Clinical trial results:
A Randomized, Double-Blind, Double Dummy, Active Comparator, Parallel Group, Multicenter Study to Evaluate the Safety of Once-Daily Fluticasone Furoate/GW642444 Inhalation Powder for 52 Weeks in Adolescent and Adult Subjects with Asthma

Summary

EudraCT number	2009-012054-20
Trial protocol	DE Outside EU/EEA
Global end of trial date	12 May 2011

Results information

Result version number	v2 (current)
This version publication date	22 April 2016
First version publication date	09 February 2015
Version creation reason	• Correction of full data set Minor revisions.

Trial information

Trial identification

Sponsor protocol code	HZA106839

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 8664357343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 8664357343,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000431-PIP01-08
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	22 June 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 May 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of 12 months treatment with two strengths of Fluticasone Furoate/GW642444 Inhalation Powder once-daily in the evening in subjects 12 years of age and older with asthma.

Protection of trial subjects:

Participants with life-threatening asthma were not enrolled in the study. Withdrawal of the participant from the trial was required if any of the following criteria were met: participant experienced a severe asthma exacerbation; worsening of asthma criteria were met; participant became pregnant; participant had an adverse event that would make continued participation in the study an unacceptable risk (in the judgment of the investigator); abnormal electrocardiogram criteria were met; abnormal Holter monitoring criteria were met; abnormal ophthalmic examination criteria were met; or liver chemistry threshold criteria were met.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 October 2009
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	Germany: 123
Country: Number of subjects enrolled	Thailand: 178
Country: Number of subjects enrolled	United States: 279
Country: Number of subjects enrolled	Ukraine: 128
Worldwide total number of subjects	708
EEA total number of subjects	123

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)	102
Adults (18-64 years)	566
From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were randomized in a 2:2:1 ratio to Fluticasone Furoate/GW642444 Inhalation Powder (two strengths: 200/25 micrograms (µg) once daily and 100/25 µg once daily) and fluticasone propionate 500 µg twice daily, respectively.

Pre-assignment

Screening details:

Participants meeting all inclusion criteria and none of the exclusion criteria during the screening visit entered a 2-week Run-in Period for completion of Baseline safety evaluations and to obtain Baseline measures of asthma status. At Visit 2, participants were randomized to a 52-week Double-blind Treatment Period.

Period 1

Period 1 title	2-week Run-in Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Current asthma therapy at a fixed dose

Arm description:

Participants were instructed to continue using an approved fixed dose of an inhaled corticosteroid (ICS) with or without an additional controller medication (i.e., long-acting beta-agonist, leukotriene modifier, etc.) for 2 weeks. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication during the Run-in Period.

Arm type	Unblinded run-in medication
Investigational medicinal product name	inhaled corticosteroid with or without additional controller medication
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Respiratory use

Dosage and administration details:

fixed dose for 2 weeks

Number of subjects in period 1	Current asthma therapy at a fixed dose
Started	617
Completed	503
Not completed	114
Did Not Meet Continuation Criteria	97
Physician decision	3
Consent withdrawn by subject	11
Lost to follow-up	2
Protocol deviation	1

Period 2

Period 2 title	52-week Double-blind Treatment Period
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

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

Arm description:

Participants received Fluticasone Furoate (FF)/Vilanterol (VI) 100/25 micrograms (µg) inhalation powder once daily (OD) in the evening via the Dry Powder Inhaler (DPI), plus a placebo via DISKUS/ACCUHALER twice daily (BID), for 52 weeks. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication during the Treatment Period.

Arm type	Experimental
Investigational medicinal product name	Fluticasone furoate/vilanterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Respiratory use

Dosage and administration details:

100/25 micrograms (µg), once daily in the evening

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Respiratory use

Dosage and administration details:

Matching placebo, once daily in the evening/twice daily

Arm title	FF/VI 200/25 µg OD

Arm description:

Participants received FF/VI 200/25 µg inhalation powder OD in the evening via the DPI, plus a placebo via
DISKUS/ACCUHALER BID, for 52 weeks. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication during the Treatment Period.

Arm type	Experimental
Investigational medicinal product name	Fluticasone furoate/vilanterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Respiratory use

Dosage and administration details:

200/25 µg, once daily in the evening

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Inhalation powder
Routes of administration	Respiratory use

Dosage and administration details:

Matching placebo, once daily in the evening/twice daily

Arm title	FP 500 µg BID

Arm description:

Participants received Fluticasone Propionate (FP) 500 µg BID via DISKUS/ACCUHALER, plus a placebo via the DPI OD in the evening, for 52 weeks. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication during the Treatment Period.

Arm type	Experimental
Investigational medicinal product name	Fluticasone propionate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Respiratory use

Dosage and administration details:

500 µg, twice daily

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Respiratory use

Dosage and administration details:

Matching placebo, once daily in the evening/twice daily

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: The randomized treatment period is considered to be the baseline period. Subject disposition data are collected for members of the Intent-to-Treat Population, defined as all randomized participants who received at least a single dose of trial medication. Not all participants enrolled in the trial (participants screened and for whom a record exists on the study database) were randomized to treatment.

Number of subjects in period 2[2]	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID
Started	201	202	100
Completed	161	161	71
Not completed	40	41	29
Physician decision	1	-	3
Consent withdrawn by subject	10	7	9
Adverse event, non-fatal	5	3	6
Protocol-defined Stopping Criteria	14	16	4
Lost to follow-up	1	3	4
Lack of efficacy	1	4	1
Protocol deviation	8	8	2

Notes:

[2] - 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: The randomized treatment period is considered to be the baseline period. Subject disposition data are collected for members of the Intent-to-Treat Population, defined as all randomized

participants who received at least a single dose of trial medication. Not all participants enrolled in the trial (participants screened and for whom a record exists on the study database) were randomized to treatment.

Baseline characteristics

Reporting groups	
Reporting group title	FF/VI 100/25 µg OD

Reporting group description:

Participants received Fluticasone Furoate (FF)/Vilanterol (VI) 100/25 micrograms (µg) inhalation powder once daily (OD) in the evening via the Dry Powder Inhaler (DPI), plus a placebo via DISKUS/ACCUHALER twice daily (BID), for 52 weeks. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication during the Treatment Period.

Reporting group title	FF/VI 200/25 µg OD

Reporting group description:

Participants received FF/VI 200/25 µg inhalation powder OD in the evening via the DPI, plus a placebo via
DISKUS/ACCUHALER BID, for 52 weeks. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication during the Treatment Period.

Reporting group title	FP 500 µg BID

Reporting group description:

Participants received Fluticasone Propionate (FP) 500 µg BID via DISKUS/ACCUHALER, plus a placebo via the DPI OD in the evening, for 52 weeks. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication during the Treatment Period.

Reporting group values	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID
Number of subjects	201	202	100
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	39.7	38.5	38.6
standard deviation	± 15.85	± 15.64	± 15.97
Gender categorical Units: Subjects			
Female	130	124	62
Male	71	78	38
Race, customized Units: Subjects			
African American/African Heritage	15	17	6
Asian - East Asian Heritage	0	0	1
Asian - South East Asian Heritage	50	51	24
Asian - Mixed Race	0	0	1
White - Arabic/North African Heritage	4	1	0
White - White/Caucasian/European Heritage	129	132	68
White - Mixed Race	2	1	0
Mixed Race	1	0	0

Reporting group values	Total		
Number of subjects	503		

Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	316		
Male	187		
Race, customized Units: Subjects			
African American/African Heritage	38		
Asian - East Asian Heritage	1		
Asian - South East Asian Heritage	125		
Asian - Mixed Race	1		
White - Arabic/North African Heritage	5		
White - White/Caucasian/European Heritage	329		
White - Mixed Race	3		
Mixed Race	1		

End points

End points reporting groups

Reporting group title	Current asthma therapy at a fixed dose

Reporting group description:

Participants were instructed to continue using an approved fixed dose of an inhaled corticosteroid (ICS) with or without an additional controller medication (i.e., long-acting beta-agonist, leukotriene modifier, etc.) for 2 weeks. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication during the Run-in Period.

Reporting group title	FF/VI 100/25 µg OD

Reporting group description:

Participants received Fluticasone Furoate (FF)/Vilanterol (VI) 100/25 micrograms (µg) inhalation powder once daily (OD) in the evening via the Dry Powder Inhaler (DPI), plus a placebo via DISKUS/ACCUHALER twice daily (BID), for 52 weeks. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication during the Treatment Period.

Reporting group title	FF/VI 200/25 µg OD

Reporting group description:

Participants received FF/VI 200/25 µg inhalation powder OD in the evening via the DPI, plus a placebo via
DISKUS/ACCUHALER BID, for 52 weeks. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication during the Treatment Period.

Reporting group title	FP 500 µg BID

Reporting group description:

Participants received Fluticasone Propionate (FP) 500 µg BID via DISKUS/ACCUHALER, plus a placebo via the DPI OD in the evening, for 52 weeks. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication during the Treatment Period.

Primary: Number of participants with any adverse event (AE) or serious adverse event (SAE) during the Treatment Period

End point title	Number of participants with any adverse event (AE) or serious adverse event (SAE) during the Treatment Period[1]

End point description:

An AE is defined as 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. A serious adverse event (SAE) is defined as any untoward medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, or is a congenital anomaly/birth defect. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations. Refer to the General Adverse AE/SAE module for a complete list of AEs and SAEs.

End point type	Primary

End point timeframe:

From the start of study medication until Visit 11 (Week 52)/Early Withdrawal

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201[2]	202[3]	100[4]	
Units: participants				
Any AE	139	134	73	
Any SAE	3	1	7	

Notes:

[2] - ITT Population: participants randomized to treatment who received >=1 dose of study medication

[3] - ITT Population: participants randomized to treatment who received >=1 dose of study medication

[4] - ITT Population: participants randomized to treatment who received >=1 dose of study medication

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with severe asthma exacerbations during the Treatment Period

End point title	Number of participants with severe asthma exacerbations during the Treatment Period[5]

End point description:

A severe asthma exacerbation is defined as the deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids. Courses of corticosteroids separated by 1 week or more were treated as separate severe exacerbations.

End point type	Primary

End point timeframe:

From the start of study medication until Visit 11 (Week 52)/Early Withdrawal

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201[6]	202[7]	100[8]	
Units: participants	3	6	3	

Notes:

[6] - Intent-to-Treat (ITT) Population

[7] - Intent-to-Treat (ITT) Population

[8] - Intent-to-Treat (ITT) Population

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in albumin and total protein at Week 12, Week 28, and Week 52/Early Withdrawal

End point title	Change from Baseline in albumin and total protein at Week 12, Week 28, and Week 52/Early Withdrawal[9]

End point description:

Blood samples were collected for the measurement of albumin and total protein values at the following scheduled time points: Baseline, Week 12, Week 28, and Week 52/Early Withdrawal. The Baseline value is defined as the most recent recorded value at Screening or prior to Day 1. Change from Baseline was calculated as the value at the post-Baseline time point minus the value at Baseline.

End point type	Primary

End point timeframe:

Baseline; Week 12, Week 28, and Week 52/Early Withdrawal

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201[10]	202[11]	100[12]	
Units: Grams per liter (G/L)				
arithmetic mean (standard deviation)				
Albumin, Week 12, n=172, 182, 87	0.1 (± 2.69)	0.2 (± 2.87)	-0.5 (± 2.64)	
Albumin, Week 28, n=180, 176, 79	-0.2 (± 2.68)	-0.3 (± 2.79)	-0.4 (± 2.76)	
Albumin, Week 52, n=157, 159, 67	-0.1 (± 2.81)	-0.8 (± 2.72)	-0.5 (± 2.54)	
Total protein, Week 12, n=172, 182, 87	-0.6 (± 4.13)	-0.1 (± 4.5)	-0.6 (± 3.96)	
Total protein, Week 28, n=180, 176, 79	-1.1 (± 3.9)	-1 (± 4.47)	-0.5 (± 4.33)	
Total protein, Week 52, n=157, 159, 67	-0.7 (± 4.53)	-1.4 (± 4.6)	-1 (± 4.38)	

Notes:

[10] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[11] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[12] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase (CK), and gamma glutamyltransferase (GGT) at Week 12, Week 28, and Week 52/Early Withdrawal

End point title	Change from Baseline in alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase (CK), and gamma glutamyltransferase (GGT) at Week 12, Week 28, and Week 52/Early Withdrawal[13]

End point description:

Blood samples were collected for the measurement of ALP, ALT, AST, CK, and GGT values at the following scheduled time points: Baseline, Week 12, Week 28, and Week 52/Early Withdrawal. The Baseline value is defined as the most recent recorded value at Screening or prior to Day 1. Change from Baseline was calculated as the value at the post-Baseline time point minus the value at Baseline.

End point type	Primary

End point timeframe:

Baseline; Week 12, Week 28, and Week 52/Early Withdrawal

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201[14]	202[15]	100[16]	
Units: International units per liter (IU/L)				
arithmetic mean (standard deviation)				
ALP, Week 12, n=158, 165, 84	-3 (± 18.76)	-2.6 (± 29.65)	-4.7 (± 24.47)	
ALP, Week 28, n=180, 176, 79	-1 (± 32.68)	-5.8 (± 30.56)	-5.7 (± 24.33)	
ALP, Week 52, n=157, 157, 67	-4 (± 30.67)	-7.2 (± 34.65)	-9.3 (± 27.54)	
ALT, Week 12, n=172, 182, 87	-1 (± 10.43)	-0.2 (± 13.51)	-0.3 (± 12.03)	
ALT, Week 28, n=180, 176, 79	-1.6 (± 10.08)	-0.1 (± 10.59)	0.4 (± 11.96)	
ALT, Week 52, n=157, 159, 67	-1.8 (± 12.4)	-1.3 (± 11.13)	-0.1 (± 9.78)	
AST, Week 12, n=171, 181, 87	-0.9 (± 8.07)	-0.3 (± 12.05)	0.3 (± 8.69)	
AST, Week 28, n=179, 176, 79	-1.4 (± 8.42)	-0.9 (± 11.6)	1.3 (± 10.65)	
AST, Week 52, n=156, 158, 67	-1.8 (± 8.78)	-1.9 (± 11.21)	-0.2 (± 9.22)	
CK, Week 12, n=172, 181, 87	10.8 (± 92.06)	-11.5 (± 254.71)	-18.3 (± 223.59)	
CK, Week 28, n=180, 176, 79	2 (± 68.72)	-9.9 (± 247.61)	15.3 (± 441.68)	
CK, Week 52, n=157, 159, 67	-0.7 (± 69.12)	-16.8 (± 266.48)	-27.7 (± 274.14)	
GGT, Week 12, n=172, 182, 87	0.9 (± 12.9)	-0.1 (± 18.23)	-1.7 (± 12.12)	
GGT, Week 28, n=180, 176, 79	3.3 (± 33.79)	-0.6 (± 17.63)	-0.2 (± 11.85)	
GGT, Week 52, n=157, 159, 67	2.7 (± 40.34)	-2.7 (± 15.99)	-0.5 (± 13.3)	

Notes:

[14] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[15] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[16] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in direct bilirubin, indirect bilirubin, total bilirubin, and creatinine at Week 12, Week 28, and Week 52/Early Withdrawal

End point title	Change from Baseline in direct bilirubin, indirect bilirubin, total bilirubin, and creatinine at Week 12, Week 28, and Week 52/Early Withdrawal[17]

End point description:

Blood samples were collected for the measurement of direct bilirubin, indirect bilirubin, total bilirubin, and creatinine values at the following scheduled time points: Baseline, Week 12, Week 28, and Week 52/Early Withdrawal. The Baseline value is defined as the most recent recorded value at Screening or prior to Day 1. Change from Baseline was calculated as the value at the post-Baseline time point minus the value at Baseline.

End point type	Primary

End point timeframe:

Baseline; Week 12, Week 28, and Week 52/Early Withdrawal

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201[18]	202[19]	100[20]	
Units: Micromoles per liter (µmol/L)				
arithmetic mean (standard deviation)				
Direct bilirubin, Week 12, n=172, 182, 87	-0.3 (± 0.99)	-0.3 (± 0.98)	-0.2 (± 0.93)	
Direct bilirubin, Week 28, n=180, 176, 79	-0.3 (± 0.97)	-0.2 (± 1.01)	-0.1 (± 0.94)	
Direct bilirubin, Week 52, n=157, 159, 67	-0.4 (± 0.99)	-0.4 (± 1)	-0.2 (± 0.9)	
Indirect bilirubin, Week 12, n=172, 182, 87	-1.4 (± 3.11)	-0.8 (± 2.86)	-0.6 (± 3.04)	
Indirect bilirubin, Week 28, n=180, 175, 79	-1.3 (± 3.09)	-0.9 (± 2.87)	-0.4 (± 3.14)	
Indirect bilirubin, Week 52, n=157, 159, 67	-2 (± 3.08)	-1.6 (± 2.51)	-0.8 (± 2.68)	
Total bilirubin, Week 12, n=172, 182, 87	-1.7 (± 3.62)	-1.1 (± 3.46)	-0.8 (± 3.44)	
Total bilirubin, Week 28, n=180, 175, 79	-1.6 (± 3.61)	-1.2 (± 3.55)	-0.5 (± 3.46)	
Total bilirubin, Week 52, n=157, 159, 67	-2.4 (± 3.58)	-2 (± 2.93)	-1 (± 3.14)	
Creatinine, Week 12, n=172, 181, 87	3 (± 10.214)	3.18 (± 7.983)	3.99 (± 8.056)	
Creatinine, Week 28, n=180, 176, 79	7.03 (± 19.264)	5.1 (± 10.316)	17.43 (± 92.175)	
Creatinine, Week 52, n=157, 159, 67	2.74 (± 9.45)	3.14 (± 11.31)	3.32 (± 9.982)	

Notes:

[18] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[19] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[20] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in chloride, carbon dioxide content/bicarbonate, glucose, potassium, sodium, and urea/blood urea nitrogen (BUN) at Week 12, Week 28, and Week 52/Early Withdrawal

End point title	Change from Baseline in chloride, carbon dioxide content/bicarbonate, glucose, potassium, sodium, and urea/blood urea nitrogen (BUN) at Week 12, Week 28, and Week 52/Early Withdrawal[21]

End point description:

Blood samples were collected for the measurement of chloride, carbon dioxide (CO2) content/bicarbonate, glucose, potassium, sodium, and urea/BUN values at the following scheduled time points: Baseline, Week 12, Week 28, and Week 52/Early Withdrawal. The Baseline value is defined as the most recent recorded value at Screening or prior to Day 1. Change from Baseline was calculated as the value at the post-Baseline time point minus the value at Baseline.

End point type	Primary

End point timeframe:

Baseline; Week 12, Week 28, and Week 52/Early Withdrawal

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201[22]	202[23]	100[24]	
Units: Millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)				
Chloride, Week 12, n=172, 182, 87	-0.7 (± 3.43)	-0.4 (± 3.5)	0.1 (± 2.28)	
Chloride, Week 28, n=180, 176, 79	-0.1 (± 2.5)	0.2 (± 2.73)	-0.1 (± 2.54)	
Chloride, Week 52, n=157, 159, 67	-0.5 (± 2.51)	0 (± 2.67)	-0.3 (± 2.31)	
CO2 content/bicarbonate, Week 12, n=171, 181, 87	-0.7 (± 3.13)	-0.8 (± 2.91)	-0.2 (± 2.72)	
CO2 content/bicarbonate, Week 28, n=179, 176, 79	0.3 (± 2.9)	0.1 (± 2.61)	0.9 (± 2.6)	
CO2 content/bicarbonate, Week 52, n=156, 158, 67	-0.1 (± 2.53)	0.1 (± 2.51)	0.5 (± 2.55)	
Glucose, Week 12, n=172, 181, 87	0.33 (± 1.873)	0.17 (± 2.085)	0.1 (± 1.233)	
Glucose, Week 28, n=180, 175, 79	0.21 (± 1.547)	0.16 (± 1.556)	0.02 (± 1.442)	
Glucose, Week 52, n=157, 159, 67	0.45 (± 1.839)	0.11 (± 1.426)	-0.2 (± 1.191)	
Potassium, Week 12, n=157, 165, 84	-0.09 (± 0.572)	0 (± 0.721)	-0.03 (± 0.606)	
Potassium, Week 28, n=179, 176, 79	-0.12 (± 0.467)	-0.15 (± 0.449)	0.02 (± 0.617)	
Potassium, Week 52, n=156, 156, 67	-0.18 (± 0.461)	-0.12 (± 0.535)	-0.1 (± 0.446)	
Sodium, Week 12, n=172, 182, 87	-0.1 (± 2.47)	0.2 (± 2.61)	0 (± 2.24)	
Sodium, Week 28, n=180, 176, 79	0 (± 2.46)	0.2 (± 2.65)	0.3 (± 2.74)	
Sodium, Week 52, n=157, 159, 67	-0.2 (± 2.57)	0.1 (± 2.52)	0 (± 2.8)	
Urea/BUN, Week 12, n=172, 182, 87	0.24 (± 1.299)	0.36 (± 1.237)	0.02 (± 1.757)	
Urea/BUN, Week 28, n=180, 176, 79	0.16 (± 1.46)	0.14 (± 1.124)	0.41 (± 2.676)	
Urea/BUN, Week 52, n=157, 159, 67	0.15 (± 1.244)	0.13 (± 1.479)	-0.04 (± 1.9)	

Notes:

[22] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[23] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[24] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in the percentage of basophils, eosinophils, hematocrit, lymphocytes, monocytes, and segmented neutrophils in the blood at Week 12, Week 28, and Week 52/Early Withdrawal

End point title	Change from Baseline in the percentage of basophils, eosinophils, hematocrit, lymphocytes, monocytes, and segmented neutrophils in the blood at Week 12, Week 28, and Week 52/Early Withdrawal[25]

End point description:

Blood samples were collected for the measurement of the percentage of basophils, eosinophils, hematocrit, lymphocytes, monocytes, and segmented neutrophils in the blood at the following scheduled time points: Baseline, Week 12, Week 28, and Week 52/Early Withdrawal. The Baseline value is defined as the most recent recorded value at Screening or prior to Day 1. Change from Baseline was calculated as the value at the post-Baseline time point minus the value at Baseline.

End point type	Primary

End point timeframe:

Baseline; Week 12, Week 28, and Week 52/Early Withdrawal

Notes:

[25] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201[26]	202[27]	100[28]	
Units: percentage				
arithmetic mean (standard deviation)				
Basophils, Week 12, n=171, 170, 86	-0.01 (± 0.33)	-0.06 (± 0.331)	-0.08 (± 0.32)	
Basophils, Week 28, n=169, 169, 77	-0.01 (± 0.319)	0 (± 0.338)	-0.06 (± 0.31)	
Basophils, Week 52, n=155, 155, 71	0.02 (± 0.314)	-0.03 (± 0.279)	-0.07 (± 0.319)	
Eosinophils, Week 12, n=171, 170, 86	-0.35 (± 4.048)	-0.88 (± 3.825)	-1.23 (± 3.391)	
Eosinophils, Week 28, n=169, 169, 77	-0.97 (± 3.991)	-1.34 (± 3.774)	-1.63 (± 3.574)	
Eosinophils, Week 52, n=155, 155, 71	-0.84 (± 4.096)	-0.9 (± 3.946)	-1.19 (± 3.611)	
Lymphocytes, Week 12, n=171, 170, 86	-0.57 (± 9.28)	-0.91 (± 8.414)	-1.72 (± 8.449)	
Lymphocytes, Week 28, n=169, 169, 77	-1.11 (± 8.816)	-1.31 (± 10.2)	-1.66 (± 11.054)	
Lymphocytes, Week 52, n=155, 155, 71	1.34 (± 9.389)	-0.03 (± 10.137)	-0.97 (± 8.532)	
Monocytes, Week 12, n=171, 170, 86	-0.6 (± 2.692)	-0.47 (± 2.5)	-0.86 (± 3.147)	
Monocytes, Week 28, n=169, 169, 77	-0.66 (± 2.594)	-0.53 (± 2.706)	-0.84 (± 3.063)	
Monocytes, Week 52, n=155, 155, 71	-0.19 (± 2.439)	0.31 (± 2.598)	-0.3 (± 2.337)	
Segmented neutrophils, Week 12, n=171, 170, 86	1.54 (± 10.883)	2.32 (± 9.635)	3.89 (± 11.397)	
Segmented neutrophils, Week 28, n=169, 169, 77	2.71 (± 10.221)	3.18 (± 12.008)	4.19 (± 13.745)	
Segmented neutrophils, Week 52, n=155, 155, 71	-0.33 (± 10.687)	0.66 (± 11.768)	2.54 (± 10.112)	

Notes:

[26] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[27] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[28] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in eosinophil count, total absolute neutrophil count (ANC), platelet count, and white blood cell (WBC) count at Week 12, Week 28, and Week 52/Early Withdrawal

End point title	Change from Baseline in eosinophil count, total absolute neutrophil count (ANC), platelet count, and white blood cell (WBC) count at Week 12, Week 28, and Week 52/Early Withdrawal[29]

End point description:

Blood samples were collected to determine the eosinophil count, total ANC, platelet count, and WBC

count at the following scheduled time points: Baseline, Week 12, Week 28, and Week 52/Early Withdrawal. The Baseline value is defined as the most recent recorded value at Screening or prior to Day 1. Change from Baseline was calculated as the value at the post-Baseline time point minus the value at Baseline.

End point type	Primary

End point timeframe:

Baseline; Week 12, Week 28, and Week 52/Early Withdrawal

Notes:

[29] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201[30]	202[31]	100[32]	
Units: 10^9 cells per liter (GI/L)				
arithmetic mean (standard deviation)				
Eosinophil count, Week 12, n=171, 170, 86	-0.01 (± 0.3226)	-0.057 (± 0.3841)	-0.073 (± 0.222)	
Eosinophil count, Week 28, n=169, 169, 77	-0.039 (± 0.331)	-0.083 (± 0.3698)	-0.083 (± 0.2363)	
Eosinophil count, Week 52, n=155, 155, 71	-0.023 (± 0.3273)	-0.037 (± 0.3171)	-0.044 (± 0.2539)	
Total ANC, Week 12, n=171, 170, 86	0.392 (± 1.6161)	0.469 (± 1.6904)	0.493 (± 1.7488)	
Total ANC, Week 28, n=169, 169, 77	0.632 (± 1.5922)	0.679 (± 2.0157)	0.75 (± 2.013)	
Total ANC, Week 52, n=136, 136, 60	0.524 (± 1.4589)	0.612 (± 1.91)	0.748 (± 1.7946)	
Platelet count, Week 12, n=167, 159, 78	-1.3 (± 39.44)	1.5 (± 68.1)	1.5 (± 43.26)	
Platelet count, Week 28, n=164, 165, 74	1 (± 44.49)	3.5 (± 35.06)	12.4 (± 43.59)	
Platelet count, Week 52, n=147, 151, 68	1.8 (± 43.8)	4.6 (± 38.49)	16.4 (± 50.99)	
WBC count, Week 12, n=173, 170, 86	0.51 (± 1.744)	0.5 (± 2.007)	0.39 (± 1.906)	
WBC count, Week 28, n=170, 169, 77	0.74 (± 1.758)	0.74 (± 2.103)	0.79 (± 2.028)	
WBC count, Week 52, n=156, 156, 71	0.91 (± 1.639)	0.83 (± 2.046)	1.01 (± 1.909)	

Notes:

[30] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[31] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[32] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in hematocrit at Week 12, Week 28, and Week 52/Early Withdrawal

End point title	Change from Baseline in hematocrit at Week 12, Week 28, and Week 52/Early Withdrawal[33]

End point description:

Blood samples were collected for the measurement of hematocrit values at the following scheduled time points: Baseline, Week 12, Week 28, and Week 52/Early Withdrawal. The Baseline value is defined as the most recent recorded value at Screening or prior to Day 1. Change from Baseline was calculated as the value at the post-Baseline time point minus the value at Baseline.

End point type	Primary

End point timeframe:

Baseline; Week 12, Week 28, and Week 52/Early Withdrawal

Notes:

[33] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201[34]	202[35]	100[36]	
Units: Proportion of 1.0				
arithmetic mean (standard deviation)				
Week 12, n=176, 172, 86	-0.0073 (± 0.02307)	-0.0013 (± 0.02654)	-0.0025 (± 0.02318)	
Week 28, n=172, 170, 77	-0.0017 (± 0.02213)	-0.0005 (± 0.02464)	-0.0028 (± 0.02168)	
Week 52, n=157, 159, 72	-0.0027 (± 0.02906)	-0.0021 (± 0.02467)	-0.0045 (± 0.02495)	

Notes:

[34] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[35] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[36] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with the indicated shift from Baseline to high, normal or no change, and low post-Baseline values for urinary cortisol excretion

End point title	Number of participants with the indicated shift from Baseline to high, normal or no change, and low post-Baseline values for urinary cortisol excretion[37]

End point description:

A 24-hour urine sample was collected for the measurement of 24-hour urinary cortisol excretion (UCE) at the following scheduled time points: Baseline, Week 12, Week 28, and Week 52/Early Withdrawal. Any visit post-baseline (AVPB) value was derived using laboratory assessments performed at scheduled, unscheduled, and Early Withdrawal visits. Participants who had a shift from Baseline in their post-Baseline UCE values relative to the normal range, are presented in the "To high and To low" categories. Participants whose post-Baseline UCE values were unchanged (e.g., High to High) or whose value became normal, are presented in the "To normal or no change" category. The normal range for UCE is defined as: 11 to 138 nanomoles per 24 hours (nmol/24 hr) for participants >=18 years of age, 8.3 to 151.7 nmol/24 hr for participants 14 to 17 years of age, and 2.8 to 124.2 nmol/24 hr for participants 12 and 13 years of age.

End point type	Primary

End point timeframe:

Baseline; Week 12, Week 28, and Week 52/Early Withdrawal

Notes:

[37] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201[38]	202[39]	100[40]	
Units: participants				
Week 12: To high, n=139, 140, 78	6	7	2	
Week 12: To normal or no change, n=139, 140, 78	131	128	67	
Week 12: To low, n=139, 140, 78	2	5	9	
Week 28: To high, n=135, 131, 59	8	8	3	
Week 28: To normal or no change, n=135, 131, 59	123	120	47	
Week 28: To low, n=135, 131, 59	4	3	9	
Week 52: To high, n=134, 140, 65	10	7	4	
Week 52: To normal or no change , n=134, 140, 65	119	131	57	
Week 52: To low, n=134, 140, 65	5	2	4	
AVBP: To high, n=156, 156, 83	25	21	8	
AVBP: To normal or no change, n=156, 156, 83	119	126	58	
AVBP: To low, n=156, 156, 83	12	9	17	

Notes:

[38] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[39] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[40] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

Statistical analyses

No statistical analyses for this end point

Primary: Ratio of 24-hour urinary cortisol excretion at Week 12 to Baseline

End point title	Ratio of 24-hour urinary cortisol excretion at Week 12 to Baseline

End point description:

A 24-hour urine sample was collected, and the least square geometric mean (LSGM) for 24-hour urinary cortisol excretion (UCE) was calculated at Baseline and at Week 12. The ratio of the Week 12 LSGM to the Baseline LSGM was calculated as the value at Week 12 divided by the value at Baseline. Analysis was performed using analysis of covariance (ANCOVA) with covariates of region, sex, age, treatment, and the log of the Baseline values. Members of the Urinary cortisol (UC) Population, defined as participants in the ITT Population whose urine samples did not have confounding factors that affected the interpretation of results, were analyzed. These participants were determined prior to breaking the blind. Only those participants available at the specified time point were analyzed.

End point type	Primary

End point timeframe:

Baseline and Week 12

End point values	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	129[41]	129[42]	71[43]	
Units: Ratio of LSGM of UCE to Baseline				
number (not applicable)	1.03	0.93	0.61	

Notes:
[41] - UC Population
[42] - UC Population
[43] - UC Population

Statistical analyses

Statistical analysis title	Statistical Analysis #1
Comparison groups	FF/VI 100/25 µg OD v FP 500 µg BID
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Ratio of LSGM to Baseline
Point estimate	1.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.34
upper limit	2.08

Statistical analysis title	Statistical Analysis #2
Comparison groups	FF/VI 200/25 µg OD v FP 500 µg BID
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Ratio of LSGM to Baseline
Point estimate	1.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.22
upper limit	1.89

Primary: Ratio of 24-hour urinary cortisol excretion at Week 28 to Baseline

End point title	Ratio of 24-hour urinary cortisol excretion at Week 28 to Baseline

End point description:

A 24-hour urine sample was collected, and the LSGM for 24-hour UCE was calculated at Baseline and at Week 28. The ratio of the Week 28 LSGM to the Baseline LSGM was calculated as the value at Week 28 divided by the value at Baseline. Analysis was performed using ANCOVA with covariates of region, sex, age, treatment, and the log of the Baseline values.

End point type	Primary

End point timeframe:
Baseline and Week 28

End point values	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	128[44]	121[45]	56[46]	
Units: Ratio of LSGM of UCE to Baseline				
number (not applicable)	1.05	0.91	0.64	

Notes:
[44] - UC Population. Only those participants available at the specified time point were analyzed.
[45] - UC Population. Only those participants available at the specified time point were analyzed.
[46] - UC Population. Only those participants available at the specified time point were analyzed.

Statistical analyses

Statistical analysis title	Statistical Analysis #1
Comparison groups	FF/VI 100/25 µg OD v FP 500 µg BID
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Ratio of LSGM to Baseline
Point estimate	1.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.29
upper limit	2.13

Statistical analysis title	Statistical Analysis #2
Comparison groups	FF/VI 200/25 µg OD v FP 500 µg BID
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	ANCOVA
Parameter estimate	Ratio of LSGM to Baseline
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.11
upper limit	1.84

Primary: Ratio of 24-hour urinary cortisol excretion at Week 52 to Baseline	
End point title	Ratio of 24-hour urinary cortisol excretion at Week 52 to Baseline

End point description:

A 24-hour urine sample was collected, and the LSGM for 24-hour UCE was calculated at Baseline and at Week 52. The ratio of the Week 52 LSGM to the Baseline LSGM was calculated as the value at Week 52 divided by the value at Baseline. Analysis was performed using ANCOVA with covariates of region, sex, age, treatment, and the log of the Baseline values.

End point type	Primary

End point timeframe:

Baseline and Week 52

End point values	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	125[47]	127[48]	60[49]	
Units: Ratio of LSGM of UCE to Baseline				
number (not applicable)	1	1.04	0.95	

Notes:

[47] - UC Population. Only those participants available at the specified time point were analyzed.

[48] - UC Population. Only those participants available at the specified time point were analyzed.

[49] - UC Population. Only those participants available at the specified time point were analyzed.

Statistical analyses

Statistical analysis title	Statistical Analysis #1
Comparison groups	FF/VI 100/25 µg OD v FP 500 µg BID
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.674
Method	ANCOVA
Parameter estimate	Ratio of LSGM to Baseline
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.33

Statistical analysis title	Statistical Analysis #2
Comparison groups	FF/VI 200/25 µg OD v FP 500 µg BID

Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.444
Method	ANCOVA
Parameter estimate	Ratio of LSGM to Baseline
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.38

Primary: Number of participants with evidence of oral candidiasis at any time post-Baseline

End point title	Number of participants with evidence of oral candidiasis at any time post-Baseline[50]

End point description:

A detailed oropharyngeal examination was done at all clinic visits for visual/clinical evidence of oral candidiasis over the entire Treatment Period (worst case any time post-Baseline). For participants with visual/clinical evidence of candidiasis during the Treatment Phase of the study, a culture swab was taken and analyzed for infection.

End point type	Primary

End point timeframe:

From Baseline until Visit 11/Early Withdrawal (52 weeks)

Notes:

[50] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	199[51]	200[52]	100[53]	
Units: participants				
Evidence of oral candidiasis	15	14	5	
Positive culture swab	13	11	3	
Negative culture swab	1	2	2	
No swab result available	1	1	0	

Notes:

[51] - ITT Population. Only those participants available at the specified time points were analyzed.

[52] - ITT Population. Only those participants available at the specified time points were analyzed.

[53] - ITT Population. Only those participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Primary: Maximum change from Baseline in systolic blood pressure (SBP) and minimum change from Baseline in diastolic blood pressure (DBP)

End point title	Maximum change from Baseline in systolic blood pressure (SBP) and minimum change from Baseline in diastolic blood

	pressure (DBP)[54]

End point description:

SBP and DBP were measured at the following scheduled time points: Screening, Day 1, Week 2, Week 4, Week 8, Week 12, Week 20, Week 28, Week 36, Week 44, and Week 52/Early Withdrawal. Baseline is defined as the Visit 1 (screening) value. Change from Baseline was calculated as the value at the post-Baseline time point minus the value at Baseline. Maximum and minimum change from Baseline for any post-Baseline visit was derived using all scheduled, unscheduled, and Early Withdrawal visits.

End point type	Primary

End point timeframe:

From Baseline until Visit 11/Early Withdrawal (52 weeks)

Notes:

[54] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201[55]	202[56]	100[57]	
Units: Millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)				
Maximum post-Baseline change in SBP	10.2 (± 11.05)	10 (± 10.17)	11.3 (± 11.09)	
Minimum post-Baseline change in DBP	-8.9 (± 7.7)	-9 (± 8.44)	-8 (± 7.76)	

Notes:

[55] - ITT Population

[56] - ITT Population

[57] - ITT Population

Statistical analyses

No statistical analyses for this end point

Primary: Maximum change from Baseline in pulse rate

End point title	Maximum change from Baseline in pulse rate[58]

End point description:

Pulse rate was measured at the following scheduled time points: Screening, Day 1, Week 2, Week 4, Week 8, Week 12, Week 20,Week 28, Week 36, Week 44, and Week 52/Early Withdrawal. Baseline is defined as the Visit 1 (screening) value. Change from Baseline was calculated as the value at the post-Baseline time point minus the value at Baseline. Maximum change from Baseline for any post-Baseline visit was derived using all scheduled, unscheduled, and Early Withdrawal visits.

End point type	Primary

End point timeframe:

From Baseline until Visit 11/Early Withdrawal (52 weeks)

Notes:

[58] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201[59]	202[60]	100[61]	
Units: Beats per minute				
arithmetic mean (standard deviation)	10.5 (± 9.3)	10 (± 10.05)	7.5 (± 8.29)	

Notes:

[59] - ITT Population

[60] - ITT Population

[61] - ITT Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with the indicated change from Baseline in Lens Opacities Classification System, Version III (LOCS III) Posterior Subcapsular Opacity (P) at Week 28 and Week 52

End point title	Number of participants with the indicated change from Baseline in Lens Opacities Classification System, Version III (LOCS III) Posterior Subcapsular Opacity (P) at Week 28 and Week 52[62]

End point description:

P is defined as the opacification at the back of the lens adjacent to the capsule (or bag) in which the lens sits. An event of P is defined as an increase of >=0.3 from Baseline in LOCS III grade for P in either eye at any time post-Baseline. Per LOC III, P ranges from 0.1 (clear or colorless) to 5.9 (very opaque). Change from Baseline was calculated as the value at the post-Baseline time point minus the value at Baseline.

End point type	Primary

End point timeframe:

Baseline; Week 28, and Week 52

Notes:

[62] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201[63]	202[64]	100[65]	
Units: participants				
Left eye, <0.3, Week 28, n=179, 177, 80	174	175	79	
Left eye, >=0.3 and <0.5, Week 28, n=179, 177, 80	5	2	1	
Left eye, >=0.5, Week 28, n=179, 177, 80	0	0	0	
Right eye, <0.3, Week 28, n=179, 177, 80	175	175	80	
Right eye, >=0.3 and <0.5, Week 28, n=179, 177, 80	4	2	0	
Right eye, >=0.5, Week 28, n=179, 177, 80	0	0	0	
Left eye, <0.3, Week 52, n=167, 166, 72	163	164	72	
Left eye, >=0.3 and <0.5, Week 52, n=167, 166, 72	2	1	0	
Left eye, >=0.5, Week 52, n=167, 166, 72	2	1	0	
Right eye, <0.3, Week 52, n=167, 166, 72	163	164	72	
Right eye, >=0.3 and <0.5, Week 52, n=167, 166, 72	3	1	0	

Right eye, >=0.5, Week 52, n=167, 166, 72	1	1	0	

Notes:

[63] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[64] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[65] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in hemoglobin at Week 12, Week 28, and Week 52/Early Withdrawal

End point title	Change from Baseline in hemoglobin at Week 12, Week 28, and Week 52/Early Withdrawal[66]

End point description:

Blood samples were collected for the measurement of hemoglobin values at the following scheduled time points: Baseline, Week 12, Week 28, and Week 52/Early Withdrawal. The Baseline value is defined as the most recent recorded value at Screening or prior to Day 1. Change from Baseline was calculated as the value at the post-Baseline time point minus the value at Baseline.

End point type	Primary

End point timeframe:

Baseline; Week 12, Week 28, and Week 52/Early Withdrawal

Notes:

[66] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201[67]	202[68]	100[69]	
Units: Grams per liter (g/L)				
arithmetic mean (standard deviation)				
Week 12, n=176, 172, 86	-3.4 (± 7.48)	-1.8 (± 8.25)	-2 (± 7.67)	
Week 28, n=172, 170, 77	-2.1 (± 7.64)	-2.2 (± 8.11)	-2.4 (± 7.72)	
Week 52, n=157, 159, 72	-2.6 (± 10.26)	-2.9 (± 7.47)	-3 (± 8.77)	

Notes:

[67] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[68] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[69] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with the indicated change from Baseline in Intraocular Pressure (IOP) at Week 28 and Week 52

End point title	Number of participants with the indicated change from Baseline in Intraocular Pressure (IOP) at Week 28 and Week 52[70]

End point description:

Intraocular pressure (IOP) is the fluid pressure inside the eye. IOP was measured twice for each eye at Baseline, Week 28, and Week 52 using Goldmann Applanation tonometry. The second IOP reading was used for analysis. The number of participants with a change from Baseline in IOP of <0 mmHg, >=0 to <4 mmHg, >=4 to <7 mmHg, >=7 to <11 mmHg, and >=11 mmHg are presented. Change from Baseline was calculated as the value at the post-Baseline time point minus the value at Baseline.

End point type	Primary

End point timeframe:

Baseline; Week 28 and Week 52

Notes:

[70] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201[71]	202[72]	100[73]	
Units: participants				
Left eye, <0 mmHg, Week 28, n=179, 177, 80	71	78	32	
Left eye, >=0 to <4 mmHg, Week 28, n=179, 177, 80	101	92	46	
Left eye, >=4 to <7 mmHg, Week 28, n=179, 177, 80	7	6	2	
Left eye, >=7 to <11 mmHg, Week 28, n=179, 177, 80	0	1	0	
Left eye, >=11 mmHg, Week 28, n=179, 177, 80	0	0	0	
Right eye, <0 mmHg, Week 28, n=179, 177, 80	73	61	38	
Right eye, >=0 to <4 mmHg, Week 28, n=179, 177, 80	101	110	38	
Right eye, >=4 to <7 mmHg, Week 28, n=179, 177, 80	5	5	4	
Right eye, >=7 to <11 mmHg,Week 28, n=179, 177, 80	0	1	0	
Right eye, >=11 mmHg, Week 28, n=179, 177, 80	0	0	0	
Left eye, <0 mmHg, Week 52, n=167, 166, 72	66	69	33	
Left eye, >=0 to <4 mmHg, Week 52, n=167, 166, 72	88	83	36	
Left eye, >=4 to <7 mmHg, Week 52, n=167, 166, 72	11	14	3	
Left eye, >=7 to <11 mmHg, Week 52, n=167, 166, 72	2	0	0	
Left eye, >=11 mmHg, Week 52, n=167, 166, 72	0	0	0	
Right eye, <0 mmHg, Week 52, n=167, 166, 72	63	61	32	
Right eye, >=0 to <4 mmHg, Week 52, n=167, 166, 72	94	93	40	
Right eye, >=4 to <7 mmHg, Week 52, n=167, 166, 72	10	12	0	
Right eye, >=7 to <11 mmHg, Week 52, n=167,166, 72	0	0	0	
Right eye, >=11 mmHg, Week 52, n=167, 166, 72	0	0	0	

Notes:

[71] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[72] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[73] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in horizontal cup-to-disc ratio at Week 28 and Week 52

End point title	Change from Baseline in horizontal cup-to-disc ratio at Week 28 and Week 52[74]

End point description:

Funduscopic examination was performed at Baseline, Week 28, and Week 52 to measure the horizontal cup-to-disc ratio of both eyes. The horizontal cup-to-disc ratio is the ratio of the horizontal diameter of the physiological cup to that of the horizontal diameter of the optic disc. Change from Baseline was calculated as the value at the post-Baseline time point minus the value at Baseline.

End point type	Primary

End point timeframe:

Baseline; Week 28 and Week 52

Notes:

[74] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201[75]	202[76]	100[77]	
Units: ratio				
arithmetic mean (standard deviation)				
Left eye, Week 28, n=179, 177, 80	0.5 (± 4.79)	-0.2 (± 5.11)	0.5 (± 4.87)	
Right eye, Week 28, n=179, 177, 80	0.2 (± 4.17)	-0.2 (± 6.49)	0.5 (± 5.1)	
Left eye, Week 52, n=167, 166, 72	0.4 (± 5.86)	0.2 (± 4.89)	0.3 (± 4.77)	
Right eye, Week 52, n=167, 166, 72	0.1 (± 4.63)	0.2 (± 5.57)	0 (± 5.26)	

Notes:

[75] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[76] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[77] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with the indicated change from Baseline in Lens Opacities Classification System, Version III (LOCS III) Cortical Opacity (C) at Week 28 and Week 52

End point title	Number of participants with the indicated change from Baseline in Lens Opacities Classification System, Version III (LOCS III) Cortical Opacity (C) at Week 28 and Week 52[78]

End point description:

C is defined as the opacification of the cortex (outer layer) of the lens. Per LOC III, C ranges from 0.1 (clear or colorless) to 5.9 (very opaque). Change from Baseline was calculated as the value at the post-Baseline time point minus the value at Baseline.

End point type	Primary

End point timeframe:

Baseline; Week 28 and Week 52

Notes:

[78] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201[79]	202[80]	100[81]	
Units: participants				
Left eye, <0.3, Week 28, n=179, 177, 80	167	166	75	
Left eye, >=0.3 and <0.5, Week 28, n=179, 177, 80	6	5	4	
Left eye, >=0.5, Week 28, n=179, 177, 80	6	6	1	
Right eye, <0.3, Week 28, n=179, 177, 80	169	172	75	
Right eye, >=0.3 and <0.5, Week 28, n=179, 177, 80	5	1	4	
Right eye, >=0.5, Week 28, n=179, 177, 80	5	4	1	
Left eye, <0.3, Week 52, n=167, 166, 72	154	156	66	
Left eye, >=0.3 and <0.5, Week 52, n=167, 166, 72	7	4	3	
Left eye, >=0.5, Week 52, n=167, 166, 72	6	6	3	
Right eye, <0.3, Week 52, n=167, 166, 72	151	158	69	
Right eye, >=0.3 and <0.5, Week 52, n=167, 166, 72	11	2	2	
Right eye, >=0.5, Week 52, n=167, 166, 72	5	6	1	

Notes:

[79] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[80] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[81] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Lens Opacities Classification System, Version III (LOCS III) Nuclear Color (NC) at Week 28 and Week 52

End point title	Change from Baseline in Lens Opacities Classification System, Version III (LOCS III) Nuclear Color (NC) at Week 28 and Week 52[82]

End point description:

NC is the color of the nucleus (central layer) of the lens. Per LOC III, NC ranges from 0.1 (clear or colorless) to 6.9 (very opaque or brunescent). Change from Baseline was calculated as the value at the post-Baseline time point minus the value at Baseline.

End point type	Primary

End point timeframe:

Baseline; Week 28 and Week 52

Notes:

[82] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201[83]	202[84]	100[85]	
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 28, Left eye, n=179, 177, 80	0.01 (± 0.282)	0 (± 0.284)	-0.02 (± 0.299)	
Week 28, Right eye, n=179, 177, 80	0.01 (± 0.292)	0.01 (± 0.292)	-0.02 (± 0.294)	
Week 52, Left eye, n=167, 166, 72	0.02 (± 0.281)	-0.02 (± 0.357)	0 (± 0.34)	
Week 52, Right eye, n=167, 166, 72	0.02 (± 0.304)	0 (± 0.339)	0.01 (± 0.336)	

Notes:

[83] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[84] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[85] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Lens Opacities Classification System, Version III (LOCS III) Nuclear Opalescence (NO) at Week 28 and Week 52

End point title	Change from Baseline in Lens Opacities Classification System, Version III (LOCS III) Nuclear Opalescence (NO) at Week 28 and Week 52[86]

End point description:

NO is the opalescence of the nucleus (central layer) of the lens. Per LOC III, NO ranges from 0.1 (clear or colorless) to 6.9 (very opaque or brunescent). Change from Baseline was calculated as the value at the post-Baseline time point minus the value at Baseline.

End point type	Primary

End point timeframe:

Baseline; Week 28 and Week 52

Notes:

[86] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201[87]	202[88]	100[89]	
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 28, Left eye, n=179, 177, 80	0.02 (± 0.236)	0.03 (± 0.316)	-0.02 (± 0.27)	
Week 28, Right eye, n=179, 177, 80	0.01 (± 0.256)	0.03 (± 0.303)	-0.03 (± 0.272)	
Week 52, Left eye, n=167, 166, 72	0.01 (± 0.33)	0.03 (± 0.303)	0.01 (± 0.369)	
Week 52, Right eye, n=167, 166, 72	0 (± 0.351)	0.04 (± 0.282)	0.02 (± 0.371)	

Notes:

[87] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[88] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[89] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in the Logarithm of the Minimum Angle of Resolution (LogMAR) visual acuity at Week 28 and Week 52

End point title	Change from Baseline in the Logarithm of the Minimum Angle of Resolution (LogMAR) visual acuity at Week 28 and Week 52[90]

End point description:

Visual acuity is defined as the acuteness or clearness of vision. The minimum angle of resolution (MAR) is the angle a viewed object subtends at the eye, usually stated in degrees/minutes of arc. Visual acuity was measured using Early Treatment Diabetic Retinopathy Study (ETDRS) charts in decimal numbers. The LogMAR scale is used to express the visual acuity in a linear scale as the logarithm to base 10 of the MAR. A lower score indicates better visual acuity; visual acuity decreases with an increasing score. Change from Baseline was calculated as the value at the post-Baseline time point minus the value at Baseline.

End point type	Primary

End point timeframe:

Baseline; Week 28 and Week 52

Notes:

[90] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201[91]	202[92]	100[93]	
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 28, Left eye, n=179, 176, 80	-0.008 (± 0.0723)	-0.01 (± 0.0706)	-0.004 (± 0.0685)	
Week 28, Right eye, n=179, 176, 80	-0.003 (± 0.0739)	-0.001 (± 0.0699)	-0.008 (± 0.0584)	
Week 52, Left eye, n=167, 165, 72	-0.011 (± 0.0747)	-0.012 (± 0.0739)	-0.007 (± 0.0638)	
Week 52, Right eye, n=167, 165, 72	-0.008 (± 0.0928)	0.003 (± 0.0755)	-0.012 (± 0.0776)	

Notes:

[91] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[92] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[93] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

Statistical analyses

No statistical analyses for this end point

Primary: Maximum change from Baseline in the QT interval using Bazett's correction (QTcB) and QT interval using Fridericia's correction (QTcF)

End point title	Maximum change from Baseline in the QT interval using Bazett's correction (QTcB) and QT interval using Fridericia's correction (QTcF)[94]

End point description:

The QT interval is an electrocardiogram (ECG) parameter that represents the electrical depolarization and repolarization of the left and right ventricles of the heart. The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the ECG. Corrected QT (QTc) is the QT interval corrected for heart rate by using Bazett's formula (QTcB) and Fridericia's formula (QTcF). 12-lead ECG measurements were perfomed at the following scheduled time points: Baseline; Week 2, Week

12, Week 28, and Week 52/Early Withdrawal. The Baseline value is defined as the value taken pre-dose at screening. The maximum post-Baseline value was derived using all scheduled, unscheduled, and Early Withdrawal ECG assessments. Maximum change from Baseline was calculated as the maximum post-Baseline value minus the value at Baseline.

End point type	Primary

End point timeframe:

Baseline; Week 2, Week 12, Week 28, and Week 52/Early Withdrawal

Notes:

[94] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	199[95]	198[96]	100[97]	
Units: Milliseconds (msec)				
arithmetic mean (standard deviation)				
QTcB	19 (± 17.33)	16.4 (± 19.49)	13.2 (± 16.57)	
QTcF	12.8 (± 14.51)	11.6 (± 15.6)	11.4 (± 12.81)	

Notes:

[95] - ITT Population. Only those participants available at the specified time points were analyzed.

[96] - ITT Population. Only those participants available at the specified time points were analyzed.

[97] - ITT Population. Only those participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Primary: Mean 24 hour Holter heart rate for participants with at least 16 hours of recorded data

End point title	Mean 24 hour Holter heart rate for participants with at least 16 hours of recorded data[98]

End point description:

Twenty-four hour Holter monitors were obtained using a 12-lead Holter monitor. The Holter monitor is worn by the participant for 24 hours, and the monitor continuously records the heart's rhythm while the monitor is worn. At the end of the 24 hour period, the data from the monitor are downloaded and transmitted to the centralized vendor for analysis and interpretation by a licensed cardiologist.

End point type	Primary

End point timeframe:

0-24 hours at Screening, Day 1, Week 28, and Week 52

Notes:

[98] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201[99]	202[100]	100[101]	
Units: beats per minute				
arithmetic mean (standard deviation)				
Screening, n=111, 116, 49	79 (± 8.23)	79.1 (± 9.55)	79.8 (± 8.75)	
Day 1, n=104, 113, 47	78.6 (± 7.89)	78.7 (± 9.45)	77.4 (± 7.66)	
Week 28, n=95, 90, 39	77.8 (± 8.9)	77.5 (± 9.01)	74.9 (± 8.54)	

Week 52, n=88, 82, 37	78.8 (± 8.72)	78 (± 10.15)	74.8 (± 8.62)	

Notes:

[99] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[100] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[101] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

Statistical analyses

No statistical analyses for this end point

Primary: Maximum 24 hour Holter heart rate for participants with at least 16 hours of recorded data

End point title	Maximum 24 hour Holter heart rate for participants with at least 16 hours of recorded data[102]

End point description:

Twenty-four hour Holter monitors were obtained using a 12-lead Holter monitor. Holter monitor data were transmitted to a centralized vendor for analysis and interpretation by a licensed cardiologist.

End point type	Primary

End point timeframe:

0-24 hours at Screening, Day 1, Week 28, and Week 52

Notes:

[102] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was conducted for this end point.

End point values	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	FP 500 µg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201[103]	202[104]	100[105]	
Units: beats per minute				
arithmetic mean (standard deviation)				
Screening, n=111, 116, 49	132.6 (± 17.18)	132.1 (± 17.85)	133 (± 16.17)	
Day 1, n=104, 113, 47	131.2 (± 18.28)	130.8 (± 19.5)	129.2 (± 18.77)	
Week 28, n=95, 90, 39	127.5 (± 17.93)	127.4 (± 16.62)	123.5 (± 14.93)	
Week 52, n=88, 82, 37	126.9 (± 18.16)	128.1 (± 16.63)	122.8 (± 13.89)	

Notes:

[103] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[104] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

[105] - ITT Population. Only participants available at the specified time points were analyzed (n=X, X, X).

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious AEs were collected from the start of study medication until Follow-up (up to 52 weeks of treatment).

Adverse event reporting additional description:

SAEs and non-serious AEs were collected in the Intent-to-Treat (ITT) Population, comprised of all participants randomized to treatment who received at least one dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	FF/VI 100/25 µg OD

Reporting group description:

Participants received Fluticasone Furoate (FF)/Vilanterol (VI) 100/25 micrograms (µg) inhalation powder once daily (OD) in the evening via the Dry Powder Inhaler (DPI), plus a placebo via DISKUS/ACCUHALER twice daily (BID), for 52 weeks. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication during the Treatment Period.

Reporting group title	FP 500 µg BID

Reporting group description:

Participants received Fluticasone Propionate (FP) 500 µg BID via DISKUS/ACCUHALER, plus a placebo via the DPI OD in the evening, for 52 weeks. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication during the Treatment Period.

Reporting group title	FF/VI 200/25 µg OD

Reporting group description:

Participants received FF/VI 200/25 µg inhalation powder OD in the evening via the DPI, plus a placebo via
DISKUS/ACCUHALER BID, for 52 weeks. Participants were provided albuterol/salbutamol inhalation aerosol to be used as rescue medication during the Treatment Period.

Serious adverse events	FF/VI 100/25 µg OD	FP 500 µg BID	FF/VI 200/25 µg OD
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 201 (1.49%)	7 / 100 (7.00%)	1 / 202 (0.50%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 201 (0.00%)	1 / 100 (1.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibroadenoma of breast			

subjects affected / exposed	0 / 201 (0.00%)	1 / 100 (1.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 201 (0.00%)	1 / 100 (1.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 201 (0.00%)	1 / 100 (1.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 201 (0.50%)	2 / 100 (2.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	1 / 201 (0.50%)	0 / 100 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Dengue fever			
subjects affected / exposed	1 / 201 (0.50%)	0 / 100 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 201 (0.00%)	1 / 100 (1.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			

subjects affected / exposed	0 / 201 (0.00%)	0 / 100 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	FF/VI 100/25 µg OD	FP 500 µg BID	FF/VI 200/25 µg OD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	108 / 201 (53.73%)	71 / 100 (71.00%)	105 / 202 (51.98%)
Cardiac disorders			
Extrasystoles			
subjects affected / exposed	4 / 201 (1.99%)	3 / 100 (3.00%)	15 / 202 (7.43%)
occurrences (all)	5	3	19
Nervous system disorders			
Tension headache			
subjects affected / exposed	1 / 201 (0.50%)	3 / 100 (3.00%)	0 / 202 (0.00%)
occurrences (all)	1	4	0
Headache			
subjects affected / exposed	39 / 201 (19.40%)	23 / 100 (23.00%)	35 / 202 (17.33%)
occurrences (all)	87	54	81
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	8 / 201 (3.98%)	6 / 100 (6.00%)	13 / 202 (6.44%)
occurrences (all)	8	6	14
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 201 (0.00%)	3 / 100 (3.00%)	1 / 202 (0.50%)
occurrences (all)	0	3	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 201 (3.48%)	2 / 100 (2.00%)	6 / 202 (2.97%)
occurrences (all)	8	2	7
Abdominal pain upper			
subjects affected / exposed	8 / 201 (3.98%)	1 / 100 (1.00%)	11 / 202 (5.45%)
occurrences (all)	10	4	20
Respiratory, thoracic and mediastinal disorders			

Rhinitis allergic			
subjects affected / exposed	7 / 201 (3.48%)	2 / 100 (2.00%)	4 / 202 (1.98%)
occurrences (all)	9	3	5
Dysphonia			
subjects affected / exposed	8 / 201 (3.98%)	3 / 100 (3.00%)	6 / 202 (2.97%)
occurrences (all)	9	4	7
Oropharyngeal pain			
subjects affected / exposed	7 / 201 (3.48%)	11 / 100 (11.00%)	12 / 202 (5.94%)
occurrences (all)	8	13	13
Cough			
subjects affected / exposed	9 / 201 (4.48%)	13 / 100 (13.00%)	11 / 202 (5.45%)
occurrences (all)	11	19	12
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	4 / 201 (1.99%)	3 / 100 (3.00%)	2 / 202 (0.99%)
occurrences (all)	4	3	4
Back pain			
subjects affected / exposed	8 / 201 (3.98%)	3 / 100 (3.00%)	13 / 202 (6.44%)
occurrences (all)	8	3	20
Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	6 / 201 (2.99%)	7 / 100 (7.00%)	5 / 202 (2.48%)
occurrences (all)	6	7	7
Sinusitis			
subjects affected / exposed	9 / 201 (4.48%)	5 / 100 (5.00%)	4 / 202 (1.98%)
occurrences (all)	9	5	5
Bronchitis			
subjects affected / exposed	7 / 201 (3.48%)	5 / 100 (5.00%)	9 / 202 (4.46%)
occurrences (all)	7	7	11
Oral candidiasis			
subjects affected / exposed	12 / 201 (5.97%)	2 / 100 (2.00%)	11 / 202 (5.45%)
occurrences (all)	25	4	15
Nasopharyngitis			
subjects affected / exposed	25 / 201 (12.44%)	10 / 100 (10.00%)	19 / 202 (9.41%)
occurrences (all)	31	17	37
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	34 / 201 (16.92%) 48	18 / 100 (18.00%) 24	30 / 202 (14.85%) 56

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported