



Clinical trial results:

A Phase 2 Study of Galicafort/Navocafort/ABBV-119 or Galicafort/Navocafort/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
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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 galicafator/navocafator/ABBV-119 or Galicafator/Navocafator/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/navocafter dual therapy for 28 days as a Run-in Period Cohort 1(d-29 to -1), followed by galicaftor/navocafter/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 + Navocafter 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/Navocafter dual combination therapy followed by Galicaftor/Navocafter/ABBV-119 triple combination therapy (Day 1- 29).

Galicaftor: 300 mg QD, Oral capsules

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

Dosage and administration details:

Navocafter: 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 Galicafort/Navocafort/ABBV-119 triple combination therapy (Day 1 - 29).

Galicafort: 300 mg QD, Oral capsules

Navocafort: 50 mg QD, Oral capsules

ABBV-119: 210 mg BID, Oral capsules

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

Dosage and administration details:

Galicafort: 300 mg QD, Oral capsules

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

Dosage and administration details:

Navocafort: 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
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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
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Arm description:

F508del Homozygous CF participants received Galicafort/Navocafort/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
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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
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Reporting group description:

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

Galicafort: 300 mg QD, Oral capsules

Navocafort: 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
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Reporting group description:

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

Galicafort: 300 mg QD, Oral capsules

Navocafort: 50 mg QD, Oral capsules

ABBV-119: 210 mg BID, Oral capsules

Reporting group title	C2 (Day 1 - 29) Placebo F508del Heterozygous
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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 Galicafort/Navocafort/ABBV-576 triple combination therapy (Day 1 - 29).

Galicafort: 300 mg QD, Oral capsules

Navocafort: 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
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Reporting group description:

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

Galicafort: 300 mg QD, Oral capsules

Navocafort: 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 Units: Subjects			

Age continuous Units: years			
arithmetic mean	33.5	35.2	30.0
standard deviation	± 8.80	± 11.09	± 10.55

Gender categorical 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 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 Units: Subjects			

Age continuous Units: years			
arithmetic mean	34.4	37.0	-
standard deviation	± 7.84	± 5.66	-
Gender categorical 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 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
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Reporting group description:

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

Galicafort: 300 mg QD, Oral capsules
Navocafort: 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
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Reporting group description:

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

Galicafort: 300 mg QD, Oral capsules
Navocafort: 50 mg QD, Oral capsules
ABBV-119: 210 mg BID, Oral capsules

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

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

Galicafort: 300 mg QD, Oral capsules
Navocafort: 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
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Reporting group description:

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

Galicafort: 300 mg QD, Oral capsules
Navocafort: 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]
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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
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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 C2 Absolute Change From Baseline in ppFEV1/C2 Absolute
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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]}
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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)	
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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
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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)
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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
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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 C2 Abs Change From Baseline Through Day 29 in FVC/C2 Abs
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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)
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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
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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 C2 Abs Change From BL Through Day 29 in FEF25-75/C2 Abs
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Statistical analyses

Statistical analysis title	C2+PBO Abs Change From BL Through D29 in FEF25-75
Statistical analysis description:	
Cohort 2 (Day 1 - 29) Triple Combination Galicaftr+ Navocaftr + 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)
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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
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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 C2 Relative Changes From Baseline in ppFEV1/C2 Relative
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Statistical analyses

Statistical analysis title	C2 + PBO Relative Changes From Baseline in ppFEV1
Statistical analysis description: Cohort 2(Day 1 - 29) Triple Combination Galicافتor+ Navocافتor + 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			
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	+ 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 C2 Relative Changes From Baseline in FVC/C2 Relative Changes
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Statistical analyses

Statistical analysis title	C2 + PBO Relative Changes From Baseline in FVC
Statistical analysis description: Cohort 2(Day 1 - 29) Triple Combination Galicaftr+ Navocaftr + 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 C2 Relative Change from BL through D29 in FEF25-75/C2
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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 Galicaftr+ Navocaftr + 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 $100 \times (\text{mean scores of all non-missing questions} - 1) / 3$, 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 C2 Absolute Change in CFQ-R Score From Baseline/C2 Absolute
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Statistical analyses

Statistical analysis title	C2 + PBO Abs Change in CFQ-R Score From Baseline
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Statistical analysis description:

Cohort 2(Day 1 - 29) Triple Combination Galicaftr+ 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]
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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
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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
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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_H eterozygous	Cohort_3_Triple_Gali caftor_Navocaftor_A BBV- 576_Homozygous	Cohort_2_Triple_Gali caftor_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

Non-serious adverse events	Cohort_1_Dual_Run - in_Galicafter_Navoc after_Homozygous	Cohort_1_Triple_Gali cafter_Navocafter_A BBV- 119_Homozygous	Cohort_3_Triple_Gali cafter_Navocafter_ 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 occurrences (all)	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0	1 / 2 (50.00%) 1
SPUTUM INCREASED subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	2 / 24 (8.33%) 2	1 / 2 (50.00%) 1
RHINORRHOEA subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0	1 / 2 (50.00%) 1
Skin and subcutaneous tissue disorders NIGHT SWEATS subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0	0 / 2 (0.00%) 0
RASH subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	2 / 24 (8.33%) 2	0 / 2 (0.00%) 0
Musculoskeletal and connective tissue disorders BACK PAIN subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 24 (4.17%) 1	0 / 2 (0.00%) 0
Infections and infestations UPPER RESPIRATORY TRACT INFECTION subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	0 / 24 (0.00%) 0	0 / 2 (0.00%) 0
INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0	0 / 2 (0.00%) 0
COVID-19 subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	4 / 24 (16.67%) 4	0 / 2 (0.00%) 0
Metabolism and nutrition disorders DECREASED APPETITE subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 24 (4.17%) 1	1 / 2 (50.00%) 1

Non-serious adverse events	Cohort_2_Placebo_Heterozygous	Cohort_3_Triple_Galicafter_Navocafter_A	Cohort_2_Triple_Galicafter_Navocafter_
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		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 occurrences (all)	0 / 4 (0.00%) 0	2 / 9 (22.22%) 2	0 / 9 (0.00%) 0
RHINORRHOEA subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Skin and subcutaneous tissue disorders NIGHT SWEATS subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0
RASH subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1
Musculoskeletal and connective tissue disorders BACK PAIN subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1
Infections and infestations UPPER RESPIRATORY TRACT INFECTION subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0
INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
COVID-19 subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Metabolism and nutrition disorders DECREASED APPETITE subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 March 2021	<p>The purpose of this version is to correct minor clerical errors for consistency throughout the protocol in addition to the following:</p> <ul style="list-style-type: none">• Clarified that home spirometry will be performed by subjects based on availability of devices at the site(s)
04 June 2021	<p>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:</p> <ul style="list-style-type: none">• Updated the risk sections based on preliminary Phase 1 data and nonclinical data, including updates to LFT requirements including the following:<ul style="list-style-type: none">o Added additional safety monitoring for LFTs considering the ABBV-119 Phase 1 data, including new Day 21 visit for all 3 cohortso 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• 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• Updated statistical methods to<ul style="list-style-type: none">o Describe that analysis of each cohort may be performed separatelyo Update the definition of the PP Populationo Add the sample size and power calculation for Cohort 3o Correct typos in the statistical analysis sectiono Clarify that AbbVie team will be blinded to the post-first-dose spirometry and SwCl data for Cohort 2 onlyo Update the definition of SAR and SUSAR to align with the current AbbVie template language
22 October 2021	<p>The purpose of this version is to make the following changes:</p> <ul style="list-style-type: none">• Removed the SCR SwCl cutoff for Cohort 3 (Rationale: SwCl cutoff is not applicable to ETI treated subjects)• Added flexible language regarding MF mutations (Rationale: MF mutation table is not exhaustive)• Added prespecified interim analysis plan• Corrected error in Operations Manual• Added COVID-19 Pandemic-Related Vaccination Guidance• Added safety language on sun protection

02 March 2022	<p>The purpose of this version is to make the following changes:</p> <ul style="list-style-type: none"> • Grammatical updates to clarify language regarding timing of events occurring prior to study start • 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. • Increased the number of subjects to have completed the triple combination treatment period or prematurely discontinue study drug treatment in Cohort 1 for the planned interim analysis from 10 to at least 15 • 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 • Elaborated and clarified the medical management of rash and clarified that options including 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	<p>The purpose of this version is to make the following changes:</p> <ul style="list-style-type: none"> • 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) • 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) • 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) • Removed protocol language regarding 'Discontinuation of Study Drug Due to COVID-19 Infection' (Rationale: Update safety measure based on the evolving COVID-19 landscape) • Added DMC review of ABBV-576 Phase 1 safety data (Rationale: Update DMC review plan for the added investigational drug, ABBV-576) • Added interim analysis for Cohort 3 (Rationale: Added interim analysis for Cohort 3 to help AbbVie's internal decision making) • 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	<p>The purpose of this version is to correct minor clerical errors for consistency throughout the protocol in addition to the following changes:</p> <ul style="list-style-type: none"> • 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) • 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) • Added further information on hepatobiliary events (Rationale: To provide further information to clarify the safety profile of the study regimen) • Added HDRS and the GAD-7 as exploratory safety endpoints for Cohort 3. Further details regarding the assessment have been included (Rationale: To update safety measure based on clinical reports for marketed CFTR modulator therapy) • Added 'and all study subjects can resume their ETI therapy after all of the study related procedures are completed on Day 29' (Rationale: To improve clarity regarding the timing of study activities at Day 29) • Clarified the eligibility criteria regarding the type of cirrhosis that must be absent for subjects to participate in the study under each cohort • Removed withdrawal criteria related to the use of triazole antimicrobial due to redundancy with the prohibited medications listed in protocol appendix • Added 'as well as mental health outcome measures' to protocol to incorporate exploratory measurements of mental health parameters in order to inform future trials. • Added recording of 'Date and time of last dose of ETI' to the Day 1 visit for Cohort 3 in protocol appendix and Operations Manual Appendix (Rationale: To update schedule of activity based on the updated Cohort 3 design) • Added criteria definition for minimal function mutations based on regulatory agency feedback • Added amylase and lipase laboratory tests to the Operations Manual (Rationale: To incorporate additional safety monitoring para
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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: