medicine Safety Team
[redacted]
1 North Waukegan Road
North Chicago, Illinois 60064

Phone: +1 (847) 935-7577
Email: GPRD_SafetyManagement_Hormones@abbvie.com

For any subject safety concerns, please contact the physician listed below:

Primary Therapeutic Area Medical Director
MEDICAL CONTACT:
[redacted]
AbbVie Inc.
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Contact Information:

Office: [redacted]
Mobile: [redacted]
Fax: [redacted]
Email: [redacted]

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie Therapeutic Area Medical Director:

HOTLINE: +1 (973) 784-6402

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC.

5 COUNTRY-SPECIFIC REQUIREMENTS

5.1 SUSAR Reporting

AbbVie will be responsible for suspected unexpected serious adverse reactions (SUSAR) reporting for the investigational medicinal product (IMP) in accordance with global and local guidelines and Appendix A of the Investigator Brochure will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a DSUR reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

6 STUDY DRUG

6.1 Treatments Administered

In Part 1, the study drugs ABBV-3067 or placebo will be dispensed in the form of film-coated tablets, and the study drugs ABBV-2222 or placebo will be dispensed in the form of capsules at the visits listed in

Section 2.1. In Part 2, the study drugs ABBV-3067 or placebo and ABBV-2222 or placebo will be dispensed in the form of capsules at the visits listed in Section 2.1. Subjects will be instructed to take study drugs once daily at the same time in the morning every day within approximately 1 hour after a meal.

Dosing times for the Day 1 and Day 15 visits and for the 3 doses before the Day 15 and Day 29 visits will be captured in the source records and eCRFs, as specified in Section 3.5.

Study drug must not be dispensed unless the IRT system is contacted. Study drug may only be dispensed to subjects enrolled in the study through the IRT system. At the end of the Treatment Period or at the Premature Discontinuation visit, the site will contact the IRT system to provide visit date information and study drug return information for each kit.

6.2 Packaging and Labeling

All study drugs will be supplied in blister cards.

Each blister card will be labeled as required per country requirements.

The labels must remain affixed to the blister cards. All blank spaces should be completed by site staff prior to dispensing to subject.

Storage and Disposition of Study Drug

Study drugs must be stored at controlled room temperature (15° to 25°C/59° to 77°F).

The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or destroyed on site as appropriate.

6.3 Method of Assigning Subjects to Treatment Groups

This is a double-blind, placebo-controlled, dose-ranging study. Once assigned to a regimen, all eligible subjects will receive that same assigned dosage for up to 28 days (± 2 days).

At the Screening visit, all subjects will be assigned a unique subject number through the use of the IRT. For subjects who do not meet the study selection criteria, the site personnel must contact the IRT system and identify the subject as a screen failure.

Subjects who are enrolled will retain their subject number assigned at the screening visit throughout the study. Upon receipt of study drug, the site will acknowledge receipt in the IRT system.

User guidelines for IRT use will be made available separately.

6.4 Selection and Timing of Dose for Each Subject

Subjects will be randomly assigned to one of 8 regimens in Part 1 and to one of 5 regimens in Part 2.

Part 1

ABBV-3067 will be given alone or in combination with dose levels of ABBV-2222 for 28 days as Regimens A through H in Part 1.

Regimen	ABBV-3067	ABBV-2222
A	50 mg	Placebo
B	150 mg	Placebo
C	150 mg	10 mg
D	150 mg	30 mg
E	150 mg	100 mg
F	150 mg	200 mg
G	150 mg	300 mg
H	Placebo	Placebo

Part 2

Different dose levels of ABBV-3067 will be given in combination with ABBV-2222 for 28 days as Regimens I through M in Part 2.

Regimen	ABBV-3067	ABBV-2222
I	5 mg	TBD
J	15 mg	TBD
K	50 mg	TBD
L	150 mg	TBD
M	Placebo	Placebo

TBD = to be determined

The tablets or capsules as assigned will be dosed together once daily. All subjects should take all doses of study drug with food at approximately the same time in the morning each day.

The maximum dose of the ABBV-2222 administrated in this study will not exceed 300 mg per day. The maximum dose of ABBV-3067 administered in this study will not exceed 250 mg per day.

7 REFERENCES

1. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38.
2. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95 year age range: the global function 2012 equations: Report of the Global Lung Function

Initiative (GLI), ERS Task Force to establish improved lung function reference values. Eur Respir J. 2012;40(6):1324-43.

APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse events of special interest
ATS/ERS	American Thoracic Society/European Respiratory Society
BSA	Body surface area
CBC	Complete blood count
CF	Cystic fibrosis
CFTR	CF transmembrane conductance regulator
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
FEF_{25-75}	Forced expiratory flow at mid-lung capacity
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
GCP	Good Clinical Practice
HBsAg	Hepatitis B virus surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
hsCRP	High-sensitivity C-reactive protein
IMP	Investigational medicinal product
IRT	Interactive response technology
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
RSI	Reference safety information
SAE	Serious adverse event
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reactions
SwCl	Sweat chloride
TBD	To be determined

APPENDIX B. ADVERSE EVENT OF SPECIAL INTEREST RASH QUESTIONNAIRE

Part 1

Adverse Event Serial Number:	
Question	**Response**
Was the subject seen by a dermatologist or allergy specialist for this event?	No _____ Yes _____ Date ____/____/_____Findings _____ DD/MM/YYYY _____
Was the event treated?	☐ Yes *(If yes, treatment should be documented under "action taken" on AE CRF.)* _____ ☐ No
Was a skin biopsy performed?	☐ Yes *(If yes, please describe findings.)* _____ ☐ No
Does the PI think there is an alternative etiology?	☐ Yes *(If yes, please specify.)* _____ ☐ No

Continued on next page.

Was the rash localized or generalized?	☐ Localized ☐ Generalized Which body areas were involved? (e.g., whole body, scalp, ear, face, oral cavity, neck, chest, abdomen, upper back, lower back, arm, forearm, hand, inguinal region, genitalia, buttock, perineum, thigh, leg, foot)
Did the rash progress?	☐ Yes, How rash progressed: _____ Where rash progressed: _____ ☐ No

Specify type of rash below:	**Yes**	**No**	**Unknown**
Wheal?			
Nodule?			
Vesicule/Bulla?			
Scaling or exfoliating?			
Macular?			
Papular?			
Raised?			
Morbilliform?			
Flat?			
Confluent?			
Mucous membrane involvement?			
Ocular involvement?			
Petechial or purpuric?			
Urticarial (hives)?			
Pustule?			
Atrophy?			
Blisters?			

Part 2

Did the subject experience any of the following symptoms associated with the reported event?	**Yes**	**No**	**Unknown**
Pruritus?			
Fever (> 101.5 degrees F or 38.5 degrees C)?			
Headache?			
Joint pain/arthralgia?			
Neck stiffness?			
Lymphadenopathy?			
Hypotension?			
Angioedema?			
Bronchospasm and/or laryngeal edema?			
Rhinoconjunctivitis?			
Nausea, vomiting and/or diarrhea?			
Other			

Part 3

Were there any lab abnormalities associated with the event?	☐ Yes, specify _____ ☐ No
Did the subject experience any viral illness in the past month?	☐ Yes *(If yes, please update Medical History eCRF or Adverse Event eCRF as appropriate.)* _____ ☐ No
Did the subject have any recent contact/exposure with an irritant (foods, chemicals, medications)?	☐ Yes, specify _____ ☐ No
Does the subject have a family history of allergies?	☐ Yes, specify _____ ☐ No
Does the subject have a history of atopy?	☐ Yes, specify if anything made it worse or improved: _____ Describe: _____ Was there anything that made it better? _____ If yes, please describe: _____ ☐ No
Does the subject have medical history of skin disorders? *(Please add to Medical History eCRF as applicable.)*	☐ Yes ☐ No
Did the subject receive prior treatment for historical condition of skin disorder? *(Please add to Prior Procedure or Prior Concomitant Medication eCRF as applicable.)*	☐ Yes ☐ No