Clinical trial results:
Phase III, 24 week, randomized, double blind, double dummy, parallel group study (with an extension to 52 weeks in a subset of subjects) comparing the efficacy, safety and tolerability of the fixed dose triple combination FF/UMEC/VI administered once daily in the morning via a dry powder inhaler with budesonide/formoterol 400mcg/12mcg administered twice-daily via a reservoir inhaler in subjects with chronic obstructive pulmonary disease.

Summary

EudraCT number	2013-003073-10
Trial protocol	IT SK GR DE CZ PL BG EE HU
Global end of trial date	07 April 2016

Results information

Result version number	v1
This version publication date	21 December 2016
First version publication date	21 December 2016

Trial information

Trial identification

Sponsor protocol code	116853

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

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	07 April 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effects of FF/UMEC/VI on lung function and health related quality of life compared with budesonide/formoterol after 24 weeks of treatment

Protection of trial subjects:

N/A

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 January 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 134
Country: Number of subjects enrolled	China: 70
Country: Number of subjects enrolled	Czech Republic: 109
Country: Number of subjects enrolled	Germany: 278
Country: Number of subjects enrolled	Greece: 115
Country: Number of subjects enrolled	Hungary: 117
Country: Number of subjects enrolled	Italy: 89
Country: Number of subjects enrolled	Korea, Republic of: 63
Country: Number of subjects enrolled	Mexico: 245
Country: Number of subjects enrolled	Estonia: 147
Country: Number of subjects enrolled	Russian Federation: 227
Country: Number of subjects enrolled	Romania: 112
Country: Number of subjects enrolled	Ukraine: 240
Country: Number of subjects enrolled	Slovakia: 46
Country: Number of subjects enrolled	Poland: 129
Worldwide total number of subjects	2121
EEA total number of subjects	1276

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)	1033
From 65 to 84 years	1076
85 years and over	12

Subject disposition

Recruitment

Recruitment details:

This was a phase IIIa, randomized, double-blind, double-dummy, parallel group multicenter study to evaluate once daily fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI; 100 micrograms [µg]/62.5 µg/25 µg) inhalation versus twice daily budesonide/formoterol (400 µg/12 µg) in participants with chronic obstructive pulmonary disease.

Pre-assignment

Screening details:

A total of 2121 participants were enrolled in this study; 1811 were randomized following 2-week run-in. Of those, 1 participant was randomized in error and did not receive randomized treatment. This was followed by a 24-week treatment and 1-week follow-up periods. A sub-set of 430 participants continued in a blinded study treatment for 52 weeks.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	FF/UMEC/VI 100/62.5/25 µg

Arm description:

Participants received FF/UMEC/VI 100/62.5/25 µg via the ELLIPTA dry powder inhaler (DPI) once daily in the morning and placebo via the Turbuhaler twice daily (BID) for 24 weeks in the treatment period and 52 weeks for participants in the extension part of the study.

Arm type	Experimental
Investigational medicinal product name	FF/UMEC/VI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

The combination was provided as inhalation via an ELLIPTA DPI having 30 doses (2 strips with 30 blisters per strip). It consisted of 100 µg of FF (blended with lactose) per blister, 62.5 µg of UMEC (blended with lactose and magnesium stearate) per blister and 25 µg of VI (blended with lactose) per blister; administered once daily in the morning

Investigational medicinal product name	Placebo to match FF/UMEC/VI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

The placebo (Lactose) was provided as inhalation via an ELLIPTA DPI having 30 doses (2 strips with 30 blisters per strip); administered twice daily

Arm title	BUD/FOR 400/12 µg

Arm description:

Participants received BUD/FOR 400/12 µg via the Turbuhaler BID and placebo via the ELLIPTA once daily in the morning for 24 weeks in the treatment period and 52 weeks for participants in the extension part of the study.

Arm type	Experimental

Investigational medicinal product name	Placebo to match BUD/FOR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

The placebo (Lactose) was provided as inhalation via TURBOHALER with 60 doses; administered twice daily

Investigational medicinal product name	BUD/FOR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

The combination (400 µg Budesonide/12 µg Formoterol) was provided as inhalation via TURBOHALER with 60 doses; administered once daily in the morning

Number of subjects in period 1[1]	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg
Started	911	899
Completed	866	842
Not completed	45	57
Consent withdrawn by subject	25	33
Physician decision	4	4
Adverse event, non-fatal	16	19
Lost to follow-up	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 1811 were randomized following 2 week run-in. Of those, 1 subject was randomized in error and did not receive randomized treatment

Baseline characteristics

Reporting groups	
Reporting group title	FF/UMEC/VI 100/62.5/25 µg
Reporting group description:	
Participants received FF/UMEC/VI 100/62.5/25 µg via the ELLIPTA dry powder inhaler (DPI) once daily in the morning and placebo via the Turbuhaler twice daily (BID) for 24 weeks in the treatment period and 52 weeks for participants in the extension part of the study.	
Reporting group title	BUD/FOR 400/12 µg
Reporting group description:	
Participants received BUD/FOR 400/12 µg via the Turbuhaler BID and placebo via the ELLIPTA once daily in the morning for 24 weeks in the treatment period and 52 weeks for participants in the extension part of the study.	

Reporting group values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg	Total
Number of subjects	911	899	1810
Age categorical Units: Subjects			
Age continuous			
Age continuous description			
Units: years			
arithmetic mean	64.2	63.7	
standard deviation	± 8.56	± 8.71	-
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	233	236	469
Male	678	663	1341
Race/Ethnicity, Customized Units: Subjects			
Amrican Indian or Alaskan Native	16	19	35
Asian-East Asian Heritage	55	49	104
Asian-South East Asian Heritag	1	1	2
Native Hawaiian or other Pacific Islander	0	1	1
White-Arabic/North African Heritage	5	8	13
White-White/Caucasina/Euorpean Heritage	771	759	1530
Mixed Race	63	62	125

End points

End points reporting groups

Reporting group title	FF/UMEC/VI 100/62.5/25 µg
Reporting group description:	
Participants received FF/UMEC/VI 100/62.5/25 µg via the ELLIPTA dry powder inhaler (DPI) once daily in the morning and placebo via the Turbuhaler twice daily (BID) for 24 weeks in the treatment period and 52 weeks for participants in the extension part of the study.	
Reporting group title	BUD/FOR 400/12 µg
Reporting group description:	
Participants received BUD/FOR 400/12 µg via the Turbuhaler BID and placebo via the ELLIPTA once daily in the morning for 24 weeks in the treatment period and 52 weeks for participants in the extension part of the study.	

Primary: Change from Baseline in trough forced expiratory volume in one second (FEV1) at Week 24

End point title	Change from Baseline in trough forced expiratory volume in one second (FEV1) at Week 24
End point description:	
FEV1 is a measure of lung function and is defined as the maximal amount of air that can be forcefully exhaled in one second. Trough FEV1 at Week 24 was defined as the FEV1 values obtained prior to morning dose of the study treatment. Baseline was defined as the value obtained predose (0 minutes) on Day 1. Change from Baseline was calculated as the pre-dose measurement at Week 24 minus the Baseline value. The analysis was performed using a mixed model repeated measures (MMRM) method including covariates of treatment group, smoking status (screening), geographical region, visit, baseline, baseline by visit and treatment by visit interactions. Only participants with analyzable data at the given time point were analyzed.	
End point type	Primary
End point timeframe:	
Baseline to Week 24	

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	836[1]	781		
Units: Liters (L)				
least squares mean (standard error)	0.142 (± 0.0083)	-0.029 (± 0.0085)		

Notes:

[1] - ITT Population comprised of all randomized subjects excluding those who were randomized in error.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg

Number of subjects included in analysis	1617
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Model Repeated Measures
Parameter estimate	Adjusted LS mean difference
Point estimate	0.171
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.148
upper limit	0.194
Variability estimate	Standard error of the mean
Dispersion value	0.0118

Primary: Change from Baseline in trough forced expiratory volume in one second (FEV1) at Week 52

End point title	Change from Baseline in trough forced expiratory volume in one second (FEV1) at Week 52

End point description:

FEV1 is a measure of lung function and is defined as the maximal amount of air that can be forcefully exhaled in one second. Trough FEV1 at Week 52 was defined as the FEV1 values obtained prior to morning dose of the study treatment. Baseline was defined as the value obtained predose (0 minutes) on Day 1. Change from Baseline was calculated as the pre-dose measurement at Week 24 minus the Baseline value. The analysis was performed using a mixed model repeated measures (MMRM) method including covariates of treatment group, smoking status (screening), geographical region, visit, baseline, baseline by visit and treatment by visit interactions. Extension Population: all participants in the ITT Population who were enrolled into the subset of participants with extension to 52 weeks. Only participants with analyzable data at the given time point were analyzed.

End point type	Primary

End point timeframe:

Baseline to Week 52

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183[2]	171		
Units: Liters (L)				
least squares mean (standard error)	0.126 (± 0.017)	-0.053 (± 0.0172)		

Notes:

[2] - Extension Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg

Number of subjects included in analysis	354
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Model Repeated Measures
Parameter estimate	Adjusted LS mean difference
Point estimate	0.179
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.131
upper limit	0.226
Variability estimate	Standard error of the mean
Dispersion value	0.0242

Primary: Change from Baseline in St George's Respiratory Questionnaire-Chronic Obstructive Pulmonary Disease (COPD; SGRQ) Total Score for COPD participants at Week 24

End point title	Change from Baseline in St George's Respiratory Questionnaire-Chronic Obstructive Pulmonary Disease (COPD; SGRQ) Total Score for COPD participants at Week 24

End point description:

The SGRQ-C is a disease-specific questionnaire designed to measure the impact of respiratory disease and its treatment on a COPD participant's health-related quality of life (HRQoL). In addition to an overall summary (total) score, scores for the individual domains of Symptoms, Activity, and Impacts are produced. A decrease in score indicated improvement in quality of life. The minimum clinically important difference (MCID) for this instrument is a 4-point improvement (decrease from Baseline). Baseline was defined as the value obtained predose on Day 1. Change from Baseline was calculated as total score at Week 24 minus the Baseline value. SGRQ-C total score was converted to SGRQ total score according to manual. The analysis for SGRQ total score was performed using a MMRM method including covariates of treatment group, smoking status (screening), geographical region, visit, baseline, baseline by visit and treatment by visit interactions

End point type	Primary

End point timeframe:

Baseline to Week 24

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	846[3]	791		
Units: Score on a scale				
least squares mean (standard error)	-6.6 (± 0.45)	-4.3 (± 0.46)		

Notes:

[3] - ITT Population; Only participants with analyzable data at the given time point were analyzed.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg

Number of subjects included in analysis	1637
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Model Repeated Measures
Parameter estimate	Adjusted LS mean difference
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	-1
Variability estimate	Standard error of the mean
Dispersion value	0.64

Primary: Change from Baseline in St George's Respiratory Questionnaire-COPD; SGRQ Total Score for COPD participants at Week 52

End point title	Change from Baseline in St George's Respiratory Questionnaire-COPD; SGRQ Total Score for COPD participants at Week 52

End point description:

The SGRQ-C is a disease-specific questionnaire designed to measure the impact of respiratory disease and its treatment on a COPD participant's health-related quality of life (HRQoL). In addition to an overall summary (total) score, scores for the individual domains of Symptoms, Activity, and Impacts are produced. A decrease in score indicated improvement in quality of life. The minimum clinically important difference (MCID) for this instrument is a 4-point improvement (decrease from Baseline). Baseline was defined as the value obtained predose on Day 1. Change from Baseline was calculated as total score at Week 24 minus the Baseline value. SGRQ-C' total score was converted to SGRQ total score according to manual'.The analysis for SGRQ total score was performed using a MMRM method including covariates of treatment group, smoking status (score).

End point type	Primary

End point timeframe:

Baseline to Week 52

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182[4]	174		
Units: Scores on a scale				
least squares mean (standard error)	-4.6 (± 1.01)	-1.9 (± 1.03)		

Notes:

[4] - Extension Population; Only participants with analyzable data at the given time point were analyzed.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg

Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.065
Method	Mixed Model Repeated Measures
Parameter estimate	Adjusted LS mean difference
Point estimate	-2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	1.44

Secondary: Transitional Dyspnea Index (TDI) focal score expressed as least square mean at Week 24

End point title	Transitional Dyspnea Index (TDI) focal score expressed as least square mean at Week 24

End point description:

The TDI measures change in the participant's dyspnoea from Baseline. The scores in both indexes depend on ratings for three different categories: functional impairment; magnitude of task; and magnitude of effort. Each of these scales had a possible score ranging from -6 (major deterioration) to +6 (major improvement). TDI focal score was calculated as the sum of the three individual scores and then divided by 2 (so the range of the TDI focal score is -9 to +9). TDI was measured at Week 4 and Week 24. Analysis performed using a repeated measures model with covariates of treatment group, smoking status (screening), geographical region, visit, BDI focal score, BDI focal score by visit and treatment by visit interactions. Only participants with analyzable data at the given time point were analyzed.

End point type	Secondary

End point timeframe:

Week 24

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	839[5]	788		
Units: Scores on a scale				
least squares mean (standard error)	2.29 (± 0.096)	1.72 (± 0.099)		

Notes:

[5] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg

Number of subjects included in analysis	1627
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed effect repeated measures model
Parameter estimate	LS Mean difference
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	0.84
Variability estimate	Standard error of the mean
Dispersion value	0.138

Secondary: Transitional Dyspnea Index (TDI) focal score expressed as least square mean at Week 52

End point title	Transitional Dyspnea Index (TDI) focal score expressed as least square mean at Week 52

End point description:

The TDI measures change in the participant's dyspnoea from Baseline. The scores in both indexes depend on ratings for three different categories: functional impairment; magnitude of task; and magnitude of effort. Each of these scales had a possible score ranging from -6 (major deterioration) to +6 (major improvement). TDI focal score was calculated as the sum of the three individual scores and then divided by 2 (so the range of the TDI focal score is -9 to +9). TDI was measured at Weeks 4, 24 and 52. Analysis performed using a repeated measures model with covariates of treatment group, smoking status (screening), geographical region, visit, BDI focal score, BDI focal score by visit and treatment by visit interactions. Only participants with analyzable data at the given time point were analyzed.

End point type	Secondary

End point timeframe:

Week 52

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182[6]	174		
Units: Scores on a scale				
least squares mean (standard error)	1.74 (± 0.221)	1.39 (± 0.226)		

Notes:

[6] - Extension Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg

Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.279
Method	Mixed effect repeated measures model
Parameter estimate	LS Mean difference
Point estimate	0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.97
Variability estimate	Standard error of the mean
Dispersion value	0.317

Secondary: Daily activity question percentage of days reporting a score of 2 up to Week 24

End point title	Daily activity question percentage of days reporting a score of 2 up to Week 24

End point description:

Participants were asked to complete the daily activity question as part of the eDiary, which included the following options: 0: fewer activities, 1: no affect on my activities, and 2: more activities than usual. Daily activity question percentage of days with score of 2 over Weeks 1-24 was analysed using an ANCOVA model with covariates of treatment group, smoking status (screening), geographical region and baseline. Only participants with analyzable data at the given time point were analyzed.

End point type	Secondary

End point timeframe:

Up to Week 24

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	909[7]	894		
Units: Percentage				
least squares mean (standard error)	0 (± 0.38)	-0.1 (± 0.39)		

Notes:

[7] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg

Number of subjects included in analysis	1803
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.817
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	1.1
Variability estimate	Standard error of the mean
Dispersion value	0.51

Secondary: Daily activity question percentage of days reporting a score of 2 up to Week 52

End point title	Daily activity question percentage of days reporting a score of 2 up to Week 52

End point description:

Participants were asked to complete the daily activity question as aprt of the eDiary, which included the following options: 0: fewer activities, 1: no affect on my activities, and 2: more activities than usual. Daily activity question percentage of days with score of 2 over Weeks 1-24 was analysed using an ANCOVA model with covariates of treatment group, smoking status (screening), geographical region and baseline. Only participants with analyzable data at the given time point were analyzed.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210[8]	219		
Units: Percentage				
least squares mean (standard error)	0 (± 0.7)	0.3 (± 0.69)		

Notes:

[8] - Extension Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg

Number of subjects included in analysis	429
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.767
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	1.6
Variability estimate	Standard error of the mean
Dispersion value	0.95

Secondary: Mean annual on-treatment moderate and/or severe COPD exacerbations up to Week 24

End point title	Mean annual on-treatment moderate and/or severe COPD exacerbations up to Week 24

End point description:

The mean annual moderate and severe COPD exacerbations during the treatment (trt) period (per participant [par.] per year) was assessed. The event rate for exacerbations was calculated as the number of events x 1000 divided by the total participant exposure during the time-period of interest. An exacerbation of COPD, is defined as the worsening of two or more major symptoms (dyspnea, sputum volume, sputum purulence [color]) for at least two consecutive days; or the worsening of any one major symptom together with any one of the minor symptoms (sore throat, cold, fever without other cause, increased cough, increased wheeze) for at least two consecutive days. Analysis performed using a generalised linear model assuming a negative binomial distribution and covariates of treatment group, exacerbation history (0, 1, >=2 moderate/severe), smoking status (screening), geographical region and post-bronchodilator percent predicted FEV1 (day 1). 99999 indicates that data were not available.

End point type	Secondary

End point timeframe:

Up to Week 24

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	907[9]	892		
Units: Exacerbations per participant per year				
arithmetic mean (standard deviation)	0.22 (± 99999)	0.34 (± 99999)		

Notes:

[9] - ITT population; Only participants with analyzable data at the given time point were analyzed.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Percentage reduction in annual exacerbation rate (95%CI): 35% (14%, 51%)

Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	1799
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.002
Method	Generalized linear modeL
Parameter estimate	Rate ratio
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.86

Notes:

[10] - Generalized linear model assuming a negative binomial distribution

Secondary: Mean annual on-treatment moderate and/or severe COPD exacerbations up to Week 52

End point title	Mean annual on-treatment moderate and/or severe COPD exacerbations up to Week 52

End point description:

The mean annual moderate and severe COPD exacerbations during the treatment (trt) period (per participant [par.] per year) was assessed. The event rate for exacerbations was calculated as the number of events x 1000 divided by the total participant exposure during the time-period of interest. An exacerbation of COPD, is defined as the worsening of two or more major symptoms (dyspnea, sputum volume, sputum purulence [color]) for at least two consecutive days; or the worsening of any one major symptom together with any one of the minor symptoms (sore throat, cold, fever without other cause, increased cough, increased wheeze) for at least two consecutive days. Analysis performed using a generalised linear model assuming a negative binomial distribution and covariates of treatment group, exacerbation history (0, 1, >=2 moderate/severe), smoking status (screening), geographical region and post-bronchodilator percent predicted FEV1 (day 1). 99999 indicates that data were not available.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210[11]	219		
Units: Exacerbations per participant per year				
arithmetic mean (standard deviation)	0.2 (± 99999)	0.36 (± 99999)		

Notes:

[11] - Extension Population; Only participants with analyzable data at the given time point were analyzed.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Percentage reduction in annual exacerbation rate (95%CI): 44% (15%, 63%)

Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg

Number of subjects included in analysis	429
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.006
Method	Generalized Linear model
Parameter estimate	Rate ratio
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	0.85

Notes:

[12] - Generalized linear model assuming a negative binomial distribution

Secondary: Assessment of respiratory symptoms by 4-weekly mean Exacerbations of Chronic Pulmonary Disease Tool (EXACT)-RS scores up to Week 24

End point title	Assessment of respiratory symptoms by 4-weekly mean Exacerbations of Chronic Pulmonary Disease Tool (EXACT)-RS scores up to Week 24

End point description:

The EXACT-PRO is a 14 item participant reported outcome instrument designed to capture information on the occurrence, frequency, severity, and duration of exacerbations of disease in participants with COPD. The total score for EXACT-PRO ranges from 0-100. EXACT-RS consists of 11 items from the 14 item EXACT-PRO instrument. The EXACT-RS has a scoring range of 0-40. Three subscales of the EXACT-RS are used to describe different symptoms; dyspnoea, cough and sputum and chest symptoms. A clinically meaningful improvement in EXACT-RS score was defined as a decrease in the 4-weekly mean score of >=2 units from Baseline. Four weekly intervals were analyzed using a MMRM method with covariates of treatment group, smoking status (screening), geographical region, time period, baseline, baseline by time period and treatment by time period interactions. Only participants with data available at the analysis time point were analyzed (represented as n=X, X in category title).

End point type	Secondary

End point timeframe:

Up to Week 24

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	911[13]	899		
Units: Scores on a scale				
least squares mean (standard error)				
Week 1-4, n=870,859	-1.45 (± 0.106)	-0.5 (± 0.106)		
Week 5-8, n=851,830	-2 (± 0.129)	-0.77 (± 0.13)		
Week 9-12, n=841,813	-2.23 (± 0.141)	-1.05 (± 0.143)		
Week 13-16, n=831,802	-2.42 (± 0.15)	-1.09 (± 0.151)		
Week 17-20, n=828,788	-2.43 (± 0.156)	-1.02 (± 0.159)		
Week 21-24, n=825,783	-2.31 (± 0.157)	-0.96 (± 0.16)		

Breathlessness score, Week 1-4, n=870,859	-0.71 (± 0.057)	-0.2 (± 0.057)		
Breathlessness score, Week 5-8, n=851,830	-0.95 (± 0.069)	-0.26 (± 0.07)		
Breathlessness score, Week 9-12, n=841,813	-1.03 (± 0.076)	-0.34 (± 0.076)		
Breathlessness score, Week 13-16, n=831, 802	-1.11 (± 0.08)	-0.36 (± 0.081)		
Breathlessness score, Week 17-20, n=828,788	-1.1 (± 0.084)	-0.31 (± 0.085)		
Breathlessness score, Week 21-24, n=825,783	-1.07 (± 0.085)	-0.3 (± 0.087)		
Cough, sputum score, Week 1-4, n=870,859	-0.41 (± 0.031)	-0.24 (± 0.031)		
Cough, sputum score, Week 5-8, n=851,830	-0.59 (± 0.037)	-0.39 (± 0.038)		
Cough, sputum score, Week 9-12, n=841,813	-0.67 (± 0.041)	-0.5 (± 0.041)		
Cough, sputum score, Week 13-16, n=831,802	-0.74 (± 0.043)	-0.53 (± 0.043)		
Cough, sputum score, Week 17-20, n=828,788	-0.77 (± 0.045)	-0.53 (± 0.045)		
Cough, sputum score, Week 21-24, n=825,783	-0.72 (± 0.046)	-0.5 (± 0.046)		
Chest score, Week 1-4, n=870,859	-0.33 (± 0.034)	-0.06 (± 0.035)		
Chest score, Week 5-8, n=851,830	-0.46 (± 0.042)	-0.12 (± 0.043)		
Chest score, Week 9-12, n=841,813	-0.54 (± 0.046)	-0.2 (± 0.047)		
Chest score, Week 13-16, n=831,802	-0.58 (± 0.048)	-0.2 (± 0.048)		
Chest score, Week 17-20, n=828,788	-0.57 (± 0.05)	-0.17 (± 0.05)		
Chest score, Week 21-24, n=825,783	-0.53 (± 0.05)	-0.17 (± 0.051)		

Notes:

[13] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Scores, Week 1-4	
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg
Number of subjects included in analysis	1810
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.25
upper limit	-0.66

Variability estimate	Standard error of the mean
Dispersion value	0.15

Statistical analysis title	Statistical analysis 2
Statistical analysis description: Scores, Week 5-8	
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg
Number of subjects included in analysis	1810
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.59
upper limit	-0.87
Variability estimate	Standard error of the mean
Dispersion value	0.183

Statistical analysis title	Statistical analysis 3
Statistical analysis description: Scores, Week 9-12	
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg
Number of subjects included in analysis	1810
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.57
upper limit	-0.78
Variability estimate	Standard error of the mean
Dispersion value	0.201

Statistical analysis title	Statistical analysis 4
Statistical analysis description: Scores, Week 13-16	

Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg
Number of subjects included in analysis	1810
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.75
upper limit	-0.91
Variability estimate	Standard error of the mean
Dispersion value	0.213

Statistical analysis title	Statistical analysis 5
Statistical analysis description: Scores, Week 17-20	
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg
Number of subjects included in analysis	1810
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.85
upper limit	-0.97
Variability estimate	Standard error of the mean
Dispersion value	0.223

Statistical analysis title	Statistical analysis 6
Statistical analysis description: Scores, Week 21-24	
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg
Number of subjects included in analysis	1810
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Model Repeated Measures
Parameter estimate	Mixed Model Repeated Measures
Point estimate	-1.35

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.79
upper limit	-0.91
Variability estimate	Standard error of the mean
Dispersion value	0.224

Statistical analysis title	Statistical analysis 7
Statistical analysis description: Breathlessness score, Week 1-4	
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg
Number of subjects included in analysis	1810
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.67
upper limit	-0.36
Variability estimate	Standard error of the mean
Dispersion value	0.08

Statistical analysis title	Statistical analysis 8
Statistical analysis description: Breathlessness score, Week 5-8	
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg
Number of subjects included in analysis	1810
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	-0.5
Variability estimate	Standard error of the mean
Dispersion value	0.098

Statistical analysis title	Statistical analysis 9
Statistical analysis description: Breathlessness score, Week 9-12	
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg
Number of subjects included in analysis	1810
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	-0.48
Variability estimate	Standard error of the mean
Dispersion value	0.108

Statistical analysis title	Statistical analysis 10
Statistical analysis description: Breathlessness score, Week 13-16	
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg
Number of subjects included in analysis	1810
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.97
upper limit	-0.52
Variability estimate	Standard error of the mean
Dispersion value	0.115

Statistical analysis title	Statistical analysis 11
Statistical analysis description: Breathlessness score, Week 17-20	
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg

Number of subjects included in analysis	1810
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.03
upper limit	-0.56
Variability estimate	Standard error of the mean
Dispersion value	0.12

Statistical analysis title	Statistical analysis 12
Statistical analysis description: Breathlessness score, Week 21-24	
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg
Number of subjects included in analysis	1810
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.01
upper limit	-0.54
Variability estimate	Standard error of the mean
Dispersion value	0.122

Statistical analysis title	Statistical analysis 13
Statistical analysis description: Cough and sputum score, Week 1-4	
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg
Number of subjects included in analysis	1810
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.17

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	-0.09
Variability estimate	Standard error of the mean
Dispersion value	0.044

Statistical analysis title	Statistical analysis 14
Statistical analysis description: Cough and sputum score, Week 5-8	
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg
Number of subjects included in analysis	1810
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.053

Statistical analysis title	Statistical analysis 15
Statistical analysis description: Cough and sputum score, Week 9-12	
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg
Number of subjects included in analysis	1810
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	-0.05
Variability estimate	Standard error of the mean
Dispersion value	0.058

Statistical analysis title	Statistical analysis 16
Statistical analysis description: Cough and sputum score, Week 13-16	
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg
Number of subjects included in analysis	1810
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.061

Statistical analysis title	Statistical analysis 17
Statistical analysis description: Cough and sputum score, Week 17-20	
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg
Number of subjects included in analysis	1810
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	-0.11
Variability estimate	Standard error of the mean
Dispersion value	0.064

Statistical analysis title	Statistical analysis 18
Statistical analysis description: Cough and sputum score, Week 21-24	
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg

Number of subjects included in analysis	1810
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.065

Statistical analysis title	Statistical analysis 19
Statistical analysis description: Chest scores, Week 1-4	
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg
Number of subjects included in analysis	1810
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	-0.18
Variability estimate	Standard error of the mean
Dispersion value	0.049

Statistical analysis title	Statistical analysis 20
Statistical analysis description: Chest scores, Week 5-8	
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg
Number of subjects included in analysis	1810
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.34

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.46
upper limit	-0.23
Variability estimate	Standard error of the mean
Dispersion value	0.06

Statistical analysis title	Statistical analysis 21
Statistical analysis description: Chest scores, Week 9-12	
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg
Number of subjects included in analysis	1810
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	-0.21
Variability estimate	Standard error of the mean
Dispersion value	0.066

Statistical analysis title	Statistical analysis 22
Statistical analysis description: Chest scores, Week 13-16	
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg
Number of subjects included in analysis	1810
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	-0.25
Variability estimate	Standard error of the mean
Dispersion value	0.068

Statistical analysis title	Statistical analysis 23
Statistical analysis description: Chest scores, Week 17-20	
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg
Number of subjects included in analysis	1810
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	-0.26
Variability estimate	Standard error of the mean
Dispersion value	0.071

Statistical analysis title	Statistical analysis 24
Statistical analysis description: Chest scores, Week 21-24	
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg
Number of subjects included in analysis	1810
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	-0.22
Variability estimate	Standard error of the mean
Dispersion value	0.072

Secondary: Assessment of respiratory symptoms by 4-weekly mean EXACT-RS scores up to Week 52

End point title	Assessment of respiratory symptoms by 4-weekly mean EXACT-RS scores up to Week 52

End point description:

The EXACT-PRO is a 14 item participant reported outcome instrument designed to capture information on the occurrence, frequency, severity, and duration of exacerbations of disease in participants with COPD. The total score for EXACT-PRO ranges from 0-100. EXACT-RS consists of 11 items from the 14 item EXACT-PRO instrument. The EXACT-RS has a scoring range of 0-40. Three subscales of the EXACT-RS are used to describe different symptoms; dyspnoea, cough and sputum and chest symptoms. A clinically meaningful improvement in EXACT-RS score was defined as a decrease in the 4-weekly mean score of >=2 units from Baseline. Four weekly intervals were analyzed using a MMRM method with covariates of treatment group, smoking status (screening), geographical region, time period, baseline, baseline by time period and treatment by time period interactions. Only participants with data available at the analysis time point were analyzed (represented as n=X, X in category title).

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210[14]	220		
Units: Scores on a scale				
least squares mean (standard error)				
Week 1-4, n=205, 213	-1.24 (± 0.222)	-0.72 (± 0.218)		
Week 5-8, n=203, 208	-1.97 (± 0.265)	-0.9 (± 0.26)		
Week 9-12, n=201, 206	-2.18 (± 0.298)	-1.21 (± 0.294)		
Week 13-16, n=201, 204	-2.53 (± 0.317)	-1.52 (± 0.313)		
Week 17-20, n=201, 199	-2.64 (± 0.342)	-1.53 (± 0.338)		
Week 21-24, n=202, 197	-2.63 (± 0.341)	-1.52 (± 0.338)		
Week 25-28, n=194, 186	-2.48 (± 0.349)	-1.16 (± 0.347)		
Week 29-32, n=192, 181	-2.33 (± 0.35)	-0.9 (± 0.349)		
Week 33-36, n=187, 180	-2.12 (± 0.367)	-0.62 (± 0.366)		
Week 37-40, n=185, 177	-2.34 (± 0.359)	-1.11 (± 0.358)		
Week 41-44, n=180, 174	-2.3 (± 0.363)	-0.81 (± 0.362)		
Week 45-48, n=180, 173	-2.17 (± 0.371)	-0.64 (± 0.371)		
Week 49-52, n=179, 171	-2.03 (± 0.37)	-0.61 (± 0.37)		
Breathlessness scores, Week 1-4, n=205, 213	-0.64 (± 0.12)	-0.31 (± 0.118)		
Breathlessness scores, Week 5-8, n=203, 208	-0.93 (± 0.147)	-0.32 (± 0.145)		
Breathlessness scores, Week 9-12, n=201, 206	-1.05 (± 0.167)	-0.44 (± 0.164)		
Breathlessness scores, Week 13-16, n=201, 204	-1.19 (± 0.175)	-0.57 (± 0.173)		
Breathlessness scores, Week 17-20, n=201, 199	-1.17 (± 0.189)	-0.5 (± 0.186)		

Breathlessness scores, Week 21-24, n=202, 197	-1.13 (± 0.19)	-0.5 (± 0.188)		
Breathlessness scores, Week 25-28, n=194, 186	-1.14 (± 0.195)	-0.38 (± 0.194)		
Breathlessness scores, Week 29-32, n=192, 181	-1.11 (± 0.196)	-0.26 (± 0.194)		
Breathlessness scores, Week 33-36, n=187, 180	-1.08 (± 0.204)	-0.14 (± 0.203)		
Breathlessness scores, Week 37-40, n=185, 177	-1.13 (± 0.203)	-0.37 (± 0.202)		
Breathlessness scores, Week 41-44, n=180, 174	-1.06 (± 0.208)	-0.24 (± 0.208)		
Breathlessness scores, Week 45-48, n=180, 173	-0.97 (± 0.211)	-0.11 (± 0.211)		
Breathlessness scores, Week 49-52, n=179, 171	-0.96 (± 0.207)	-0.08 (± 0.207)		
Cough and sputum scores, Week 1-4, n=205, 213	-0.34 (± 0.065)	-0.32 (± 0.064)		
Cough and sputum scores, Week 5-8, n=203, 208	-0.59 (± 0.076)	-0.44 (± 0.074)		
Cough and sputum scores, Week 9-12, n=201, 206	-0.63 (± 0.083)	-0.52 (± 0.082)		
Cough and sputum scores, Week 13-16, n=201, 204	-0.73 (± 0.088)	-0.62 (± 0.087)		
Cough and sputum scores, Week 17-20, n=201, 199	-0.83 (± 0.095)	-0.73 (± 0.094)		
Cough and sputum scores, Week 21-24, n=202, 197	-0.83 (± 0.098)	-0.71 (± 0.097)		
Cough and sputum scores, Week 25-28, n=194, 186	-0.73 (± 0.097)	-0.57 (± 0.097)		
Cough and sputum scores, Week 29-32, n=192, 181	-0.68 (± 0.096)	-0.48 (± 0.096)		
Cough and sputum scores, Week 33-36, n=187, 180	-0.56 (± 0.099)	-0.4 (± 0.099)		
Cough and sputum scores, Week 37-40, n=185, 177	-0.65 (± 0.097)	-0.54 (± 0.097)		
Cough and sputum scores, Week 41-44, n=180, 174	-0.66 (± 0.101)	-0.41 (± 0.102)		
Cough and sputum scores, Week 45-48, n=180, 173	-0.66 (± 0.098)	-0.39 (± 0.099)		
Cough and sputum scores, Week 49-52, n=179, 171	-0.61 (± 0.1)	-0.44 (± 0.1)		
Chest scores, Week 1-4, n=205, 213	-0.27 (± 0.069)	-0.09 (± 0.068)		
Chest scores, Week 5-8, n=203, 208	-0.46 (± 0.084)	-0.13 (± 0.082)		
Chest scores, Week 9-12, n=201, 206	-0.51 (± 0.093)	-0.24 (± 0.092)		
Chest scores, Week 13-16, n=201, 204	-0.61 (± 0.097)	-0.31 (± 0.095)		
Chest scores, Week 17-20, n=201, 199	-0.67 (± 0.104)	-0.29 (± 0.103)		
Chest scores, Week 21-24, n=202, 197	-0.68 (± 0.102)	-0.3 (± 0.101)		
Chest scores, Week 25-28, n=194, 186	-0.63 (± 0.105)	-0.21 (± 0.104)		
Chest scores, Week 29-32, n=192, 181	-0.55 (± 0.107)	-0.16 (± 0.107)		
Chest scores, Week 33-36, n=187, 180	-0.48 (± 0.111)	-0.08 (± 0.111)		
Chest scores, Week 37-40, n=185, 177	-0.57 (± 0.107)	-0.2 (± 0.107)		

Chest scores, Week 41-44, n=180, 174	-0.58 (± 0.108)	-0.16 (± 0.108)		
Chest scores, Week 45-48, n=180, 173	-0.57 (± 0.113)	-0.13 (± 0.113)		
Chest scores, Week 49-52, n=179, 171	-0.49 (± 0.115)	-0.08 (± 0.115)		

Notes:

[14] - Extension Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: Scores, Week 1-4	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.094
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.13
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	0.311

Statistical analysis title	Statistical analysis 2
Statistical analysis description: Scores, Week 5-8	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	-0.34
Variability estimate	Standard error of the mean
Dispersion value	0.371

Statistical analysis title	Statistical analysis 3
Statistical analysis description: Scores, Week 9-12	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.79
upper limit	-0.14
Variability estimate	Standard error of the mean
Dispersion value	0.419

Statistical analysis title	Statistical analysis 4
Statistical analysis description: Scores, Week 13-16	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.024
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.88
upper limit	-0.13
Variability estimate	Standard error of the mean
Dispersion value	0.445

Statistical analysis title	Statistical analysis 5
Statistical analysis description: Scores, Week 17-20	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg

Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.021
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.06
upper limit	-0.17
Variability estimate	Standard error of the mean
Dispersion value	0.481

Statistical analysis title	Statistical analysis 6
Statistical analysis description: Score, Week 21-24	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.05
upper limit	-0.16
Variability estimate	Standard error of the mean
Dispersion value	0.481

Statistical analysis title	Statistical analysis 7
Statistical analysis description: Scores, Week 25-28	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-1.32

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.29
upper limit	-0.35
Variability estimate	Standard error of the mean
Dispersion value	0.492

Statistical analysis title	Statistical analysis 8
Statistical analysis description: Scores, Week 29-32	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	-0.46
Variability estimate	Standard error of the mean
Dispersion value	0.494

Statistical analysis title	Statistical analysis 9
Statistical analysis description: Scores, Week 33-36	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.52
upper limit	-0.48
Variability estimate	Standard error of the mean
Dispersion value	0.519

Statistical analysis title	Statistical analysis 10
Statistical analysis description: Scores, Week 37-40	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.22
upper limit	-0.23
Variability estimate	Standard error of the mean
Dispersion value	0.507

Statistical analysis title	Statistical analysis 11
Statistical analysis description: Scores, Week 41-44	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-1.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	-0.48
Variability estimate	Standard error of the mean
Dispersion value	0.513

Statistical analysis title	Statistical analysis 12
Statistical analysis description: Scores, Week 45-49	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg

Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-1.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.56
upper limit	-0.5
Variability estimate	Standard error of the mean
Dispersion value	0.525

Statistical analysis title	Statistical analysis 13
Statistical analysis description: Scores, Week 49-52	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.45
upper limit	-0.39
Variability estimate	Standard error of the mean
Dispersion value	0.524

Statistical analysis title	Statistical analysis 14
Statistical analysis description: Breathlessness score, Week 1-4	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.051
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.33

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.66
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.169

Statistical analysis title	Statistical analysis 15
Statistical analysis description: Breathlessness score, Week 5-8	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.02
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.207

Statistical analysis title	Statistical analysis 16
Statistical analysis description: Breathlessness score, Week 9-12	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.07
upper limit	-0.15
Variability estimate	Standard error of the mean
Dispersion value	0.234

Statistical analysis title	Statistical analysis 17
Statistical analysis description: Breathlessness score, Week 13-16	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	-0.13
Variability estimate	Standard error of the mean
Dispersion value	0.247

Statistical analysis title	Statistical analysis 18
Statistical analysis description: Breathlessness score, Week 17-20	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.19
upper limit	-0.15
Variability estimate	Standard error of the mean
Dispersion value	0.265

Statistical analysis title	Statistical analysis 19
Statistical analysis description: Breathlessness score, Week 21-24	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg

Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.018
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.16
upper limit	-0.11
Variability estimate	Standard error of the mean
Dispersion value	0.268

Statistical analysis title	Statistical analysis 20
Statistical analysis description: Breathlessness score, Week 25-28	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	-0.21
Variability estimate	Standard error of the mean
Dispersion value	0.275

Statistical analysis title	Statistical analysis 21
Statistical analysis description: Breathlessness score, Week 29-32	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.85

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	-0.31
Variability estimate	Standard error of the mean
Dispersion value	0.276

Statistical analysis title	Statistical analysis 22
Statistical analysis description: Breathlessness score, Week 33-36	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.51
upper limit	-0.38
Variability estimate	Standard error of the mean
Dispersion value	0.288

Statistical analysis title	Statistical analysis 23
Statistical analysis description: Breathlessness score, Week 37-40	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.32
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.287

Statistical analysis title	Statistical analysis 24
Statistical analysis description: Breathlessness score, Week 41-44	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	-0.24
Variability estimate	Standard error of the mean
Dispersion value	0.294

Statistical analysis title	Statistical analysis 25
Statistical analysis description: Breathlessness score, Week 45-48	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Breathlessness score, Week 41-44
Parameter estimate	LS Mean difference
Point estimate	-0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.44
upper limit	-0.27
Variability estimate	Standard error of the mean
Dispersion value	0.299

Statistical analysis title	Statistical analysis 26
Statistical analysis description: Breathlessness score, Week 49-52	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg

Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.45
upper limit	-0.3
Variability estimate	Standard error of the mean
Dispersion value	0.294

Statistical analysis title	Statistical analysis 27
Statistical analysis description: Cough and sputum score, Week 1-4	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.84
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.16
Variability estimate	Standard error of the mean
Dispersion value	0.091

Statistical analysis title	Statistical analysis 28
Statistical analysis description: Cough and sputum score, Week 5-8	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.167
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	-0.06
Variability estimate	Standard error of the mean
Dispersion value	0.106

Statistical analysis title	Statistical analysis 29
Statistical analysis description: Cough and sputum score, Week 9-12	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.359
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	0.12
Variability estimate	Standard error of the mean
Dispersion value	0.117

Statistical analysis title	Statistical analysis 30
Statistical analysis description: Cough and sputum score, Week 13-16	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	0.13
Variability estimate	Standard error of the mean
Dispersion value	0.124

Statistical analysis title	Statistical analysis 31
Statistical analysis description: Cough and sputum score, Week 17-20	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.49
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	0.17
Variability estimate	Standard error of the mean
Dispersion value	0.134

Statistical analysis title	Statistical analysis 32
Statistical analysis description: Cough and sputum score, Week 21-24	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.388
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.39
upper limit	0.15
Variability estimate	Standard error of the mean
Dispersion value	0.138

Statistical analysis title	Statistical analysis 33
Statistical analysis description: Cough and sputum score, Week 25-28	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg

Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.218
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.44
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.137

Statistical analysis title	Statistical analysis 34
Statistical analysis description: Cough and sputum score, Week 29-32	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.138
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	0.07
Variability estimate	Standard error of the mean
Dispersion value	0.136

Statistical analysis title	Statistical analysis 35
Statistical analysis description: Cough and sputum score, Week 33-36	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.239
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.17

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.44
upper limit	0.11
Variability estimate	Standard error of the mean
Dispersion value	0.14

Statistical analysis title	Statistical analysis 36
Statistical analysis description: Cough and sputum score, Week 37-40	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.417
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	0.16
Variability estimate	Standard error of the mean
Dispersion value	0.138

Statistical analysis title	Statistical analysis 37
Statistical analysis description: Cough and sputum score, Week 41-44	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.078
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	0.03
Variability estimate	Standard error of the mean
Dispersion value	0.144

Statistical analysis title	Statistical analysis 38
Statistical analysis description: Cough and sputum score, Week 45-48	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.058
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	0.01
Variability estimate	Standard error of the mean
Dispersion value	0.14

Statistical analysis title	Statistical analysis 39
Statistical analysis description: Cough and sputum score, Week 49-52	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.231
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.45
upper limit	0.11
Variability estimate	Standard error of the mean
Dispersion value	0.141

Statistical analysis title	Statistical analysis 40
Statistical analysis description: Chest score, Week 1-4	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg

Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.068
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	0.01
Variability estimate	Standard error of the mean
Dispersion value	0.097

Statistical analysis title	Statistical analysis 41
Statistical analysis description: Chest score, Week 5-8	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	-0.09
Variability estimate	Standard error of the mean
Dispersion value	0.118

Statistical analysis title	Statistical analysis 42
Statistical analysis description: Chest score, Week 9-12	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.042
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.27

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	-0.01
Variability estimate	Standard error of the mean
Dispersion value	0.131

Statistical analysis title	Statistical analysis 43
Statistical analysis description: Chest score, Week 13-16	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.027
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.57
upper limit	-0.03
Variability estimate	Standard error of the mean
Dispersion value	0.136

Statistical analysis title	Statistical analysis 44
Statistical analysis description: Chest score, Week 17-20	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.67
upper limit	-0.09
Variability estimate	Standard error of the mean
Dispersion value	0.146

Statistical analysis title	Statistical analysis 45
Statistical analysis description: Chest score, Week 21-24	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.66
upper limit	-0.09
Variability estimate	Standard error of the mean
Dispersion value	0.144

Statistical analysis title	Statistical analysis 46
Statistical analysis description: Chest score, Week 25-28	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	-0.12
Variability estimate	Standard error of the mean
Dispersion value	0.148

Statistical analysis title	Statistical analysis 47
Statistical analysis description: Chest score, Week 29-32	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg

Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.68
upper limit	-0.09
Variability estimate	Standard error of the mean
Dispersion value	0.152

Statistical analysis title	Statistical analysis 48
Statistical analysis description: Chest score, Week 33-36	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.71
upper limit	-0.09
Variability estimate	Standard error of the mean
Dispersion value	0.157

Statistical analysis title	Statistical analysis 49
Statistical analysis description: Chest score, Week 37-40	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.014
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.37

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.67
upper limit	-0.07
Variability estimate	Standard error of the mean
Dispersion value	0.151

Statistical analysis title	Statistical analysis 50
Statistical analysis description: Chest score, Week 41-44	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.72
upper limit	-0.12
Variability estimate	Standard error of the mean
Dispersion value	0.153

Statistical analysis title	Statistical analysis 51
Statistical analysis description: Chest score, Week 45-48	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	-0.13
Variability estimate	Standard error of the mean
Dispersion value	0.16

Statistical analysis title	Statistical analysis 52
Statistical analysis description: Chest score, Week 49-52	
Comparison groups	FF/UMEC/VI 100/62.5/25 µg v BUD/FOR 400/12 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.73
upper limit	-0.09
Variability estimate	Standard error of the mean
Dispersion value	0.163

Secondary: Number of participants with any on-treatment adverse event (AE) and serious adverse event (SAE) in the treatment period

End point title	Number of participants with any on-treatment adverse event (AE) and serious adverse event (SAE) in the treatment period

End point description:

An AE was any untoward medical occurrence in a participant or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. These included an exacerbation of a chronic or intermittent pre-existing condition. A SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly; or all events of possible drug-induced liver injury. Abnormal and clinically significant laboratory test results were also recorded as an AE or SAE. COPD exacerbations were an expected disease-related outcome and were not to be recorded as an AE, unless they met the definition of an SAE. Participants were not to be withdrawn from the study due to COPD exacerbations and their evaluation was an efficacy endpoint.

End point type	Secondary

End point timeframe:

Up to Week 24

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	911[15]	899		
Units: Participants				
Any AE	354	339		
Any SAE	49	51		

Notes:
[15] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any on-treatment AE/SAEs in the extension part of the study

End point title	Number of participants with any on-treatment AE/SAEs in the extension part of the study

End point description:

An AE was any untoward medical occurrence in a participant or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. These included an exacerbation of a chronic or intermittent pre-existing condition. A SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly; or all events of possible drug-induced liver injury. Abnormal and clinically significant laboratory test results were also recorded as an AE or SAE. COPD exacerbations were an expected disease-related outcome and were not to be recorded as an AE, unless they met the definition of an SAE. Participants were not to be withdrawn from the study due to COPD exacerbations and their evaluation was an efficacy endpoint.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210[16]	220		
Units: Participants				
Any AE	100	122		
Any SAE	21	28		

Notes:
[16] - Extension Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with an on-treatment penumonia event in the treatment period

End point title	Number of participants with an on-treatment penumonia event in the treatment period

End point description:

All suspected pneumonias required confirmation as defined by the presence of new infiltrate(s) on chest x-ray and at least 2 of the following signs and symptoms: Increased cough, Increased sputum purulence (colour) or production, Auscultatory findings of adventitious sounds , Dyspnea or tachypnea, Fever (oral temperature > 37.5 °C), Elevated white blood cells (WBC) (>10,000/millimeter [mm^3] or >15 percent

immature forms) or Hypoxemia (hemoglobin/oxygen [HbO2] saturation <88 percent or at least 2 percent lower than Baseline value).

End point type	Secondary

End point timeframe:

Up to Week 24

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	911[17]	899		
Units: Participants	20	7		

Notes:

[17] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with an on-treatment penumonia event in the extension part of the study

End point title	Number of participants with an on-treatment penumonia event in the extension part of the study

End point description:

All suspected pneumonias required confirmation as defined by the presence of new infiltrate(s) on chest x-ray AND at least 2 of the following signs and symptoms: Increased cough, Increased sputum purulence (colour) or production, Auscultatory findings of adventitious sounds , Dyspnea or tachypnea, Fever (oral temperature > 37.5 °C), Elevated WBC (>10,000/mm3 or >15 percent immature forms) orr Hypoxemia (HbO2 saturation <88 percent or at least 2 percent lower than Baseline value).

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210[18]	220		
Units: Participants	4	4		

Notes:

[18] - Extension Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any on-treatment cardiovascular (CV) events (including supraventricular arrhythmia and non fatal myocardial infarction)

in the treatment period

End point title	Number of participants with any on-treatment cardiovascular (CV) events (including supraventricular arrhythmia and non fatal myocardial infarction) in the treatment period

End point description:

Cardiovascular safety was monitored via AE reporting with categorization and analysis of adverse events of special interest (AESIs) including cardiac arrhythmia, cardiac failure, ischemic heart disease, hypertension, and central nervous system hemorrhages and cerebrovascular conditions. In addition, ECGs and vital signs were measured in all subjects and24-hour Holter monitoring was performed in a predefined subset. Pre-specified MACE analysis was conducted based on adjudicated CV deaths and investigator-reported non-fatal AEs. Number of participants with any of the following MACE events were to be included per the broad and narrow analyses: Broad MACE criteria (ischemic heart disease standardized MedDRA query [SMQ; myocardial infarction SMQ and other ischemic diseases]) and narrow MACE criteria (myocardial infarction [acute myocardial infarction].

End point type	Secondary

End point timeframe:

Up to Week 24

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	911[19]	899		
Units: Participants				
Any MACE, Narrow definition	4	7		
Any MACE, Broad definition	12	11		

Notes:

[19] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any on-treatment CV events (including supraventricular arrhythmia and non fatal myocardial infarction) in the extension part of the study

End point title	Number of participants with any on-treatment CV events (including supraventricular arrhythmia and non fatal myocardial infarction) in the extension part of the study

End point description:

Cardiovascular safety was monitored via AE reporting with categorization and analysis of adverse events of special interest (AESIs) including cardiac arrhythmia, cardiac failure, ischemic heart disease, hypertension, and central nervous system hemorrhages and cerebrovascular conditions. In addition, ECGs and vital signs were measured in all subjects and24-hour Holter monitoring was performed in a predefined subset. Pre-specified MACE analysis was conducted based on adjudicated CV deaths and investigator-reported non-fatal AEs. Number of participants with any of the following MACE events were to be included per the broad and narrow analyses: Broad MACE criteria (ischemic heart disease standardized MedDRA query [SMQ; myocardial infarction SMQ and other ischemic diseases]) and narrow MACE criteria (myocardial infarction [acute myocardial infarction].

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210[20]	220		
Units: Participants				
Any MACE, Narrow definition	5	2		
Any MACE, Broad definition	7	5		

Notes:

[20] - Extension Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in heart rate at Week 24

End point title	Change from Baseline in heart rate at Week 24

End point description:

A single 12-lead electrocardiogram (ECG) and rhythm strip were recorded after measurement of vital signs and spirometry. Recordings were made at Screening (Visit 1) and approximately 15-45 minutes after dosing on treatment Week 4 and Week 24 or IP Discontinuation Visit. Change from Baseline in ECG heart rate was summarized for each post-Baseline assessment up to Week 24. Change from Baseline was calculated as the individual post-Baseline value at Week 24 minus the Baseline value. Baseline value is defined as the most recent individual value prior to randomization (generally Screening but could be a test repeat). All ECG measurements were made with the participants in a supine position having rested in this position for approximately 5 minutes before each reading. Only participants with analyzable data at the given time point were analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	840[21]	787		
Units: Beats per minute (Bpm)				
arithmetic mean (standard deviation)	-1.1 (± 11.51)	-1.2 (± 10.91)		

Notes:

[21] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in heart rate at Week 52

End point title	Change from Baseline in heart rate at Week 52

End point description:

A single 12-lead ECG and rhythm strip were recorded after measurement of vital signs and spirometry. Recordings were made at Screening (Visit 1) and approximately 15-45 minutes after dosing on treatment Week 4, Week 24 and Week 52 or IP Discontinuation Visit. Change from Baseline in ECG heart rate was summarized for each post-Baseline assessment up to Week 24. Change from Baseline was calculated as the individual post-Baseline value at Week 52 minus the Baseline value. Baseline value is defined as the most recent individual value prior to randomization (generally Screening but could be a test repeat). All ECG measurements were made with the participants in a supine position having rested in this position for approximately 5 minutes before each reading. Only participants with analyzable data at the given time point were analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181[22]	169		
Units: Bpm				
arithmetic mean (standard deviation)	0.2 (± 11.3)	-1 (± 10.77)		

Notes:

[22] - Extension Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Corrected QT Interval using Fridericia's Correction (QTcF) and PR interval at Week 24

End point title	Change from Baseline in Corrected QT Interval using Fridericia's Correction (QTcF) and PR interval at Week 24

End point description:

A single 12-lead ECG and rhythm strip were recorded after measurement of vital signs and spirometry. Recordings were made at Screening (Visit 1) and approximately 15-45 minutes after dosing on treatment Week 4 and Week 24 or IP Discontinuation Visit. Change from Baseline in ECG QTcF and PR interval was summarized for each post-Baseline assessment up to Week 24. Change from Baseline was calculated as the individual post-Baseline value at Week 24 minus the Baseline value. Baseline value is defined as the most recent individual value prior to randomization (generally Screening but could be a test repeat). Only participants with data available at the analysis time point were analyzed (represented as n=X, X in category title). All ECG measurements were made with the participants in a supine position having rested in this position for approximately 5 minutes before each reading.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	911[23]	899		
Units: Milliseconds (msec)				
least squares mean (standard error)				
QTcF, n=840,787	2.5 (± 0.56)	0.6 (± 0.58)		
PR, n=812,766	-0.1 (± 0.54)	0.5 (± 0.56)		

Notes:

[23] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: For QTcF	
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg
Number of subjects included in analysis	1810
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.023
Method	Mixed Model Repeated Measures
Parameter estimate	LS mean difference
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	3.4
Variability estimate	Standard error of the mean
Dispersion value	0.81

Statistical analysis title	Statistical analysis 2
Statistical analysis description: For PR interval	
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg
Number of subjects included in analysis	1810
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.471
Method	Mixed Model Repeated Measures
Parameter estimate	LS mean difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	1

Variability estimate	Standard error of the mean
Dispersion value	0.78

Secondary: Change from baseline in QTcF and PR interval at Week 52

End point title	Change from baseline in QTcF and PR interval at Week 52

End point description:

Single 12-lead ECG and rhythm strip were recorded after measurement of vital signs and spirometry. Recordings were made at Screening (Visit 1) and approximately 15-45 minutes after dosing on treatment Week 4, Week 24 and Week 52 or IP Discontinuation Visit. Change from Baseline in ECG QTcF and PR interval was summarized for each post-Baseline assessment up to Week 24. Change from Baseline was calculated as the individual post-Baseline value at Week 52 minus the Baseline value. Baseline value is defined as the most recent individual value prior to randomization (generally Screening but could be a test repeat). Only participants with data available at the analysis time point were analyzed (represented as n=X, X in category title).

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210[24]	220		
Units: Msec				
least squares mean (standard error)				
QTcF, n=181,169	1.4 (± 1.27)	2.4 (± 1.31)		
PR, n=174,160	1.6 (± 1.09)	1.4 (± 1.13)		

Notes:

[24] - Extension Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

For QTcF

Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.564
Method	Mixed Model Repeated Measures
Parameter estimate	LS mean difference
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.7
upper limit	2.5

Variability estimate	Standard error of the mean
Dispersion value	1.83

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
For PR interval	
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.908
Method	Mixed Model Repeated Measures
Parameter estimate	LS mean difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	3.3
Variability estimate	Standard error of the mean
Dispersion value	1.57

Secondary: Change from Baseline in QT Interval Corrected for Heart Rate According to Bazett's Formula (QTcB) at Week 24

End point title	Change from Baseline in QT Interval Corrected for Heart Rate According to Bazett's Formula (QTcB) at Week 24

End point description:

A single 12-lead ECG and rhythm strip were recorded after measurement of vital signs and spirometry. Recordings were made at Screening (Visit 1) and approximately 15-45 minutes after dosing on treatment Week 4 and Week 24 or IP Discontinuation Visit. Change from Baseline in QTcB was summarized for each post-Baseline assessment up to Week 24. Change from Baseline was calculated as the individual post-Baseline value at Week 24 minus the Baseline value. Baseline value is defined as the most recent individual value prior to randomization (generally Screening but could be a test repeat). All ECG measurements were made with the participants in a supine position having rested in this position for approximately 5 minutes before each reading. Only participants with analyzable data at the given time point were analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	840[25]	787		
Units: Msec				
arithmetic mean (standard deviation)	1.5 (± 21)	-0.7 (± 20.48)		

Notes:

[25] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in QTcB at Week 52

End point title	Change from baseline in QTcB at Week 52

End point description:

A single 12-lead ECG and rhythm strip were recorded after measurement of vital signs and spirometry. Recordings were made at Screening (Visit 1) and approximately 15-45 minutes after dosing on treatment Week 4, Week 24, and Week 52 or IP Discontinuation Visit. Change from Baseline in QTcB was summarized for each post-Baseline assessment up to Week 52. Change from Baseline was calculated as the individual post-Baseline value at Week 52 minus the Baseline value. Baseline value is defined as the most recent individual value prior to randomization (generally Screening but could be a test repeat). All ECG measurements were made with the participants in a supine position having rested in this position for approximately 5 minutes before each reading. Only participants with analyzable data at the given time point were analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181[26]	169		
Units: Msec				
arithmetic mean (standard deviation)	0.9 (± 21.3)	2.2 (± 22.46)		

Notes:

[26] - Extension Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in systolic and diastolic blood pressures (BP) at Week 24

End point title	Change from Baseline in systolic and diastolic blood pressures (BP) at Week 24

End point description:

Vital signs were obtained at the Screening Visit and prior to taking the morning dose of study treatment and prior to conducting spirometry at Week 4 and Week 24 or at the Study Treatment Discontinuation Visit. A single set of blood pressure (systolic and diastolic) measurements were collected taken after the

participant had rested for 5 minutes in the sitting position. Change from Baseline values for systolic and diastolic BP (SBP and DBP) at Week 24 were summarised and these data were analyzed using MMRM analysis. Baseline was defined as the values from most recent assessment prior to randomization which records both systolic and diastolic BP (generally Screening but could be a test repeat). Only participants with analyzable data at the given time point were analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	855[27]	805		
Units: Millimeter of mercury (mmHg)				
least squares mean (standard error)				
SBP	-1 (± 0.39)	-1.1 (± 0.4)		
DBP	-0.3 (± 0.27)	-0.5 (± 0.27)		

Notes:

[27] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Week 24, SBP

Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg
Number of subjects included in analysis	1660
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.849
Method	Mixed Model Repeated Measures
Parameter estimate	LS mean difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	1.2
Variability estimate	Standard error of the mean
Dispersion value	0.56

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Week 24, DBP

Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg

Number of subjects included in analysis	1660
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.613
Method	Mixed Model Repeated Measures
Parameter estimate	LS mean difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0.9
Variability estimate	Standard error of the mean
Dispersion value	0.38

Secondary: Change from Baseline in systolic and diastolic blood pressures (BP) at Week 52

End point title	Change from Baseline in systolic and diastolic blood pressures (BP) at Week 52

End point description:

Vital signs were obtained at the Screening Visit and prior to taking the morning dose of study treatment and prior to conducting spirometry at Week 4, Week 24, and Week 52 or at the Study Treatment Discontinuation Visit. A single set of blood pressure (systolic and diastolic) measurements were taken after the participant had rested for 5 minutes in the sitting position. Change from Baseline values for systolic and diastolic BP (SBP and DBP) at Week 52 were summarised and these data were analyzed using MMRM analysis. Baseline was defined as the values from most recent assessment prior to randomization which records both systolic and diastolic BP (generally Screening but could be a test repeat). Only participants with analyzable data at the given time point were analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184[28]	175		
Units: mmHg				
least squares mean (standard error)				
SBP	-1.3 (± 0.83)	0.3 (± 0.85)		
DBP	-0.4 (± 0.52)	0.4 (± 0.53)		

Notes:

[28] - Extension Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Week 52, SBP

Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg
Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.183
Method	Mixed Model Repeated Measures
Parameter estimate	LS mean difference
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9
upper limit	0.8
Variability estimate	Standard error of the mean
Dispersion value	1.19

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
Week 52, DBP	
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg
Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.253
Method	Mixed Model Repeated Measures
Parameter estimate	LS mean difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	0.6
Variability estimate	Standard error of the mean
Dispersion value	0.75

Secondary: Number of participants with any abnormal holter electrocardiogram (ECG) finding at Week 24

End point title	Number of participants with any abnormal holter electrocardiogram (ECG) finding at Week 24
End point description:	
The 24-hour holter measurements were obtained at Screening and 24 hours prior to Week 24 (Visits 1 and 6). The number of participants with clinically significant change (abnormal) were reported. Holter Monitoring Population: all participants in the ITT Population who had at least one holter monitoring evaluation. Only participants with analyzable data at the given time point were analyzed.	
End point type	Secondary
End point timeframe:	
Up to Week 24	

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212[29]	206		
Units: Participants	180	165		

Notes:

[29] - Holter Monitoring Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in pulse rate at Week 24

End point title	Change from Baseline in pulse rate at Week 24

End point description:

Pulse rate was obtained at the Screening Visit and prior to taking the morning dose of study treatment and prior to conducting spirometry at Week 4 and Week 24 or at the Study Treatment Discontinuation. Pulse rate was measured in a sitting position after the participant was kept at rest for at least 5 minutes. Change from Baseline values for pulse rate at Week 24 were summarised and these data were analyzed using MMRM analysis. Baseline was defined as the values from most recent assessment prior to randomization (generally Screening but could be a test repeat). Only participants with analyzable data at the given time point were analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	855[30]	805		
Units: Bpm				
least squares mean (standard error)	-0.5 (± 0.31)	-0.8 (± 0.32)		

Notes:

[30] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg

Number of subjects included in analysis	1660
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.526
Method	Mixed Model Repeated Measures
Parameter estimate	LS mean difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	1.2
Variability estimate	Standard error of the mean
Dispersion value	0.45

Secondary: Change from Baseline in pulse rate at Week 52

End point title	Change from Baseline in pulse rate at Week 52

End point description:

Pulse rate was obtained at the Screening Visit and prior to taking the morning dose of study treatment and prior to conducting spirometry at Week 4, Week 24, and Week 52 or at the Study Treatment Discontinuation. Pulse rate was measured in a sitting position after the participant was kept at rest for at least 5 minutes. Change from Baseline values for pulse rate at Week 52 were summarized and these data were analyzed using MMRM analysis. Baseline was defined as the values from most recent assessment prior to randomization (generally Screening but could be a test repeat). Only participants with analyzable data at the given time point were analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184[31]	175		
Units: Bpm				
least squares mean (standard error)	0.7 (± 0.67)	-1.9 (± 0.69)		

Notes:

[31] - Extension Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	BUD/FOR 400/12 µg v FF/UMEC/VI 100/62.5/25 µg

Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Mixed Model Repeated Measures
Parameter estimate	LS mean difference
Point estimate	2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	4.5
Variability estimate	Standard error of the mean
Dispersion value	0.96

Secondary: Change from Baseline in basophils, eosinophils, monocytes, neutrophils, leukocytes, lymphocytes, and platelets at Week 24

End point title	Change from Baseline in basophils, eosinophils, monocytes, neutrophils, leukocytes, lymphocytes, and platelets at Week 24

End point description:

Hematology laboratory assessments included basophils, eosinophils, lymphocytes, monocytes, neutrophils, total neutrophil, leukocytes, and platelets; parameters were measured at Baseline (BL), Week 12 and Week 24. Change from Baseline was calculated by subtracting the Baseline value from the individual post-dose value at Week 24. Baseline was defined as the most recent individual value prior to randomization (generally Screening but could be a repeat test). Only participants with data available at the analysis time point were analyzed (represented as n=X, X in category title). The maximum post-Baseline values have also been presented.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	911[32]	899		
Units: 10^9 per liter (10^9/L)				
arithmetic mean (standard deviation)				
Week 24, Basophils, n=817,761	-0.001 (± 0.0217)	-0.001 (± 0.0204)		
Maximum post BL, Basophils, n=876,853	0.005 (± 0.0211)	0.005 (± 0.0206)		
Week 24, Eosinophils, n=817, 761	-0.008 (± 0.1926)	-0.015 (± 0.1926)		
Maxmium post BL, Eosinophils, n=876,853	0.034 (± 0.1941)	0.019 (± 0.1952)		
Category title 5. Week 24, Monocytes, n=817,761	-0.006 (± 0.1977)	0.004 (± 0.2125)		
Maximum post BL, Monocytes, n=876,853	0.04 (± 0.1985)	0.048 (± 0.2069)		

Week 24, Neutrophils, n=817,761	0.071 (± 1.7682)	0.142 (± 1.8552)		
Maximum post BL, Neutrophils, n=876,853	0.481 (± 1.8761)	0.649 (± 1.9143)		
Week 24, Leukocytes, n=819,761	0.06 (± 1.847)	0.11 (± 1.915)		
Maximum post BL, Leukocytes, n=877,853	0.52 (± 1.94)	0.64 (± 1.947)		
Week 24, Platelets, n=810,759	-0.7 (± 43.12)	-0.7 (± 44.26)		
Maximum post BL, Platelets, n=871,846	10.8 (± 42.5)	10.2 (± 45.46)		
Week 24, Lymphocytes, n=817,761	0.002 (± 0.5311)	-0.023 (± 0.5669)		
Maximum post BL, Lymphocytes, n=876,853	0.187 (± 0.5468)	0.15 (± 0.5767)		

Notes:

[32] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in basophils, eosinophils, monocytes, neutrophils, leukocytes, lymphocytes, and platelets at Week 52

End point title	Change from Baseline in basophils, eosinophils, monocytes, neutrophils, leukocytes, lymphocytes, and platelets at Week 52

End point description:

Hematology laboratory assessments included Basophils, eosinophils, lymphocytes, monocytes,neutrophils, total neutrophil, leukocytes, and platelets; parameters were measured at Baseline (BL), Week 12, Week 24, and Week 52 for the extension part of the study. Change from Baseline was calculated by subtracting the Baseline value from the individual post-dose value at Week 52. Baseline was defined as the most recent individual value prior to randomization (generally Screening but could be a test repeat). Only participants with data available at the analysis time point were analyzed (represented as n=X, X in category title). The maximum post-Baseline values have also been

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210[33]	220		
Units: 10^9/L				
arithmetic mean (standard deviation)				
Week 52, Basophils, n=168,166	0.002 (± 0.0203)	0.003 (± 0.0241)		
Maximum post BL, Basophils, n=205,212	0.011 (± 0.0196)	0.01 (± 0.0226)		
Week 52, Eosinophils, n=168,166	0.002 (± 0.1819)	-0.011 (± 0.2567)		
Maximum post BL, Eosinophils, n=205,212	0.074 (± 0.246)	0.057 (± 0.2884)		
Week 52, Monocytes, n=168,166	0.025 (± 0.2382)	0.028 (± 0.2164)		
Maximum post BL, Monocytes, n=205,212	0.075 (± 0.2359)	0.072 (± 0.2123)		

Week 52, Neutrophils, n=168,166	0.246 (± 2.1768)	-0.163 (± 2.3222)		
Maximum post BL, Neutrophils, n=205,212	0.923 (± 2.1444)	0.835 (± 2.1223)		
Week 52, Leukocytes, n=168,166	0.33 (± 2.243)	-0.17 (± 2.387)		
Maximum post BL, Leukocytes, n=205,212	0.97 (± 2.163)	0.87 (± 2.168)		
Week 52, Platelets, n=170,166	-1.8 (± 39.96)	-2.7 (± 49.22)		
Maximum post BL, Platelets, n=203,210	13.6 (± 40.57)	13.9 (± 51.61)		
Week 52, Lymphocytes, n=168,166	0.06 (± 0.685)	-0.027 (± 0.5714)		
Maximum post BL, Lymphocytes, n=202,212	0.325 (± 0.6299)	0.295 (± 0.591)		

Notes:

[33] - Extension Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in erythrocytes at Week 24

End point title	Change from Baseline in erythrocytes at Week 24

End point description:

Hematology laboratory assessments included erythrocytes and was measured at Baseline, Week 12 and Week 24. Change from Baseline was calculated by subtracting the Baseline value from the individual post-dose value at Week 24. Baseline was defined as the most recent individual value prior to randomization (generally Screening but could be a test repeat). Only participants with data available at the analysis time point were analyzed (represented as n=X, X in category title). The maximum post-Baseline values have also been presented.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	911[34]	899		
Units: 10^12 per liter (10^12/L)				
arithmetic mean (standard deviation)				
Week 24, n=822,769	-0.02 (± 0.292)	-0.04 (± 0.294)		
Maximum post BL, n=880,857	0.06 (± 0.27)	0.04 (± 0.273)		

Notes:

[34] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in erythrocytes at Week 52

End point title	Change from Baseline in erythrocytes at Week 52

End point description:

Hematology laboratory assessments included erythrocytes and was measured at Baseline, Week 12 and Week 24, and Week 52 for the extension part of the study. Change from Baseline was calculated by subtracting the Baseline value from the individual post-dose value at Week 52. Baseline was defined as the most recent individual value prior to randomization (generally Screening but could be a test repeat). Only participants with data available at the analysis time point were analyzed (represented as n=X, X in category title). The maximum post-Baseline values have also been presented.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210[35]	220		
Units: 10^12/L				
arithmetic mean (standard deviation)				
Week 52, n=174,170	0.02 (± 0.282)	0 (± 0.313)		
Maximum post BL, n=206,212	0.11 (± 0.261)	0.07 (± 0.289)		

Notes:

[35] - Extension Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in hemoglobin at Week 24

End point title	Change from Baseline in hemoglobin at Week 24

End point description:

Blood samples were collected for the measurement of hemoglobin at Baseline, Week 12, and Week 24. Change from Baseline was calculated as the post-Baseline value at Week 24 minus the Baseline value. Baseline was defined as the most recent individual value prior to randomization (generally Screening but could be a test repeat). Only participants with data available at the analysis time point were analyzed (represented as n=X, X in category title). The maximum post-Baseline values have also been presented.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	911[36]	899		
Units: Grams per liter (g/L)				
arithmetic mean (standard deviation)				
Week 24, n=822,769	-0.9 (± 8.17)	-1 (± 8.65)		
Maximum post BL, n=880,857	1.5 (± 7.55)	1.5 (± 8.26)		

Notes:
[36] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in hemoglobin at Week 52

End point title	Change from Baseline in hemoglobin at Week 52

End point description:

Blood samples were collected for the measurement of hemoglobin at Baseline, Week 12, Week 24, and Week 52 for the extension part of the study. Change from Baseline was calculated as the post-Baseline value at Week 52 minus the Baseline value. Baseline was defined as the most recent individual value prior to randomization (generally Screening but could be a test repeat). Only participants with data available at the analysis time point were analyzed (represented as n=X, X in category title). The maximum post-Baseline values have also been presented.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210[37]	220		
Units: g/L				
arithmetic mean (standard deviation)				
Week 52, n=174,170	-2.5 (± 8.06)	-2.5 (± 9.82)		
Maximum post BL, n=206,212	2.2 (± 7.67)	1.9 (± 8.55)		

Notes:
[37] - Extension Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in hematocrit at Week 24

End point title	Change from Baseline in hematocrit at Week 24

End point description:

Blood samples were collected for the measurement of hematocrit (proportion of red blood cells in blood) at Baseline, Week 12, and Week 24. Change from Baseline was calculated as the post-Baseline value at Week 24 minus the Baseline value. Baseline was defined as the most recent individual value prior to randomization (generally Screening but could be a test repeat). Only participants with data available at the analysis time point were analyzed (represented as n=X, X in category title). The maximum post-Baseline values have also been presented.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	911[38]	899		
Units: Fraction of 1				
arithmetic mean (standard deviation)				
Week 24, n=822,769	0.0024 (± 0.02627)	0.0024 (± 0.02798)		
Maximum post BL, n=880,857	0.0115 (± 0.02533)	0.0123 (± 0.02669)		

Notes:

[38] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in hematocrit at Week 52

End point title	Change from Baseline in hematocrit at Week 52

End point description:

Blood samples were collected for the measurement of hematocrit (proportion of red blood cells in blood) at Baseline, Week 12, Week 24, and Week 52 for the extension part of the study. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Baseline was defined as Most recent individual value prior to randomization (generally Screening but could be a test repeat). Only participants with data available at the analysis time point were analyzed (represented as n=X, X in category title). The maximum post-Baseline values have also been presented.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210[39]	220		
Units: Fraction of 1				
arithmetic mean (standard deviation)				
Week 52, n=174,170	-0.0056 (± 0.02468)	-0.0056 (± 0.0317)		
Maximum post BL, n=206,212	0.0153 (± 0.02552)	0.0149 (± 0.02793)		

Notes:

[39] - Extension Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in albumin and protein at Week 24

End point title	Change from Baseline in albumin and protein at Week 24

End point description:

Blood samples were collected for the measurement of albumin and protein at Baseline, Week 12 and Week 24. Change from Baseline (BL) was calculated as the post-Baseline value at Week 24 minus the Baseline value. Baseline was defined as the most recent individual value prior to randomization (generally Screening but could be a test repeat). The maximum post BL values have been presented. Only participants with data available at the analysis time point were analyzed (represented as n=X, X in category title). The maximum post-Baseline values have also been presented.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	911[40]	899		
Units: g/L				
arithmetic mean (standard deviation)				
Week 24, Albumin, n=839,787	-0.7 (± 2.55)	-0.5 (± 2.41)		
Maximum post BL, Albumin, n=888,866	0.1 (± 2.36)	0.2 (± 2.24)		
Week 24, Protein, n=839,787	-0.6 (± 3.7)	-1 (± 3.64)		
Maximum post BL, Protein, n=888,866	0.4 (± 3.42)	0.1 (± 3.43)		

Notes:

[40] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in albumin and protein at Week 52

End point title	Change from Baseline in albumin and protein at Week 52

End point description:

Blood samples were collected for the measurement of albumin and protein at Baseline, Week 12, Week 24, and Week 52 for the extension part of the study. Change from Baseline was calculated as the post-Baseline value at Week 52 minus the Baseline value. Baseline was defined as the most recent individual value prior to randomization (generally Screening but could be a test repeat). Only participants with data available at the analysis time point were analyzed (represented as n=X, X in category title). The maximum post-Baseline values have also been presented.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210[41]	220		
Units: g/L				
arithmetic mean (standard deviation)				
Week 52, Albumin, n=181,174	-0.8 (± 2.77)	-0.7 (± 2.64)		
Maximum post BL,Albumin, n=207,214	0.4 (± 2.45)	0.2 (± 2.25)		
Week 52, Protein, n=181,174	-1.1 (± 4.04)	-1.6 (± 3.86)		
Maximum post BL, Protein, n=207,214	0.6 (± 3.57)	0 (± 3.3)		

Notes:

[41] - Extension Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl aminotransferase (GGT), alkaline phosphatase (ALP), and creatine kinase at Week 24

End point title	Change from Baseline in alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl aminotransferase (GGT), alkaline phosphatase (ALP), and creatine kinase at Week 24

End point description:

Blood samples were collected for the measurement of ALP, ALT, AST, CK, and GGT at Baseline, Week 12 and Week 24. Change from Baseline was calculated as the post-Baseline value at Week 24 minus the Baseline value. Baseline was defined as the most recent individual value prior to randomization (generally Screening but could be a test repeat). Only participants with data available at the analysis time point were analyzed (represented as n=X, X in category title). The maximum post-Baseline values have also been presented.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	911[42]	899		
Units: International units per liter (IU/L)				
arithmetic mean (standard deviation)				
Week 24, ALT, n=838,785	1.4 (± 10.81)	3.8 (± 69.15)		
Maximum post BL, ALT, n=887,864	3 (± 11.99)	5.5 (± 66.01)		
Week 24, AST, n=835,785	1.1 (± 10.3)	4 (± 86.63)		
Maximum post BL, AST, n=887,866	3.2 (± 12.61)	5.6 (± 82.66)		
Week 24, ALP, n=839,787	1.1 (± 15.42)	-2.8 (± 12.47)		
Maximum post BL, ALP, n=888,866	4.3 (± 16.46)	0.8 (± 11.96)		
Week 24, GGT, n=839,787	3.4 (± 31.65)	0.5 (± 21.84)		
Maximum post BL, GGT, n=888,866	7.5 (± 42.66)	4.7 (± 27.76)		

Week 24, Creatine Kinase, n=839,787	-3.9 (± 106.48)	-3.4 (± 191.25)		
Maximum post BL, Creatine Kinase, n=888,866	20.6 (± 138.17)	20.6 (± 185.06)		

Notes:

[42] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in ALT, AST, GGT, ALP, and creatine kinase at Week 52

End point title	Change from Baseline in ALT, AST, GGT, ALP, and creatine kinase at Week 52

End point description:

Blood samples were collected for the measurement of ALP, ALT, AST, CK, and GGT at Baseline, Week 12, Week 24 and Week 52 for the extension part of the study. Change from Baseline was calculated as the post-Baseline value at Week 52 minus the Baseline value. Baseline was defined as the most recent individual value prior to randomization (generally Screening but could be a test repeat). Only participants with data available at the analysis time point were analyzed (represented as n=X, X in category title). The maximum post-Baseline values have also been presented.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210[43]	220		
Units: International units per liter (IU/L)				
arithmetic mean (standard deviation)				
Week 52, ALT, n=181,173	1.7 (± 10.64)	1.3 (± 12.38)		
Maximum post BL, ALT, n=207,212	5.4 (± 15.45)	4.5 (± 12.84)		
Week 52, AST, n=180,174	1.7 (± 9.72)	0.8 (± 11.16)		
Maximum post BL, AST, n=207,214	5.5 (± 15.55)	3.7 (± 11.65)		
Week 52, ALP, n=181,174	1.7 (± 13.77)	-2.7 (± 10.83)		
Maximum post BL, ALP, n=207,214	6.7 (± 12.84)	1.2 (± 11.73)		
Week 52, GGT, n=181,174	0.2 (± 28.77)	0.2 (± 26.86)		
Maximum post BL, GGT, n=207,214	7.7 (± 31.33)	8.9 (± 34.98)		
Week 52, Creatine Kinase, n=181,174	6.1 (± 68.48)	16.7 (± 97.17)		
Maximum post BL, Creatine Kinase, n=207,214	39.9 (± 79.71)	46.9 (± 90.78)		

Notes:

[43] - Extension Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in glucose, calcium, carbon dioxide (CO2), chloride, phosphate, potassium, sodium, and urea at Week 24

End point title	Change from Baseline in glucose, calcium, carbon dioxide (CO2), chloride, phosphate, potassium, sodium, and urea at Week 24

End point description:

Blood samples were collected for the measurement of Glucose, calcium, CO2, chloride, phophate, potassium, sodium, and urea at Baseline, Week 12, and Week 24. Change from Baseline was calculated as the post-Baseline value at Week 24 minus the Baseline value. Baseline was defined as the most recent individual value prior to randomization (generally Screening but could be a test repeat). Only participants with data available at the analysis time point were analyzed (represented as n=X, X in category title). The maximum post-Baseline values have also been presented.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	911[44]	899		
Units: Millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)				
Week 24, Calcium, n=835,785	-0.016 (± 0.0887)	-0.014 (± 0.0931)		
Maximum post BL, Calcium, n=887,866	0.013 (± 0.0817)	0.012 (± 0.0868)		
Week 24, Chloride, n=838,787	-0.4 (± 2.76)	-0.7 (± 2.6)		
Maximum post BL, Chloride, n=888,866	0.9 (± 2.53)	0.6 (± 2.35)		
Week 24, CO2, n=835,785	-0.6 (± 2.54)	0 (± 2.61)		
Maximum post BL, CO2, n=835,785	0 (± 2.38)	0.5 (± 2.48)		
Week 24, Glucose, n=839,787	0.12 (± 1.433)	0 (± 1.449)		
Maximum post BL, Glucose, n=887,866	0.53 (± 1.506)	0.37 (± 1.463)		
Week 24, Potassium, n=834,785	0.04 (± 0.457)	-0.03 (± 0.456)		
Maximum post BL, Potassium, n=887,866	0.18 (± 0.428)	0.13 (± 0.417)		
Week 24, Phosphate, n=839,787	-0.028 (± 0.2373)	-0.029 (± 0.2728)		
Maximum post BL, Phosphate, n=888,866	0.039 (± 0.231)	0.043 (± 0.2576)		
Week 24, Sodium, n=837,787	-0.3 (± 2.35)	-0.2 (± 2.38)		
Maximum post BL, Sodium, n=888,866	0.6 (± 2.15)	0.7 (± 2.22)		
Week 24, Urea, n=839,787	0.08 (± 1.591)	0.04 (± 1.549)		
Maximum post BL, Urea, n=888,866	0.68 (± 1.601)	0.64 (± 1.604)		

Notes:

[44] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in glucose, calcium, CO2, chloride, magnesium,

phosphate, potassium, sodium, and urea at Week 52

End point title	Change from Baseline in glucose, calcium, CO2, chloride, magnesium, phosphate, potassium, sodium, and urea at Week 52

End point description:

Blood samples were collected for the measurement of Glucose, calcium, CO2, chloride, magnesium, phophate, potassium, sodium, and urea at Baseline, Week 12, Week 24, and Week 52 for the extension part of the study. Change from Baseline was calculated as the post-Baseline value at Week 52 minus the Baseline value. Baseline was defined as the most recent individual value prior to randomization (generally Screening but could be a test repeat). Only participants with data available at the analysis time point were analyzed (represented as n=X, X in category title). The maximum post-Baseline values have also been presented.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210[45]	220		
Units: Mmol/L				
arithmetic mean (standard deviation)				
Week 52, Calcium, n=180,174	-0.033 (± 0.0943)	-0.04 (± 0.0968)		
Maximum post BL,Calcium, n=207,214	0.026 (± 0.0849)	0.008 (± 0.0868)		
Week 52, Chloride, n=181,174	-0.1 (± 3)	-0.2 (± 2.71)		
Maximum post BL,Chloride, n=207,214	1.4 (± 2.63)	1.3 (± 2.39)		
Week 52, CO2, n=180,174	-1.2 (± 2.46)	-1 (± 2.58)		
Maximum post BL,CO2, n=207,214	-0.2 (± 2.26)	0.3 (± 2.28)		
Week 52, Glucose, n=181,174	0.31 (± 1.538)	0.22 (± 1.546)		
Maximum post BL,Glucose, n=207,214	0.92 (± 1.683)	0.63 (± 1.738)		
Week 52, Potassium, n=180,174	-0.02 (± 0.443)	-0.1 (± 0.454)		
Maximum post BL,Potassium, n=207,214	0.29 (± 0.456)	0.2 (± 0.418)		
Week 52, Phosphate, n=181,174	-0.003 (± 0.1645)	0.005 (± 0.18)		
Maximum post BL,Phosphate, n=207,214	0.109 (± 0.1551)	0.11 (± 0.177)		
Week 52, Sodium, n=181,174	-0.2 (± 2.34)	-0.1 (± 2.51)		
Maximum post BL,Sodium, n=207,214	1.1 (± 2.13)	1.1 (± 2.22)		
Week 52, Urea, n=181,174	0.16 (± 1.625)	0.12 (± 1.553)		
Maximum post BL, Urea, n=207,214	1.06 (± 1.755)	1.08 (± 1.629)		

Notes:

[45] - Extension Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in bilirubin, creatinine, and urate at Week 24

End point title	Change from Baseline in bilirubin, creatinine, and urate at Week 24

End point description:

Blood samples were collected for the measurement of bilirubin, creatinine, and urate at Baseline, Week 12, and Week 24. Change from Baseline was calculated as the post-Baseline value at Week 24 minus the Baseline value. Baseline was defined as the most recent individual value prior to randomization (generally Screening but could be a test repeat). Only participants with data available at the analysis time point were analyzed (represented as n=X, X in category title). The maximum post-Baseline values have also been presented.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	911[46]	899		
Units: Micromoles per liter				
arithmetic mean (standard deviation)				
Week 24, Bilirubin, n=839,786	-0.2 (± 3.88)	0.1 (± 3.77)		
Maximum post BL, Bilirubin, n=888,865	1.1 (± 4.09)	1.2 (± 3.67)		
Week 24, Creatinine, n=839,787	1.05 (± 9.816)	1.14 (± 9.58)		
Maximum post BL, Creatinine, n=888,866	4.12 (± 9.711)	3.99 (± 9.509)		
Week 24, Urate, n=839,787	2.8 (± 60.87)	1.7 (± 62.96)		
Maximum post BL, Urate, n=888,866	23.7 (± 58.64)	21.9 (± 59.2)		

Notes:

[46] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in bilirubin, creatinine, and urate at Week 52

End point title	Change from Baseline in bilirubin, creatinine, and urate at Week 52

End point description:

Blood samples were collected for the measurement of bilirubin, creatinine, and urate at Baseline, Week 12, Week 24, and Week 52 of the extension part of the study. Change from Baseline was calculated as the post-Baseline value at Week 52 minus the Baseline value. Baseline was defined as the most recent individual value prior to randomization (generally Screening but could be a test repeat).

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210[47]	220		
Units: Micromoles per liter				
arithmetic mean (standard deviation)				
Week 52, Bilirubin, n=181,174	0.3 (± 3.41)	0.1 (± 3.94)		
Maximum post BL, Bilirubin, n=207,214	2 (± 3.88)	2.3 (± 4.28)		
Week 52, Creatinine, n=181,174	2.95 (± 11.663)	1.28 (± 11.563)		
Maximum post BL, Creatinine, n=207,214	6.99 (± 11.425)	6 (± 11.392)		
Week 52, Urate, n=181,174	3.6 (± 60.92)	3.9 (± 64.85)		
Maximum post BL, Urate, n=207,214	42 (± 62.06)	40 (± 63.47)		

Notes:

[47] - Extension Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants reporting an adverse event of special interest (AESI) of oropharyngeal origin in the treatment period

End point title	Number of participants reporting an adverse event of special interest (AESI) of oropharyngeal origin in the treatment period

End point description:

Oropharyngeal examinations for clinical evidence of infection (e.g., Candida albicans) were performed at each clinic visit. All suspected cases of candidiasis were reported as AEs. The number of participants with oral candidiasis, Candida infection, oral fungal infection, and oropharyngeal candidiasis were reported.

End point type	Secondary

End point timeframe:

Up to Week 24

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	911[48]	899		
Units: Participants				
Oral candidiasis	2	4		
Candida infection	1	4		
Oral fungal infection	2	3		
Oropharyngeal candidiasis	2	0		

Notes:

[48] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants reporting an AESI of oropharyngeal origin in the extension part of the study

End point title	Number of participants reporting an AESI of oropharyngeal origin in the extension part of the study

End point description:

Oropharyngeal examinations for clinical evidence of infection (e.g., Candida albicans) were performed at each clinic visit. All suspected cases of candidiasis were reported as AEs. The number of participants with oral candidiasis, candida infection, oral fungal infection, and oropharyngeal candidiasis were reported.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210[49]	220		
Units: Participants				
Candida infection	0	3		
Oral fungal infection	0	2		

Notes:

[49] - Extension Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with at least one on-treatment bone fracture incident in the treatment period

End point title	Number of participants with at least one on-treatment bone fracture incident in the treatment period

End point description:

To evaluate the potential for bone systemic corticosteroid effects, the incidence of bone fractures was assessed. It was categorized as an adverse event of special interest.

End point type	Secondary

End point timeframe:

Up to Week 24

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	911[50]	899		
Units: Participants	4	6		

Notes:
[50] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with at least one on-treatment bone fracture incident in the extension part of the study

End point title	Number of participants with at least one on-treatment bone fracture incident in the extension part of the study

End point description:

To evaluate the potential for bone systemic corticosteroid effects, the incidence of bone fractures was assessed. It was categorized as an adverse event of special interest.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210[51]	220		
Units: Participants	0	1		

Notes:
[51] - Extension Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment serious adverse events (SAEs) and non-serious AEs were collected from start of the study drug until Week 24 and follow-up period for participants in ITT population and up to Week 52 and follow-up for participants in Extension Population

Adverse event reporting additional description:

On-treatment SAEs and non-serious AEs are reported for ITT and extension populations

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	FF/UMEC/VI 100/62.5/25 µg

Reporting group description:

Participants received FF/UMEC/VI 100/62.5/25 µg via the ELLIPTA dry powder inhaler (DPI) once daily in the morning and placebo via the Turbuhaler twice daily (BID) for 24 weeks in the treatment period and 52 weeks for participants in the extension part of the study.

Reporting group title	BUD/FOR 400/12 µg

Reporting group description:

Participants received BUD/FOR 400/12 µg via the Turbuhaler BID and placebo via the ELLIPTA once daily in the morning for 24 weeks in the treatment period and 52 weeks for participants in the extension part of the study.

Serious adverse events	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg	
Total subjects affected by serious adverse events			
subjects affected / exposed	61 / 911 (6.70%)	64 / 899 (7.12%)	
number of deaths (all causes)	6	10	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm			
subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brian neoplasm malignant			

subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	1 / 911 (0.11%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 911 (0.00%)	2 / 899 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to lung			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			

subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Coronary artery bypass			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart valve replacement			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia repair			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Catheter site phlebitis			
subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-cardiac chest pain			
subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	2 / 911 (0.22%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Acute pulmonary edema			
subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic obstructive pulmonary disease			
subjects affected / exposed	16 / 911 (1.76%)	31 / 899 (3.45%)	
occurrences causally related to treatment / all	0 / 20	0 / 36	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic respiratory failure			
subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hemoptysis			
subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary edema			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			

subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Electrocardiogram ST segment elevation			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	2 / 911 (0.22%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural hemorrhage			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Radius fracture			
subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronory syndrome			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 911 (0.11%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina pectoris			
subjects affected / exposed	1 / 911 (0.11%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 911 (0.11%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 911 (0.11%)	2 / 899 (0.22%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cardiac failure acute			

subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cyanosis			
subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 911 (0.00%)	2 / 899 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocaridal ischemia			
subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemorrhagic stroke			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ischemic stroke			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Postical paralysis			
subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			

subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischemic attack			
subjects affected / exposed	1 / 911 (0.11%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 911 (0.22%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric Ulcer			
subjects affected / exposed	1 / 911 (0.11%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal mass			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal hemorrhage			
subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Chronic kideny disease			
subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hemorrhage urinary tract			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebra; disc protrusion			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			

subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected dermal cyst			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic onstructive airways diseas			
subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	10 / 911 (1.10%)	5 / 899 (0.56%)	
occurrences causally related to treatment / all	1 / 11	1 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory tract infection			

subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 911 (0.00%)	1 / 899 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tuberculosis			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 911 (0.11%)	0 / 899 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	FF/UMEC/VI 100/62.5/25 µg	BUD/FOR 400/12 µg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	105 / 911 (11.53%)	104 / 899 (11.57%)	
Nervous system disorders			
Headache			
subjects affected / exposed	44 / 911 (4.83%)	56 / 899 (6.23%)	
occurrences (all)	79	85	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	72 / 911 (7.90%)	51 / 899 (5.67%)	
occurrences (all)	89	59	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 December 2014	Amendment 1 applies to China only. This amendment confirms that SAE's, in China, will be recorded from consent to the follow-up visit/telephone contact or until Visit 6 (telephone contact) for participants who have discontinued IP but continue in the study.
16 April 2015	Amendment 2 applies to China only. Due to a new interpretation of Chinese regulations, the main study cannot be initiated until the pharmacogenetic research portion obtained a permit from the Human Genetic Resource Administration of China (HGRAC). This would incur a substantial delay to the start of the study in China and prevent China from being able to recruit a sufficient number of participants into the study. Therefore, China will not participate in the pharmacogenetic research portion of the study.
04 March 2016	The following 2 amendments were approved on the same date: Amendment 3 applies to China only: The purpose was to amend the multiplicity adjustment to be applied in the statistical analysis and correct minor discrepancies, make some minor clarifications and update references and citations. The changes made in Amendment 3 are the same as the changes made in Amendment 4 (see below for details) but Amendment 3 incorporates the China-specific amendments 1 and 2. Amendment 4: This country specific protocol amendment applies to all countries except for China, where this amendment has been incorporated into Amendment 3. Amendment 3 purpose is to amend the multiplicity adjustment to be applied in the statistical analysis and correct minor discrepancies, make some minor clarifications and update references and citations.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported