# 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 | v1 |
| This version publication date | 08 April 2016 |
| First version publication date | 09 February 2015 |

## 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<br>Units: Subjects | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 39.7 | 38.5 | 38.6 |
| standard deviation | ± 15.85 | ± 15.64 | ± 15.97 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 130 | 124 | 62 |
| Male | 71 | 78 | 38 |
| Race, customized<br>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<br>Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | -<br>- | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 316 | | |
| Male | 187 | | |
| Race, customized<br>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 (± 0.572) | -0.15 (± 0.449) | 0.02 (± 0.617) | |
| Potassium, Week 52, n=156, 156, 67 | -0.18 (± 0.572) | -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 (± 1.744) | 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 | 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.

| Serious adverse events | FF/VI 100/25 µg OD | FF/VI 200/25 µg OD | FP 500 µg BID |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 201 (1.49%) | 1 / 202 (0.50%) | 7 / 100 (7.00%) |
| 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%) | 0 / 202 (0.00%) | 1 / 100 (1.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fibroadenoma of breast | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 202 (0.00%) | 1 / 100 (1.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 202 (0.00%) | 1 / 100 (1.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 0 / 202 (0.00%) | 1 / 100 (1.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| 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%) | 0 / 202 (0.00%) | 2 / 100 (2.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| 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 / 202 (0.00%) | 0 / 100 (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 / 202 (0.00%) | 0 / 100 (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%) | 0 / 202 (0.00%) | 1 / 100 (1.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis acute | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | 0 / 100 (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 |

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

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

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

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

## 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