# Clinical trial results:
# A Phase 2 Study of Galicaftor/Navocaftor/ABBV-119 or Galicaftor/Navocaftor/ABBV-576 Combination Therapies in Subjects With Cystic Fibrosis Who Are Homozygous or Heterozygous for the F508del Mutation

## Summary

| | |
|---|---|
| EudraCT number | 2020-005805-25 |
| Trial protocol | BE HU NL |
| Global end of trial date | 05 June 2023 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 20 June 2024 |
| First version publication date | 20 June 2024 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | M19-771 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04853368 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | AbbVie Deutschland GmbH & Co. KG |
| Sponsor organisation address | AbbVie House, Vanwall Business Park, Vanwall Road, , Maidenhead, Berkshire, United Kingdom, SL6 4UB |
| Public contact | Global Medical Services, AbbVie, AbbVie Deutschland GmbH & Co. KG , 001 8006339110, abbvieclinicaltrials@abbvie.com |
| Scientific contact | Global Medical Services, AbbVie, AbbVie Deutschland GmbH & Co. KG , 001 8006339110, abbvieclinicaltrials@abbvie.com |

Notes:

### Paediatric regulatory details

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 05 June 2023 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 05 June 2023 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this study is to assess how safe and effective is the combination therapy of galicaftor/navocaftor/ABBV-119 or Galicaftor/Navocaftor/ABBV-576 in adult participants with CF who are homozygous or heterozygous for the F508del mutation in each arm.

Protection of trial subjects:

The investigator or his/her representative explained the nature of the study to the subject and answered all questions regarding this study. Subject and/or legal guardian/representative read and understood the information provided about the study and gave written permission.

| |
|---|
| Background therapy: - |
| Evidence for comparator: - |

| | |
|---|---|
| Actual start date of recruitment | 20 September 2021 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United States: 10 |
| Country: Number of subjects enrolled | Australia: 16 |
| Country: Number of subjects enrolled | Hungary: 7 |
| Country: Number of subjects enrolled | Netherlands: 3 |
| Country: Number of subjects enrolled | New Zealand: 8 |
| Country: Number of subjects enrolled | Slovakia: 4 |
| Worldwide total number of subjects | 48 |
| EEA total number of subjects | 14 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |

| | |
|---|---|
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 46 |
| From 65 to 84 years | 2 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Subjects were enrolled at 41 sites in 6 countries. Cohort 1 subjects (C1),
received galicaftor/navocaftor dual therapy for 28 days as a Run-in Period Cohort 1(d-29 to -1), followed by galicaftor/navocaftor/ABBV-119 triple therapy for 28 days as a Triple Combination Treatment Period.

### Pre-assignment

Screening details:

Subjects either homozygous or heterozygous for F508del mutation were placed in cohorts based on genotype and treatment status of ETI therapy. In Part 1, Cohort 1(d-29 to -1) (C1) completed g/n dual combo therapy for 28 days (d) and started Part 2. In Part 2, C1(d 1 – 29) and C2 received g/n/ABBV-119 triple combo, and C3 received g/n/ABBV-576 triple

### Period 1

| | |
|---|---|
| Period 1 title | Study Period (Days 1 to 29) (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Blinding implementation details:

Participants in Cohorts 1 and 3 will receive Open-label therapy. Participants in Cohorts 2 will receive Double-blinded therapy.
Part 1 of this study includes Cohort 1 (Day -29 to -1) Dual Combination Galicaftor + Navocaftor for F508del Homozygous (n=24).
Part 2 of this study includes Cohort 1 (Day 1 to 29) and Cohorts 2 and 3 (Day 1 to 29).

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | C1 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Homo |

Arm description:

F508del homozygous CF participants from Cohort 1(Day -29 to -1) who received Galicaftor/Navocaftor dual combination therapy followed by Galicaftor/Navocaftor/ABBV-119 triple combination therapy (Day 1- 29).

Galicaftor: 300 mg QD, Oral capsules
Navocaftor: 50 mg QD, Oral capsules
ABBV-119: 210 mg BID, Oral capsules

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Galicaftor |
| Investigational medicinal product code | |
| Other name | ABBV-2222 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Galicaftor: 300 mg QD, Oral capsules

| | |
|---|---|
| Investigational medicinal product name | Navocaftor |
| Investigational medicinal product code | |
| Other name | ABBV-3067 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Navocaftor: 50 mg QD, Oral capsules

| | |
|---|---|
| Investigational medicinal product name | ABBV-119 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

210 mg BID, Oral capsules

| | |
|---|---|
| **Arm title** | C2 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Hete |

Arm description:

F508del Heterozygous CF participants received Galicaftor/Navocaftor/ABBV-119 triple combination therapy (Day 1 - 29).

Galicaftor: 300 mg QD, Oral capsules
Navocaftor: 50 mg QD, Oral capsules
ABBV-119: 210 mg BID, Oral capsules

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Galicaftor |
| Investigational medicinal product code | |
| Other name | ABBV-2222 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Galicaftor: 300 mg QD, Oral capsules

| | |
|---|---|
| Investigational medicinal product name | Navocaftor |
| Investigational medicinal product code | |
| Other name | ABBV-3067 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Navocaftor: 50 mg QD, Oral capsules

| | |
|---|---|
| Investigational medicinal product name | ABBV-119 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

210 mg BID, Oral capsules

| | |
|---|---|
| **Arm title** | C2 (Day 1 - 29) Placebo F508del Heterozygous |

Arm description:

F508del Heterozygous CF participants received placebo (Day 1 - 29).
Placebo: Oral capsules

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Oral capsules

| | |
|---|---|
| **Arm title** | C3 (Day 1 - 29) Triple Combo G + N + ABBV-576 for F508del Homo |

Arm description:

F508del Homozygous CF participants received Galicaftor/Navocaftor/ABBV-576 triple combination

therapy
(Day 1 - 29).

Galicaftor: 300 mg QD, Oral capsules
Navocaftor: 50 mg QD, Oral capsules
ABBV-576: 5 mg QD, Oral capsules

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Galicaftor |
| Investigational medicinal product code | |
| Other name | ABBV-2222 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Galicaftor: 300 mg QD, Oral capsules

| | |
|---|---|
| Investigational medicinal product name | Navocaftor |
| Investigational medicinal product code | |
| Other name | ABBV-3067 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Navocaftor: 50 mg QD, Oral capsules

| | |
|---|---|
| Investigational medicinal product name | ABBV-576 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

ABBV-576: 5 mg QD, Oral capsules

| | |
|---|---|
| **Arm title** | C3 (Day 1 - 29) Triple Combo G + N + ABBV-576 for F508del Hete |

Arm description:

F508del Heterozygous CF participants received Galicaftor/Navocaftor/ABBV-576 triple combination therapy (Day 1 - 29).

Galicaftor: 300 mg QD, Oral capsules
Navocaftor: 50 mg QD, Oral capsules
ABBV-576: 5 mg QD, Oral capsules

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Galicaftor |
| Investigational medicinal product code | |
| Other name | ABBV-2222 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Galicaftor: 300 mg QD, Oral capsules

| | |
|---|---|
| Investigational medicinal product name | Navocaftor |
| Investigational medicinal product code | |
| Other name | ABBV-3067 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Navocaftor: 50 mg QD, Oral capsules

| | |
|---|---|
| Investigational medicinal product name | ABBV-576 |
| Investigational medicinal product code | |
| Other name | |

| | |
|---|---|
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

ABBV-576: 5 mg QD, Oral capsules

| **Number of subjects in period 1** | C1 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Homo | C2 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Hete | C2 (Day 1 - 29) Placebo F508del Heterozygous |
|---|---|---|---|
| Started | 24 | 9 | 4 |
| Completed | 22 | 9 | 4 |
| Not completed | 2 | 0 | 0 |
| Consent withdrawn by subject | - | - | - |
| other | 2 | - | - |

| **Number of subjects in period 1** | C3 (Day 1 - 29) Triple Combo G + N + ABBV-576 for F508del Homo | C3 (Day 1 - 29) Triple Combo G + N + ABBV-576 for F508del Hete |
|---|---|---|
| Started | 9 | 2 |
| Completed | 8 | 2 |
| Not completed | 1 | 0 |
| Consent withdrawn by subject | 1 | - |
| other | - | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | C1 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Homo |

Reporting group description:

F508del homozygous CF participants from Cohort 1(Day -29 to -1) who received Galicaftor/Navocaftor dual combination therapy followed by Galicaftor/Navocaftor/ABBV-119 triple combination therapy (Day 1- 29).

Galicaftor: 300 mg QD, Oral capsules
Navocaftor: 50 mg QD, Oral capsules
ABBV-119: 210 mg BID, Oral capsules

| Reporting group title | C2 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Hete |
|---|---|

Reporting group description:

F508del Heterozygous CF participants received Galicaftor/Navocaftor/ABBV-119 triple combination therapy (Day 1 - 29).

Galicaftor: 300 mg QD, Oral capsules
Navocaftor: 50 mg QD, Oral capsules
ABBV-119: 210 mg BID, Oral capsules

| Reporting group title | C2 (Day 1 - 29) Placebo F508del Heterozygous |
|---|---|

Reporting group description:

F508del Heterozygous CF participants received placebo (Day 1 - 29).
Placebo: Oral capsules

| Reporting group title | C3 (Day 1 - 29) Triple Combo G + N + ABBV-576 for F508del Homo |
|---|---|

Reporting group description:

F508del Homozygous CF participants received Galicaftor/Navocaftor/ABBV-576 triple combination therapy
(Day 1 - 29).

Galicaftor: 300 mg QD, Oral capsules
Navocaftor: 50 mg QD, Oral capsules
ABBV-576: 5 mg QD, Oral capsules

| Reporting group title | C3 (Day 1 - 29) Triple Combo G + N + ABBV-576 for F508del Hete |
|---|---|

Reporting group description:

F508del Heterozygous CF participants received Galicaftor/Navocaftor/ABBV-576 triple combination therapy (Day 1 - 29).

Galicaftor: 300 mg QD, Oral capsules
Navocaftor: 50 mg QD, Oral capsules
ABBV-576: 5 mg QD, Oral capsules

| Reporting group values | C1 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Homo | C2 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Hete | C2 (Day 1 - 29) Placebo F508del Heterozygous |
|---|---|---|---|
| Number of subjects | 24 | 9 | 4 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 33.5 | 35.2 | 30.0 |
| standard deviation | ± 8.80 | ± 11.09 | ± 10.55 |

| | | | |
|---|---|---|---|
| Gender categorical<br>Units: Subjects | | | |
| Female | 9 | 3 | 1 |
| Male | 15 | 6 | 3 |
| Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) (%) at Baseline (Day 1) | | | |
| FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. | | | |
| Units: percent predicted FEV1 (%) | | | |
| arithmetic mean | 57.0 | 62.9 | 67.3 |
| standard deviation | ± 14.63 | ± 18.27 | ± 19.97 |
| Sweat Chloride (SwCl) in mmol/L at Baseline (Day 1) Cohort 3<br>Units: mmol/L | | | |
| arithmetic mean | 76.71 | 93.61 | 98.38 |
| standard deviation | ± 13.127 | ± 12.437 | ± 9.978 |

| **Reporting group values** | C3 (Day 1 - 29) Triple Combo G + N + ABBV-576 for F508del Homo | C3 (Day 1 - 29) Triple Combo G + N + ABBV-576 for F508del Hete | Total |
|---|---|---|---|
| Number of subjects | 9 | 2 | 48 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 34.4 | 37.0 | |
| standard deviation | ± 7.84 | ± 5.66 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 2 | 2 | 17 |
| Male | 7 | 0 | 31 |
| Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) (%) at Baseline (Day 1) | | | |
| FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. | | | |
| Units: percent predicted FEV1 (%) | | | |
| arithmetic mean | 57.0 | 51.0 | |
| standard deviation | ± 19.77 | ± 5.66 | - |
| Sweat Chloride (SwCl) in mmol/L at Baseline (Day 1) Cohort 3<br>Units: mmol/L | | | |
| arithmetic mean | 42.94 | 26.50 | |
| standard deviation | ± 10.333 | ± 4.950 | - |

## End points

### End points reporting groups

| Reporting group title | C1 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Homo |
|---|---|

Reporting group description:

F508del homozygous CF participants from Cohort 1(Day -29 to -1) who received Galicaftor/Navocaftor dual combination therapy followed by Galicaftor/Navocaftor/ABBV-119 triple combination therapy (Day 1- 29).

Galicaftor: 300 mg QD, Oral capsules
Navocaftor: 50 mg QD, Oral capsules
ABBV-119: 210 mg BID, Oral capsules

| Reporting group title | C2 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Hete |
|---|---|

Reporting group description:

F508del Heterozygous CF participants received Galicaftor/Navocaftor/ABBV-119 triple combination therapy (Day 1 - 29).

Galicaftor: 300 mg QD, Oral capsules
Navocaftor: 50 mg QD, Oral capsules
ABBV-119: 210 mg BID, Oral capsules

| Reporting group title | C2 (Day 1 - 29) Placebo F508del Heterozygous |
|---|---|

Reporting group description:

F508del Heterozygous CF participants received placebo (Day 1 - 29).
Placebo: Oral capsules

| Reporting group title | C3 (Day 1 - 29) Triple Combo G + N + ABBV-576 for F508del Homo |
|---|---|

Reporting group description:

F508del Homozygous CF participants received Galicaftor/Navocaftor/ABBV-576 triple combination therapy
(Day 1 - 29).

Galicaftor: 300 mg QD, Oral capsules
Navocaftor: 50 mg QD, Oral capsules
ABBV-576: 5 mg QD, Oral capsules

| Reporting group title | C3 (Day 1 - 29) Triple Combo G + N + ABBV-576 for F508del Hete |
|---|---|

Reporting group description:

F508del Heterozygous CF participants received Galicaftor/Navocaftor/ABBV-576 triple combination therapy (Day 1 - 29).

Galicaftor: 300 mg QD, Oral capsules
Navocaftor: 50 mg QD, Oral capsules
ABBV-576: 5 mg QD, Oral capsules

### Primary: Cohorts 1 and 2: Absolute Change From Baseline Through Day 29 in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1)

| End point title | Cohorts 1 and 2: Absolute Change From Baseline Through Day 29 in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1)[1] |
|---|---|

End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration and is used as a measure of lung function. Mixed-effect model with repeated measures (MMRM) was used for the analyses.

| End point type | Primary |
|---|---|

End point timeframe:

Day 1 (Baseline) through Day 29

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The arms as shown are aligned with the sub study and planned analysis population for this end point per protocol and statistical analysis plan.

| **End point values** | C1 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Homo | C2 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Hete | C2 (Day 1 - 29) Placebo F508del Heterozygous | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 20[2] | 7[3] | 4 | |
| Units: percent predicted FEV1 (%ppFEV1) | | | | |
| arithmetic mean (standard deviation) | 2.2 (± 3.68) | 2.6 (± 5.62) | -2.0 (± 6.63) | |

Notes:

[2] - 2-sided CI was calculated as 90% and 1.22 to 4.04 CI

[3] - 2-sided CI was calculated as 90% and -2.07 to 4.67 CI

| **Attachments (see zip file)** | C1 Absolute Change From Baseline in ppFEV1/C1 Absolute<br>C2 Absolute Change From Baseline in ppFEV1/C2 Absolute |
|---|---|

### Statistical analyses

| **Statistical analysis title** | C2 + PBO Absolute Change From Baseline in ppFEV1 |
|---|---|
| Comparison groups | C2 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Hete v C2 (Day 1 - 29) Placebo F508del Heterozygous |
| Number of subjects included in analysis | 11 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[4] |
| P-value | = 0.402 [5] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.9 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -5.07 |
| upper limit | 6.77 |

Notes:

[4] - Primary analysis of ppFEV1 using MMRM excludes data inconsistent with baseline in terms of the timing of bronchodilator or airway clearance regimen.
[5] - One-sided p-value; p-value <=0.05 indicates significance

## Primary: Cohort 3: Absolute Change From Baseline Through Day 29 in Sweat Chloride (SwCl) in mmol/L

| End point title | Cohort 3: Absolute Change From Baseline Through Day 29 in Sweat Chloride (SwCl) in mmol/L[6][7] |
|---|---|

End point description:

Sweat collection was performed to evaluate sweat chloride concentration. SwCl is a biomarker of cystic fibrosis transmembrane conductance regulator (CFTR) activity. Persons with CF have higher levels of

chloride in their sweat.
MMRM was used for the analysis.

| End point type | Primary |
|---|---|

End point timeframe:

Day 1 (Baseline) through Day 29

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The arms as shown are aligned with the sub study and planned analysis population for this end point per protocol and statistical analysis plan.
[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The arms as shown are aligned with the sub study and planned analysis population for this end point per protocol and statistical analysis plan.

| **End point values** | C3 (Day 1 - 29) Triple Combo G + N + ABBV-576 for F508del Homo | C3 (Day 1 - 29) Triple Combo G + N + ABBV-576 for F508del Hete | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1 | 1 | | |
| Units: mmol/L | | | | |
| arithmetic mean (full range (min-max)) | 24 (24 to 24) | 40 (40 to 40) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Cohorts 1 and 2: Absolute Change From Baseline Through Day 29 in Sweat Chloride (SwCl) in mmol/L

| End point title | Cohorts 1 and 2: Absolute Change From Baseline Through Day 29 in Sweat Chloride (SwCl) in mmol/L[8] |
|---|---|

End point description:

Sweat collection was performed to evaluate sweat chloride concentration. SwCl is a biomarker of CFTR activity.
Persons with CF have higher levels of chloride in their sweat. MMRM was used for the analysis.

| End point type | Secondary |
|---|---|

End point timeframe:

Day 1 (Baseline) through Day 29

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The arms as shown are aligned with the sub study and planned analysis population for this end point per protocol and statistical analysis plan.

| **End point values** | C1 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Homo | C2 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Hete | C2 (Day 1 - 29) Placebo F508del Heterozygous | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 20[9] | 7 | 4 | |
| Units: mmol/L | | | | |

| | | | | |
|---|---|---|---|---|
| arithmetic mean (standard deviation) | 5.7 (± 10.78) | -11.5 (± 16.61) | 2.5 (± 4.56) | |

Notes:

[9] - 2-sided CI was calculated as 90% and 1.07 to 9.92 CI

| | |
|---|---|
| **Attachments (see zip file)** | C1 Absolute Change From Baseline in Sweat Chloride/C1 |

**Statistical analyses**

| **Statistical analysis title** | C2+ PBO Abs Change From Baseline in Sweat Chloride |
|---|---|
| Comparison groups | C2 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Hete v C2 (Day 1 - 29) Placebo F508del Heterozygous |
| Number of subjects included in analysis | 11 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.043 [10] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -14.1 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -27.59 |
| upper limit | -0.62 |

Notes:

[10] - One-sided p-value; p-value <=0.05 indicates significance.

**Secondary: Absolute Change From Baseline Through Day 29 in Forced Vital Capacity (FVC)**

| End point title | Absolute Change From Baseline Through Day 29 in Forced Vital Capacity (FVC) |
|---|---|

End point description:

FVC is the total amount of air exhaled during forced expiratory volume (FEV) test and is a lung function test that is measured during spirometry. MMRM was used for the analyses.

| End point type | Secondary |
|---|---|

End point timeframe:

Day 1 (Baseline) through Day 29

| **End point values** | C1 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Homo | C2 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Hete | C2 (Day 1 - 29) Placebo F508del Heterozygous | C3 (Day 1 - 29) Triple Combo G + N + ABBV-576 for F508del Homo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 20[11] | 7[12] | 4 | 3 |
| Units: Liters (L) | | | | |
| arithmetic mean (standard deviation) | 0.10 (± 0.256) | 0.05 (± 0.269) | -0.07 (± 0.297) | -0.22 (± 0.318) |

Notes:

[11] - 2-sided CI was calculated as 90% and 0.059 to 0.219 CI

[12] - 2-sided CI was calculated as 90% and -0.162 to 0.150 CI

| **End point values** | C3 (Day 1 - 29) Triple Combo G + N + ABBV-576 for F508del Hete | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 1[13] | | | |
| Units: Liters (L) | | | | |
| arithmetic mean (standard deviation) | -0.28 (± 9999) | | | |

Notes:

[13] - SD not applicable; value could not be estimated due to n=1

| **Attachments (see zip file)** | C1 Absolute Change From Baseline in FVC/C1 Absolute Change<br>C2 Abs Change From Baseline Through Day 29 in FVC/C2 Abs |
|---|---|

### Statistical analyses

| **Statistical analysis title** | C2 + PBO Abs Change From BL Through Day 29 in FVC |
|---|---|
| Comparison groups | C2 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Hete v C2 (Day 1 - 29) Placebo F508del Heterozygous |
| Number of subjects included in analysis | 11 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.352 [14] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.06 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -0.332 |
| upper limit | 0.212 |

Notes:

[14] - One-sided p-value; p-value <=0.05 indicates significance.

### Secondary: Absolute Change From Baseline Through Day 29 in Forced Expiratory Flow at Mid-Lung Capacity (FEF25-75)

| End point title | Absolute Change From Baseline Through Day 29 in Forced Expiratory Flow at Mid-Lung Capacity (FEF25-75) |
|---|---|

End point description:

FEF25-75 is a lung function test that is measured during spirometry, and is defined as the forced expiratory flow between 25% and 75% of vital capacity (mid-lung capacity). MMRM was used for analyses.

| End point type | Secondary |
|---|---|

End point timeframe:

Day 1 (Baseline) through Day 29

| End point values | C1 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Homo | C2 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Hete | C2 (Day 1 - 29) Placebo F508del Heterozygous | C3 (Day 1 - 29) Triple Combo G + N + ABBV-576 for F508del Homo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 20[15] | 7[16] | 4 | 3 |
| Units: Liters/second (L/sec) | | | | |
| arithmetic mean (standard deviation) | 0.067 (± 0.2038) | 0.134 (± 0.2506) | -0.082 (± 0.1947) | -0.329 (± 0.378) |

Notes:

[15] - 2-sided CI was calculated as 90% and 0.0209 to 0.1568 CI

[16] - 2-sided CI was calculated as 90% and -0.1814 to 0.2880 CI

| End point values | C3 (Day 1 - 29) Triple Combo G + N + ABBV-576 for F508del Hete | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 1[17] | | | |
| Units: Liters/second (L/sec) | | | | |
| arithmetic mean (standard deviation) | -0.263 (± 9999) | | | |

Notes:

[17] - SD not applicable; value could not be estimated due to n=1

| Attachments (see zip file) | C1 Abs Change From BL through Day 29 in FEF25-75/C1 Abs<br>C2 Abs Change From BL Through Day 29 in FEF25-75/C2 Abs |
|---|---|

## Statistical analyses

| Statistical analysis title | C2+PBO Abs Change From BL Through D29 in FEF25-75 |
|---|---|
| Statistical analysis description:<br>Cohort 2 (Day 1 - 29) Triple Combination Galicaftor+ Navocaftor + ABBV-119 for F508del Heterozygous, Cohort 2 (Day 1 - 29) Placebo F508del Heterozygous | |
| Comparison groups | C2 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Hete v C2 (Day 1 - 29) Placebo F508del Heterozygous |
| Number of subjects included in analysis | 11 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[18] |
| P-value | = 0.23 [19] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.136 |

| Confidence interval | |
|---|---|
| level | 90 % |
| sides | 2-sided |
| lower limit | -0.1809 |
| upper limit | 0.4527 |

Notes:

[18] - The LS mean is estimated using the mixed-Effect model repeat measurement method.

[19] - One-sided p-value; p-value <=0.05 indicates significance

## Secondary: Relative Changes From Baseline Through Day 29 in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1)

| End point title | Relative Changes From Baseline Through Day 29 in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) |
|---|---|

End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration and is used as a measure of lung function. MMRM was used for the analyses. Note: The primary analysis of ppFEV1 using MMRM excludes data that are inconsistent with baseline in terms of the timing of bronchodilator or airway clearance regimen.

| End point type | Secondary |
|---|---|

End point timeframe:

Day 1 (Baseline) through Day 29

| **End point values** | C1 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Homo | C2 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Hete | C2 (Day 1 - 29) Placebo F508del Heterozygous | C3 (Day 1 - 29) Triple Combo G + N + ABBV-576 for F508del Homo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 20[20] | 7[21] | 4 | 3 |
| Units: % ppFEV1 | | | | |
| arithmetic mean (standard deviation) | 3.8 (± 6.07) | 3.3 (± 8.15) | -4.9 (± 12.25) | -9.1 (± 5.12) |

Notes:

[20] - 2-sided CI was calculated as 90% and 2.04 to 6.78 CI

[21] - 2-sided CI was calculated as 90% and -4.42 to 6.97 CI

| **End point values** | C3 (Day 1 - 29) Triple Combo G + N + ABBV-576 for F508del Hete | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 1[22] | | | |
| Units: % ppFEV1 | | | | |
| arithmetic mean (standard deviation) | -19.1 (± 99999) | | | |

Notes:

[22] - SD not applicable; value could not be estimated due to n=1

| **Attachments (see zip file)** | C1 Relative Changes From Baseline in ppFEV1/C1 Relative<br>C2 Relative Changes From Baseline in ppFEV1/C2 Relative |
|---|---|

**Statistical analyses**

| **Statistical analysis title** | C2 + PBO Relative Changes From Baseline in ppFEV1 |
|---|---|

Statistical analysis description:

Cohort 2(Day 1 - 29) Triple Combination Galicaftor+ Navocaftor + ABBV-119 for F508del Heterozygous, Cohort 2 (Day 1 - 29) Placebo F508del Heterozygous

| | |
|---|---|
| Comparison groups | C2 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Hete v C2 (Day 1 - 29) Placebo F508del Heterozygous |
| Number of subjects included in analysis | 11 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.412 [23] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.3 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -8.75 |
| upper limit | 11.34 |

Notes:

[23] - Comments One-sided p-value; p-value <=0.05 indicates significance.

**Secondary: Relative Changes From Baseline Through Day 29 in Forced Vital Capacity (FVC)**

| End point title | Relative Changes From Baseline Through Day 29 in Forced Vital Capacity (FVC) |
|---|---|

End point description:

FVC is the total amount of air exhaled during FEV test and is a lung function test that is measured during spirometry.
MMRM was used for the analyses.

| End point type | Secondary |
|---|---|

End point timeframe:

Day 1 (Baseline) through Day 29

| **End point values** | C1 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Homo | C2 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Hete | C2 (Day 1 - 29) Placebo F508del Heterozygous | C3 (Day 1 - 29) Triple Combo G + N + ABBV-576 for F508del Homo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 20[24] | 7[25] | 4 | 3 |
| Units: Liters (L) | | | | |
| arithmetic mean (standard deviation) | 3.75 (± 7.006) | 1.07 (± 6.524) | -2.06 (± 8.004) | -6.01 (± 8.782) |

Notes:

[24] - 2-sided CI was calculated as 90% and 2.190 to 6.524 CI

[25] - 2-sided CI was calculated as 90% and -4.449 to 3.268 CI

| **End point values** | C3 (Day 1 - 29) Triple Combo G + N | | | |
|---|---|---|---|---|

| | + ABBV-576 for F508del Hete | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 1[26] | | | |
| Units: Liters (L) | | | | |
| arithmetic mean (standard deviation) | -16.91 (± 99999) | | | |

Notes:

[26] - SD value could not be estimated due to n=1

| **Attachments (see zip file)** | C1 Relative Changes From Baseline in FVC/C1 Relative Changes<br>C2 Relative Changes From Baseline in FVC/C2 Relative Changes |
|---|---|

**Statistical analyses**

| **Statistical analysis title** | C2 + PBO Relative Changes From Baseline in FVC |
|---|---|

Statistical analysis description:

Cohort 2(Day 1 - 29) Triple Combination Galicaftor+ Navocaftor + ABBV-119 for F508del Heterozygous, Cohort 2 (Day 1 - 29) Placebo for F508del Heterozygous

| Comparison groups | C2 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Hete v C2 (Day 1 - 29) Placebo F508del Heterozygous |
|---|---|
| Number of subjects included in analysis | 11 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.305 [27] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -2 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -8.724 |
| upper limit | 4.732 |

Notes:

[27] - One-sided p-value; p-value <=0.05 indicates significance.

**Secondary: Relative Changes From Baseline Through Day 29 in Forced Expiratory Flow at Mid-Lung Capacity (FEF25-75)**

| End point title | Relative Changes From Baseline Through Day 29 in Forced Expiratory Flow at Mid-Lung Capacity (FEF25-75) |
|---|---|

End point description:

FEF25-75 is a lung function test that is measured during spirometry, and is defined as the forced expiratory flow between 25% and 75% of vital capacity (mid-lung capacity). MMRM was used for analyses.

| End point type | Secondary |
|---|---|

End point timeframe:

Day 1 (Baseline) through Day 29

| End point values | C1 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Homo | C2 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Hete | C2 (Day 1 - 29) Placebo F508del Heterozygous | C3 (Day 1 - 29) Triple Combo G + N + ABBV-576 for F508del Homo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 20[28] | 7[29] | 4 | 3 |
| Units: Liters/second (L/sec) | | | | |
| arithmetic mean (standard deviation) | 4.553 (± 13.2453) | 8.701 (± 12.9781) | -6.449 (± 25.1954) | -8.288 (± 24.409) |

Notes:

[28] - 2-sided CI was calculated as 90% and 1.4443 to 11.5056 CI

[29] - 2-sided CI was calculated as 90% and -7.1464 to 19.1844 CI

| End point values | C3 (Day 1 - 29) Triple Combo G + N + ABBV-576 for F508del Hete | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 1[30] | | | |
| Units: Liters/second (L/sec) | | | | |
| arithmetic mean (standard deviation) | -25.784 (± 99999) | | | |

Notes:

[30] - SD value could not be estimated due to n=1

| Attachments (see zip file) | C1 Relative Change from BL through D29 in FEF25-75/C1<br>C2 Relative Change from BL through D29 in FEF25-75/C2 |
|---|---|

## Statistical analyses

| Statistical analysis title | C2+PBO Rel Change from BL through D29 in FEF25-75 |
|---|---|
| Statistical analysis description: | |
| Cohort 2(Day 1 - 29) Triple Combination Galicaftor+ Navocaftor + ABBV-119 for F508del Heterozygous, Cohort 2 (Day 1 - 29) Placebo for F508del Heterozygous | |
| Comparison groups | C2 (Day 1 - 29) Placebo F508del Heterozygous v C2 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Hete |
| Number of subjects included in analysis | 11 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.286 [31] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 7.29 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -15.186 |
| upper limit | 29.766 |

Notes:

[31] - One-sided p-value; p-value <=0.05 indicates significance.

## Secondary: Absolute Change in CF Questionnaire-Revised (CFQ-R) Respiratory Domain Score From Baseline.

| End point title | Absolute Change in CF Questionnaire-Revised (CFQ-R) Respiratory Domain Score From Baseline. |
|---|---|

End point description:

The CF Questionnaire-Revised (CFQ-R) Respiratory Domain Score is designed for use in participants with a diagnosis of cystic fibrosis and is designed to measure impact on overall health, daily life, perceived well-being, and symptoms. CFQ-R has a total of 50 questions. Questions 40, 41, 42, 44, 45, 46, scored 1, 2, 3, or 4, from worst to best, were used to calculate the respiratory domain score. The scaled score for the domain is calculated as 100 × (mean scores of all non-missing questions – 1) / 3, ranging from 0 to 100. If more than 3 questions in the domain have missing scores, the scaled score was set as missing. Note: The LS mean is estimated using the linear regression on the change in CFQ-R from baseline to day 29.

| End point type | Secondary |
|---|---|

End point timeframe:

Day 1 (Baseline) through Day 29

| **End point values** | C1 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Homo | C2 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Hete | C2 (Day 1 - 29) Placebo F508del Heterozygous | C3 (Day 1 - 29) Triple Combo G + N + ABBV-576 for F508del Homo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 19[32] | 7[33] | 4 | 3 |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | 5.56 (± 15.930) | 10.32 (± 19.092) | -5.56 (± 21.754) | -9.26 (± 22.453) |

Notes:

[32] - 2-sided CI was calculated as 90% and -0.26 to 11.37 CI

[33] - 2-sided CI was calculated as 90% and -2.18 to 19.40 CI

| **End point values** | C3 (Day 1 - 29) Triple Combo G + N + ABBV-576 for F508del Hete | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 1[34] | | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | -22.22 (± 99999) | | | |

Notes:

[34] - ] value could not be estimated due to n=1

| **Attachments (see zip file)** | C1 Absolute Change in CFQ-R Score From Baseline/C1 Absolute<br>C2 Absolute Change in CFQ-R Score From Baseline/C2 Absolute |
|---|---|

### Statistical analyses

| **Statistical analysis title** | C2 + PBO Abs Change in CFQ-R Score From Baseline |
|---|---|

Statistical analysis description:

Cohort 2(Day 1 - 29) Triple Combination Galicaftor+ Navocaftor + ABBV-119 for F508del Heterozygous, Cohort 2 (Day 1 - 29) Placebo for F508del Heterozygous

| | |
|---|---|
| Comparison groups | C2 (Day 1 - 29) Placebo F508del Heterozygous v C2 (Day 1 - 29) Triple Combo G + N + ABBV-119 for F508del Hete |
| Number of subjects included in analysis | 11 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.142 [35] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 11.2 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -6.9 |
| upper limit | 29.25 |

Notes:

[35] - One-sided p-value; p-value <=0.05 indicates significance.

## Secondary: Cohorts 3: Absolute Change From Baseline Through Day 29 in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1)

| | |
|---|---|
| End point title | Cohorts 3: Absolute Change From Baseline Through Day 29 in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1)[36] |

End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration and is used as a measure of lung function. MMRM was used for the analyses. Note: The primary analysis of ppFEV1 using MMRM excludes data that are inconsistent with baseline in terms of the timing of bronchodilator or airway clearance regimen.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Day 1 (Baseline) through Day 29

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The arms as shown are aligned with the sub study and planned analysis population for this end point per protocol and statistical analysis plan.

| **End point values** | C3 (Day 1 - 29) Triple Combo G + N + ABBV-576 for F508del Homo | C3 (Day 1 - 29) Triple Combo G + N + ABBV-576 for F508del Hete | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 | 1 | | |
| Units: % ppFEV1 | | | | |
| arithmetic mean (full range (min-max)) | -5.7 (-9.0 to -3.0) | -9.0 (-9.0 to -9.0) | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All-cause mortality is reported from enrollment to the end of study, median time on follow up in Part 1 was 28d for C1. In Part 2, was 28d for C1; 28, 28d for C2;14, 20.5, and 14d for C3. AEs were collected from first dose until 30d after last dose.

Adverse event reporting additional description:

For Cohort 1 - Triple Combination Treatment arm, a TEAE was collected through day 56 and within 30 days after the last dose of study drug.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 26.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Cohort_1_Dual_Run-in_Galicaftor_Navocaftor_Homozygous |
| Reporting group description: - | |
| Reporting group title | Cohort_1_Triple_Galicaftor_Navocaftor_ABBV-119_Homozygous |
| Reporting group description: - | |
| Reporting group title | Cohort_3_Triple_Galicaftor_Navocaftor_ABBV-576_Heterozygous |
| Reporting group description: - | |
| Reporting group title | Cohort_2_Placebo_Heterozygous |
| Reporting group description: - | |
| Reporting group title | Cohort_3_Triple_Galicaftor_Navocaftor_ABBV-576_Homozygous |
| Reporting group description: - | |
| Reporting group title | Cohort_2_Triple_Galicaftor_Navocaftor_ABBV-119_Heterozygous |

Reporting group description: -

| Serious adverse events | Cohort_1_Dual_Run-in_Galicaftor_Navocaftor_Homozygous | Cohort_1_Triple_Galicaftor_Navocaftor_ABBV-119_Homozygous | Cohort_3_Triple_Galicaftor_Navocaftor_ABBV-576_Heterozygous |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 24 (4.17%) | 0 / 2 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Congenital, familial and genetic disorders | | | |
| CYSTIC FIBROSIS | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 24 (4.17%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |

| | | | |
|---|---|---|---|
| GENERAL PHYSICAL HEALTH DETERIORATION | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 24 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| INFECTIVE EXACERBATION OF BRONCHIECTASIS | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 24 (0.00%) | 0 / 2 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Cohort_2_Placebo_Heterozygous | Cohort_3_Triple_Galicaftor_Navocaftor_ABBV-576_Homozygous | Cohort_2_Triple_Galicaftor_Navocaftor_ABBV-119_Heterozygous |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 9 (11.11%) | 0 / 9 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Congenital, familial and genetic disorders | | | |
| CYSTIC FIBROSIS | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| GENERAL PHYSICAL HEALTH DETERIORATION | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 9 (11.11%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| INFECTIVE EXACERBATION OF BRONCHIECTASIS | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 9 (11.11%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | Cohort_1_Dual_Run-in_Galicaftor_Navocaftor_Homozygous | Cohort_1_Triple_Galicaftor_Navocaftor_ABBV-119_Homozygous | Cohort_3_Triple_Galicaftor_Navocaftor_ABBV-576_Heterozygous |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 4 / 24 (16.67%) | 10 / 24 (41.67%) | 2 / 2 (100.00%) |
| Investigations | | | |
| SPIROMETRY ABNORMAL | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 24 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| FORCED VITAL CAPACITY DECREASED | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 24 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| FORCED EXPIRATORY VOLUME DECREASED | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 24 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| NASAL INJURY | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 24 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| HEADACHE | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 2 / 24 (8.33%) | 0 / 2 (0.00%) |
| occurrences (all) | 1 | 5 | 0 |
| LETHARGY | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 24 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| POST-TRAUMATIC HEADACHE | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 24 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| FATIGUE | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 2 / 24 (8.33%) | 0 / 2 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| INFLUENZA LIKE ILLNESS | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 24 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| CHEST DISCOMFORT | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 0 / 24 (0.00%) | 1 / 2 (50.00%) |
| occurrences (all) | 1 | 0 | 1 |
| NON-CARDIAC CHEST PAIN | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 24 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| PAIN | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 24 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| ABDOMINAL PAIN LOWER | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 24 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| CONSTIPATION | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 24 (4.17%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| DIARRHOEA | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 2 / 24 (8.33%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| DYSPEPSIA | | | |
| subjects affected / exposed | 2 / 24 (8.33%) | 1 / 24 (4.17%) | 0 / 2 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| DISTAL INTESTINAL OBSTRUCTION SYNDROME | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 24 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| ABDOMINAL PAIN UPPER | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 2 / 24 (8.33%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| VOMITING | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 24 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| STEATORRHOEA | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 24 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| NAUSEA | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 24 (0.00%) | 1 / 2 (50.00%) |
| occurrences (all) | 0 | 0 | 1 |
| FLATULENCE | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 24 (4.17%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| GASTROOESOPHAGEAL REFLUX DISEASE | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 2 / 24 (8.33%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| RESPIRATORY TRACT CONGESTION | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 24 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| CATARRH | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 24 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| COUGH | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 24 (4.17%) | 2 / 2 (100.00%) |
| occurrences (all) | 0 | 1 | 2 |
| DYSPNOEA | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 24 (0.00%) | 2 / 2 (100.00%) |
| occurrences (all) | 0 | 0 | 2 |
| DYSPNOEA EXERTIONAL | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 24 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| EPISTAXIS | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 24 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| HAEMOPTYSIS | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 24 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| UPPER-AIRWAY COUGH SYNDROME | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 24 (0.00%) | 1 / 2 (50.00%) |
| occurrences (all) | 0 | 0 | 1 |
| SPUTUM INCREASED | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 2 / 24 (8.33%) | 1 / 2 (50.00%) |
| occurrences (all) | 0 | 2 | 1 |
| RHINORRHOEA | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 24 (0.00%) | 1 / 2 (50.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| NIGHT SWEATS | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 24 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| RASH | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 2 / 24 (8.33%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| BACK PAIN | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 24 (4.17%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infections and infestations | | | |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | 0 / 24 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 24 (0.00%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 4 / 24 (16.67%) | 0 / 2 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Metabolism and nutrition disorders | | | |
| DECREASED APPETITE | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 24 (4.17%) | 1 / 2 (50.00%) |
| occurrences (all) | 0 | 1 | 1 |

| **Non-serious adverse events** | Cohort_2_Placebo_Heterozygous | Cohort_3_Triple_Galicaftor_Navocaftor_A | Cohort_2_Triple_Galicaftor_Navocaftor_ |
|---|---|---|---|

| | | BBV-576_Homozygous | ABBV-119_Heterozygous |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | 7 / 9 (77.78%) | 4 / 9 (44.44%) |
| Investigations | | | |
| SPIROMETRY ABNORMAL | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| FORCED VITAL CAPACITY DECREASED | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| FORCED EXPIRATORY VOLUME DECREASED | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| NASAL INJURY | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 9 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Nervous system disorders | | | |
| HEADACHE | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 9 (11.11%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| LETHARGY | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 9 (11.11%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| POST-TRAUMATIC HEADACHE | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 9 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| General disorders and administration site conditions | | | |
| FATIGUE | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 9 (11.11%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| INFLUENZA LIKE ILLNESS | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| CHEST DISCOMFORT | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 9 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| NON-CARDIAC CHEST PAIN | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 9 (11.11%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| PAIN | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 9 (11.11%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastrointestinal disorders | | | |
| ABDOMINAL PAIN LOWER | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 9 (11.11%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| CONSTIPATION | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 9 (11.11%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| DIARRHOEA | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| DYSPEPSIA | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| DISTAL INTESTINAL OBSTRUCTION SYNDROME | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 9 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| ABDOMINAL PAIN UPPER | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| VOMITING | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| STEATORRHOEA | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 9 (11.11%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| NAUSEA | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| FLATULENCE | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 9 (11.11%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| GASTROOESOPHAGEAL REFLUX DISEASE | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| RESPIRATORY TRACT CONGESTION | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 9 (11.11%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| CATARRH | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 9 (11.11%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| COUGH | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | 4 / 9 (44.44%) | 0 / 9 (0.00%) |
| occurrences (all) | 2 | 5 | 0 |
| DYSPNOEA | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 3 / 9 (33.33%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| DYSPNOEA EXERTIONAL | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 9 (11.11%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| EPISTAXIS | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 9 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| HAEMOPTYSIS | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 9 (11.11%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| UPPER-AIRWAY COUGH SYNDROME | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| SPUTUM INCREASED | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 4 (0.00%) | 2 / 9 (22.22%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| RHINORRHOEA | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| NIGHT SWEATS | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 9 (11.11%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| RASH | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 9 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| BACK PAIN | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 9 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Infections and infestations | | | |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 9 (11.11%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| DECREASED APPETITE | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 24 March 2021 | The purpose of this version is to correct minor clerical errors for consistency throughout the protocol in addition to the following:<br>• Clarified that home spirometry will be performed by subjects based on availability of devices at the site(s) |
| 04 June 2021 | The purpose of this version is to update the ABBV-119 final dose and dosing regimen, and add Cohort 3 for participating countries with access to ETI, in addition to the following:<br>• Updated the risk sections based on preliminary Phase 1 data and nonclinical data, including updates to LFT requirements including the following:<br>o Added additional safety monitoring for LFTs considering the ABBV-119 Phase 1 data, including new Day 21 visit for all 3 cohorts<br>o Updated eligibility criteria to better exclude patients with underlying conditions that may increase risk of hepatic AEs: Excluded subjects with cirrhosis with or without portal hypertension or history of clinically significant liver disease<br>• Added language to allow subjects to have LFTs done in a local laboratory if a subject cannot return to the site for testing and provide guidance on handling and reporting elevations in LFTs at the local laboratory<br>• Updated statistical methods to<br>o Describe that analysis of each cohort may be performed separately<br>o Update the definition of the PP Population<br>o Add the sample size and power calculation for Cohort 3<br>o Correct typos in the statistical analysis section<br>o Clarify that AbbVie team will be blinded to the post-first-dose spirometry and SwCl data for Cohort 2 only<br>o Update the definition of SAR and SUSAR to align with the current AbbVie template language |
| 22 October 2021 | The purpose of this version is to make the following changes:<br>• Removed the SCR SwCl cutoff for Cohort 3 (Rationale: SwCl cutoff is not applicable to ETI treated subjects)<br>• Added flexible language regarding MF mutations (Rationale: MF mutation table is not exhaustive)<br>• Added prespecified interim analysis plan<br>• Corrected error in Operations Manual<br>• Added COVID-19 Pandemic-Related Vaccination Guidance<br>• Added safety language on sun protection |

| | |
|---|---|
| 02 March 2022 | The purpose of this version is to make the following changes:<br>• Grammatical updates to clarify language regarding timing of events occurring prior to study start<br>• Updated the timing for the primary analysis and added clarity about which endpoints will be analyzed for the primary analysis to clarify appropriate timing for primary and secondary endpoint analyses.<br>• Increased the number of subjects to have completed the triple combination treatment period or<br>prematurely discontinue study drug treatment in Cohort 1 for the planned interim analysis from 10 to at least 15<br>• Clarified expectations of subjects to return the home spirometers and associated smart phones to the site after the completion of their participation in the study in the Operations Manual<br>• Elaborated and clarified the medical management of rash and clarified that options including<br>study drug interruption and/or resumption of study drug after interruption (if clinically appropriate) will be at the investigator's discretion, in the Operations Manual |
| 30 June 2022 | The purpose of this version is to make the following changes:<br>• Added target engagement as one of the primary objectives of the study. Changed SwCl from secondary endpoint to primary endpoint and changed ppFEV1 from primary endpoint to secondary endpoint (Rationale: update study objectives and endpoint plan for the added investigational drug, ABBV-576)<br>• Removed washout periods in Cohort 3 and added Day 4 phone call and Day 8 (Rationale: to minimize the risk of withdrawal syndromes and strengthen safety monitoring for the first week of the treatment period)<br>• Changed spirometry assessment to be pre-bronchodilator use for all study visits, except for screening visit (Rationale: Minimize the potential impact of bronchodilator use on spirometry measurements)<br>• Removed protocol language regarding 'Discontinuation of Study Drug Due to COVID-19 Infection' (Rationale: Update safety measure based on the evolving COVID-19 landscape)<br>• Added DMC review of ABBV-576 Phase 1 safety data (Rationale: Update DMC review plan for the added investigational drug, ABBV-576)<br>• Added interim analysis for Cohort 3 (Rationale: Added interim analysis for Cohort 3 to help AbbVie's internal decision making)<br>• Removed Day 21 visit, ocular exam and neurologic examinations for Cohort 3 in Activity Schedule (Rationale: Update safety measures based on the safety profile of ABBV-576) |

| | |
|---|---|
| 26 August 2022 | The purpose of this version is to correct minor clerical errors for consistency throughout the protocol in addition to the following changes:<br>• Added that Cohorts 1 and 2 were terminated based on efficacy results of an interim analysis (Rationale: To provide further details on the reason for changing the study regimen)<br>• Added 'with and without other CFTR modulators (such as ABBV-119)' (Rationale: To provide further information to clarify the safety profile of the study Regimen)<br>• Added further information on hepatobiliary events (Rationale: To provide further information to clarify the safety profile of the study regimen)<br>• Added HDRS and the GAD-7 as exploratory safety endpoints for Cohort 3. Further details regarding the assessment have been included (Rationale: To update safety measure based on clinical reports for marketed CFTR modulator therapy)<br>• Added 'and all study subjects can resume their ETI therapy after all of the study related procedures are completed on Day 29' (Rationale: To improve clarity regarding the timing of study activities at Day 29)<br>• Clarified the eligibility criteria regarding the type of cirrhosis that must be absent for subjects to participate in the study under each cohort<br>• Removed withdrawal criteria related to the use of triazole antimicrobial due to redundancy with the prohibited medications listed in protocol appendix<br>• Added 'as well as mental health outcome measures' to protocol to incorporate exploratory measurements of mental health parameters in order to inform future trials.<br>• Added recording of 'Date and time of last dose of ETI' to the Day 1 visit for Cohort 3 in protocol appendix and Operations Manual Appendix (Rationale: To update schedule of activity based on the updated Cohort 3 design)<br>• Added criteria definition for minimal function mutations based on regulatory agency feedback<br>• Added amylase and lipase laboratory tests to the Operations Manual (Rationale: To incorporate additional safety monitoring para |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| |
|---|
| Study prematurely ended early due to business decision. |

Notes: