



## Clinical trial results:

### A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Study to Evaluate the Effects of a One-Year Course of Fluticasone Furoate Nasal Spray 110mcg QD on Growth in Pre-Pubescent, Pediatric Subjects with Perennial Allergic Rhinitis

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2007-005148-26 |
| Trial protocol           | FR IT          |
| Global end of trial date | 17 March 2011  |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 13 April 2016 |
| First version publication date | 24 June 2015  |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | FFR101782 |
|-----------------------|-----------|

##### Additional study identifiers

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

Notes:

#### Sponsors

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

Notes:

#### Paediatric regulatory details

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

Notes:

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**Results analysis stage**

|                                                      |               |
|------------------------------------------------------|---------------|
| Analysis stage                                       | Final         |
| Date of interim/final analysis                       | 12 May 2011   |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 17 March 2011 |
| Was the trial ended prematurely?                     | No            |

Notes:

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**General information about the trial**

Main objective of the trial:

The primary objective of this study is to characterize, as accurately as possible, the estimation of the difference in pre-pubescent growth velocities between subjects treated continuously for one year with FFNS 110mcg QD, the highest dose approved for pediatric use in the US, and placebo nasal spray as determined by stadiometry.

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 26 November 2007 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | France: 18         |
| Country: Number of subjects enrolled | Argentina: 88      |
| Country: Number of subjects enrolled | Canada: 12         |
| Country: Number of subjects enrolled | Chile: 154         |
| Country: Number of subjects enrolled | Peru: 37           |
| Country: Number of subjects enrolled | United States: 165 |
| Worldwide total number of subjects   | 474                |
| EEA total number of subjects         | 18                 |

Notes:

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**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)                     | 474 |
| Adolescents (12-17 years)                 | 0   |

|                      |   |
|----------------------|---|
| Adults (18-64 years) | 0 |
| From 65 to 84 years  | 0 |
| 85 years and over    | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

After screening and a 16-week Baseline Period (Pd.), participants (par.) were randomized 1:1 to each treatment arm during the 52-week Treatment Pd. After the Treatment Pd., par. entered an 8-week Follow-up (FU) Pd. during which all par. received placebo nasal spray. Par. completing at least 12 weeks of treatment were to complete the FU Pd.

### Period 1

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

### Arms

|                              |                                        |
|------------------------------|----------------------------------------|
| Are arms mutually exclusive? | Yes                                    |
| <b>Arm title</b>             | Placebo: Double-blind Treatment Period |

Arm description:

Participants were randomized to receive matching placebo nasal spray OD as 2 sprays per nostril during the 52-week Double-blind Treatment Period

|                                        |                |
|----------------------------------------|----------------|
| Arm type                               | Placebo        |
| Investigational medicinal product name | Placebo        |
| Investigational medicinal product code |                |
| Other name                             |                |
| Pharmaceutical forms                   | Nasal spray    |
| Routes of administration               | Intranasal use |

Dosage and administration details:

Once daily for 52 weeks

|                  |                                             |
|------------------|---------------------------------------------|
| <b>Arm title</b> | FFNS 110 mcg: Double-blind Treatment Period |
|------------------|---------------------------------------------|

Arm description:

Participants were randomized to receive fluticasone furoate nasal spray (FFNS) 110 micrograms (mcg) OD as 2 sprays per nostril during the 52-week Double-blind Treatment Period

|                                        |                                             |
|----------------------------------------|---------------------------------------------|
| Arm type                               | Experimental                                |
| Investigational medicinal product name | Fluticasone furoate nasal spray (110 mg QD) |
| Investigational medicinal product code |                                             |
| Other name                             |                                             |
| Pharmaceutical forms                   | Nasal spray                                 |
| Routes of administration               | Intranasal use                              |

Dosage and administration details:

Once daily fluticasone furoate nasal spray (110 mg) once daily for 52 weeks

| <b>Number of subjects in period 1</b>  | Placebo: Double-blind Treatment Period | FFNS 110 mcg: Double-blind Treatment Period |
|----------------------------------------|----------------------------------------|---------------------------------------------|
| Started                                | 237                                    | 237                                         |
| Completed                              | 187                                    | 186                                         |
| Not completed                          | 50                                     | 51                                          |
| Consent withdrawn by subject           | 20                                     | 20                                          |
| Physician decision                     | 2                                      | 4                                           |
| Adverse event, non-fatal               | 5                                      | 5                                           |
| Reached Protocol-defined Stop Criteria | 3                                      | -                                           |
| Lost to follow-up                      | 5                                      | 7                                           |
| Lack of efficacy                       | 3                                      | -                                           |
| Protocol deviation                     | 12                                     | 15                                          |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                 |                                             |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| Reporting group title                                                                                                                                                           | Placebo: Double-blind Treatment Period      |
| Reporting group description:                                                                                                                                                    |                                             |
| Participants were randomized to receive matching placebo nasal spray OD as 2 sprays per nostril during the 52-week Double-blind Treatment Period                                |                                             |
| Reporting group title                                                                                                                                                           | FFNS 110 mcg: Double-blind Treatment Period |
| Reporting group description:                                                                                                                                                    |                                             |
| Participants were randomized to receive fluticasone furoate nasal spray (FFNS) 110 micrograms (mcg) OD as 2 sprays per nostril during the 52-week Double-blind Treatment Period |                                             |

| Reporting group values | Placebo: Double-blind Treatment Period | FFNS 110 mcg: Double-blind Treatment Period | Total |
|------------------------|----------------------------------------|---------------------------------------------|-------|
| Number of subjects     | 237                                    | 237                                         | 474   |
| Age categorical        |                                        |                                             |       |
| Units: Subjects        |                                        |                                             |       |

|                                                                                                                                                                                                               |         |         |     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|---------|-----|
| Age continuous                                                                                                                                                                                                |         |         |     |
| Baseline characteristics were collected for the Intent-to-Treat (ITT) Population, which included all participants who had been randomized to and received at least one dose of Double-blind study medication. |         |         |     |
| Units: years                                                                                                                                                                                                  |         |         |     |
| arithmetic mean                                                                                                                                                                                               | 6.61    | 6.64    |     |
| standard deviation                                                                                                                                                                                            | ± 0.969 | ± 0.933 | -   |
| Gender categorical                                                                                                                                                                                            |         |         |     |
| Baseline characteristics were collected for the Intent-to-Treat (ITT) Population, which included all participants who had been randomized to and received at least one dose of Double-blind study medication. |         |         |     |
| Units: Subjects                                                                                                                                                                                               |         |         |     |
| Female                                                                                                                                                                                                        | 73      | 75      | 148 |
| Male                                                                                                                                                                                                          | 164     | 162     | 326 |
| Race, Customized                                                                                                                                                                                              |         |         |     |
| Baseline characteristics were collected for the Intent-to-Treat (ITT) Population, which included all participants who had been randomized to and received at least one dose of Double-blind study medication. |         |         |     |
| Units: Subjects                                                                                                                                                                                               |         |         |     |
| African American (Amc)/African Heritage                                                                                                                                                                       | 16      | 12      | 28  |
| Amc Indian or Alaska Native (Alk N)                                                                                                                                                                           | 19      | 18      | 37  |
| Asian                                                                                                                                                                                                         | 7       | 5       | 12  |
| Native Hawaiian or Other Pacific Islander                                                                                                                                                                     | 1       | 0       | 1   |
| White                                                                                                                                                                                                         | 189     | 199     | 388 |
| African Amc/African and Amc Indian or Alk N                                                                                                                                                                   | 1       | 0       | 1   |
| African Amc/African Heritage and White                                                                                                                                                                        | 1       | 2       | 3   |
| Amc Indian or Alk N and White                                                                                                                                                                                 | 1       | 0       | 1   |
| Asian and White                                                                                                                                                                                               | 1       | 1       | 2   |
| Native Hawaiian/ Other Pacific Islander and White                                                                                                                                                             | 1       | 0       | 1   |



## End points

### End points reporting groups

|                                                                                                                                                                                                                 |                                             |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| Reporting group title                                                                                                                                                                                           | Placebo: Double-blind Treatment Period      |
| Reporting group description:<br>Participants were randomized to receive matching placebo nasal spray OD as 2 sprays per nostril during the 52-week Double-blind Treatment Period                                |                                             |
| Reporting group title                                                                                                                                                                                           | FFNS 110 mcg: Double-blind Treatment Period |
| Reporting group description:<br>Participants were randomized to receive fluticasone furoate nasal spray (FFNS) 110 micrograms (mcg) OD as 2 sprays per nostril during the 52-week Double-blind Treatment Period |                                             |

### Primary: Mean difference in growth velocities between subjects treated with FFNS 110 µg QD and placebo nasal spray as determined by stadiometry

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                        |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Mean difference in growth velocities between subjects treated with FFNS 110 µg QD and placebo nasal spray as determined by stadiometry |
| End point description:<br>Height was measured (triplicate measurements) in pre-pubescent pediatric participants via stadiometry at each clinic visit during the entire 76-week study period (16-week Baseline Period, 52-week DB Treatment Period and 8-week Follow-up Period). For each study period (Baseline, Treatment, and Follow-up), growth velocity was calculated by fitting a regression line to all height measurements recorded for the participant during the period and was determined by the slope of the fitted regression line. Growth Population: all randomized participants with height assessments via stadiometry from at least three post-randomization clinic visits during the DB Treatment Period. |                                                                                                                                        |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Primary                                                                                                                                |
| End point timeframe:<br>Baseline Period (Weeks -16 to 0) and DB Treatment Period (Weeks 1 to 52)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                        |

| End point values                      | Placebo: Double-blind Treatment Period | FFNS 110 mcg: Double-blind Treatment Period |  |  |
|---------------------------------------|----------------------------------------|---------------------------------------------|--|--|
| Subject group type                    | Reporting group                        | Reporting group                             |  |  |
| Number of subjects analysed           | 218 <sup>[1]</sup>                     | 217 <sup>[2]</sup>                          |  |  |
| Units: Centimeters per year (cm/year) |                                        |                                             |  |  |
| least squares mean (standard error)   | 5.46 (± 0.1)                           | 5.19 (± 0.1)                                |  |  |

Notes:

[1] - Growth Population

[2] - Growth Population

### Statistical analyses

|                                                                                                                                                                                                                                                 |                                                                                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| Statistical analysis title                                                                                                                                                                                                                      | Statistical Analysis 1                                                               |
| Statistical analysis description:<br>An analysis of covariance (ANCOVA) was performed to estimate the mean treatment difference in growth velocity over the treatment period, adjusting for baseline growth velocity, age, gender, and country. |                                                                                      |
| Comparison groups                                                                                                                                                                                                                               | Placebo: Double-blind Treatment Period v FFNS 110 mcg: Double-blind Treatment Period |



|                                         |                                |
|-----------------------------------------|--------------------------------|
| Number of subjects included in analysis | 435                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -0.27                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.48                          |
| upper limit                             | -0.06                          |

## Secondary: Mean 24-hour urinary free cortisol excretion

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                              |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Mean 24-hour urinary free cortisol excretion |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                              |
| Hypothalamic-pituitary-adrenal (HPA) axis function was assessed by the measurement of urinary free cortisol, using urine samples collected over the course of 24 hours by the parent/guardian in the participants' home on an out-patient basis within 7 days prior to the indicated time points. Detailed verbal instructions and a take-home instruction card on how to conduct the 24-hour urine collection were provided to the parent/guardian before each collection interval. Urine Cortisol Population: all randomized participants excluding those whose urine samples were considered to have confounding factors affecting the interpretation of the 24-hour urinary cortisol results. One participant in each arm had a Baseline value <1.0 and was not analyzed. Some participants had samples that were not acceptable for analysis. |                                              |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Secondary                                    |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                              |
| Randomization/end of 16-week Baseline Period (Week 0), End of 52-week DB Treatment Period (Week 52), and end of 8-week Follow-up Period (Week 60)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                              |

| End point values                                  | Placebo:<br>Double-blind<br>Treatment<br>Period | FFNS 110 mcg:<br>Double-blind<br>Treatment<br>Period |  |  |
|---------------------------------------------------|-------------------------------------------------|------------------------------------------------------|--|--|
| Subject group type                                | Reporting group                                 | Reporting group                                      |  |  |
| Number of subjects analysed                       | 168 <sup>[3]</sup>                              | 172 <sup>[4]</sup>                                   |  |  |
| Units: Micrograms per 24 hours<br>(mcg/24 hours)  |                                                 |                                                      |  |  |
| arithmetic mean (standard deviation)              |                                                 |                                                      |  |  |
| End of 16-week Baseline Period, n=168,<br>172     | 9.771 (±<br>6.0479)                             | 9.242 (±<br>5.5821)                                  |  |  |
| End of 52-week DB Treatment Period,<br>n=163, 169 | 11.34 (±<br>9.6775)                             | 11.125 (±<br>9.2195)                                 |  |  |
| End of 8-week Follow-up Period, n=161,<br>167     | 10.615 (±<br>6.6903)                            | 10.311 (±<br>5.9986)                                 |  |  |

Notes:

[3] - Urine Cortisol Population

[4] - Urine Cortisol Population

## Statistical analyses

No statistical analyses for this end point

**Secondary: Number of participants with the indicated shifts from Baseline in nasal examination (NE) results**

|                 |                                                                                                  |
|-----------------|--------------------------------------------------------------------------------------------------|
| End point title | Number of participants with the indicated shifts from Baseline in nasal examination (NE) results |
|-----------------|--------------------------------------------------------------------------------------------------|

## End point description:

NE included the evaluation of the size of ulcers/polyps (of nasal turbinates/septa) and assessment for mucosal bleeding (MB) at all study visits. Polyps are non-cancerous growths; ulcers are breaks in the skin/mucous membrane with loss of surface tissue, disintegration, and necrosis of epithelial tissue. For MB, Improved=shift from present ( $\geq 1$  nostril) to absent (both nostrils); Worsened=shift from absent (both nostrils) to present ( $\geq 1$  nostril). For polyps/ulcers, Improved=shift from large to small or from small to none; Worsened=shift from none to small or from small to none ( $\geq 1$  nostril). ITT=Intent to Treat: all participants who had been randomized to and received at least one dose of double-blind study medication. Most participants received examinations at each visit; however, on some occasions, some assessments were not completed for various reasons.

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

## End point timeframe:

Baseline Period (Weeks -16 to 0) and DB Treatment Period (Weeks 1 to 52)

| End point values            | Placebo:<br>Double-blind<br>Treatment<br>Period | FFNS 110 mcg:<br>Double-blind<br>Treatment<br>Period |  |  |
|-----------------------------|-------------------------------------------------|------------------------------------------------------|--|--|
| Subject group type          | Reporting group                                 | Reporting group                                      |  |  |
| Number of subjects analysed | 191 <sup>[5]</sup>                              | 188 <sup>[6]</sup>                                   |  |  |
| Units: Participants         |                                                 |                                                      |  |  |
| Mucosal Bleeding, Improved  | 1                                               | 0                                                    |  |  |
| Mucosal Bleeding, No Change | 190                                             | 187                                                  |  |  |
| Mucosal Bleeding, Worsened  | 0                                               | 1                                                    |  |  |
| Ulcers, Improved            | 0                                               | 0                                                    |  |  |
| Ulcers, No Change           | 191                                             | 188                                                  |  |  |
| Ulcers, Worsened            | 0                                               | 0                                                    |  |  |
| Polyps, Improved            | 1                                               | 0                                                    |  |  |
| Polyps, No Change           | 190                                             | 188                                                  |  |  |
| Polyps, Worsened            | 0                                               | 0                                                    |  |  |

## Notes:

[5] - ITT Population: participants who had been randomized to and received  $\geq 1$  dose of study medication

[6] - ITT Population: participants who had been randomized to and received  $\geq 1$  dose of study medication

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Mean values for the laboratory parameters of Alkaline (Alk) Phosphatase (P), Alanine Aminotransferase (ALT), and Aspartate Aminotransferase (AST)**

|                 |                                                                                                                                                   |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Mean values for the laboratory parameters of Alkaline (Alk) Phosphatase (P), Alanine Aminotransferase (ALT), and Aspartate Aminotransferase (AST) |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------|

## End point description:

Participants in the study were evaluated for the following clinical laboratory parameters at the indicated time points: Alk P, ALT, and AST. Only those participants remaining in the study and contributing viable samples at the various time points were analyzed.

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

End point timeframe:

Baseline Period (Weeks -16 to 0), DB Treatment Period (Weeks 1 to 52), and Follow-up Period (Weeks 53 to 60)

| End point values                            | Placebo:<br>Double-blind<br>Treatment<br>Period | FFNS 110 mcg:<br>Double-blind<br>Treatment<br>Period |  |  |
|---------------------------------------------|-------------------------------------------------|------------------------------------------------------|--|--|
| Subject group type                          | Reporting group                                 | Reporting group                                      |  |  |
| Number of subjects analysed                 | 231 <sup>[7]</sup>                              | 234 <sup>[8]</sup>                                   |  |  |
| Units: International Units per liter (IU/L) |                                                 |                                                      |  |  |
| arithmetic mean (standard deviation)        |                                                 |                                                      |  |  |
| Alk P, Baseline Period, n=231, 234          | 246.8 (± 57.45)                                 | 249.8 (± 67.81)                                      |  |  |
| Alk P, DB Treatment Period, n=184, 182      | 261.9 (± 61.96)                                 | 262.9 (± 71.22)                                      |  |  |
| Alk P, Follow-up Period, n=175, 174         | 264.2 (± 59.67)                                 | 264.6 (± 67.44)                                      |  |  |
| ALT, Baseline Period, n=231, 234            | 14.8 (± 4.54)                                   | 15.1 (± 4.73)                                        |  |  |
| ALT, DB Treatment Period, n=184, 182        | 15.9 (± 8.5)                                    | 15.8 (± 5.12)                                        |  |  |
| ALT, Follow-up Period, n=175, 174           | 16.7 (± 14.41)                                  | 17.2 (± 13.15)                                       |  |  |
| AST, Baseline Period, n=229, 232            | 27.4 (± 4.89)                                   | 28.1 (± 4.89)                                        |  |  |
| AST, DB Treatment Period, n=175, 179        | 27 (± 5.49)                                     | 27.6 (± 4.87)                                        |  |  |
| AST, Follow-up Period, n=169, 174           | 27.7 (± 8.93)                                   | 28.3 (± 10.44)                                       |  |  |

Notes:

[7] - ITT Population

[8] - ITT Population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean values for the laboratory parameters of Albumin and Total Protein

|                 |                                                                        |
|-----------------|------------------------------------------------------------------------|
| End point title | Mean values for the laboratory parameters of Albumin and Total Protein |
|-----------------|------------------------------------------------------------------------|

End point description:

Participants in the study were evaluated for the following clinical laboratory parameters at the indicated time points: Albumin and Total Protein. Only those participants remaining in the study and contributing viable samples at the various time points were analyzed.

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

End point timeframe:

Baseline Period (Weeks -16 to 0), DB Treatment Period (Weeks 1 to 52), and Follow-up Period (Weeks 53 to 60)

| End point values                               | Placebo:<br>Double-blind<br>Treatment<br>Period | FFNS 110 mcg:<br>Double-blind<br>Treatment<br>Period |  |  |
|------------------------------------------------|-------------------------------------------------|------------------------------------------------------|--|--|
| Subject group type                             | Reporting group                                 | Reporting group                                      |  |  |
| Number of subjects analysed                    | 231 <sup>[9]</sup>                              | 234 <sup>[10]</sup>                                  |  |  |
| Units: Grams per liter (g/L)                   |                                                 |                                                      |  |  |
| arithmetic mean (standard deviation)           |                                                 |                                                      |  |  |
| Albumin, Baseline Period, n=231, 234           | 45.8 (± 2.29)                                   | 46 (± 2.33)                                          |  |  |
| Albumin, DB Treatment Period, n=184, 182       | 45.7 (± 2.24)                                   | 45.9 (± 2.25)                                        |  |  |
| Albumin, Follow-up Period, n=175, 175          | 45.8 (± 2.31)                                   | 45.6 (± 2.36)                                        |  |  |
| Total Protein, Baseline Period, n=231, 234     | 72 (± 3.78)                                     | 71.9 (± 4.3)                                         |  |  |
| Total Protein, DB Treatment Period, n=184, 182 | 71.7 (± 3.76)                                   | 71.7 (± 3.95)                                        |  |  |
| Total Protein, Follow-up Period, n=175, 175    | 71.5 (± 3.66)                                   | 71.5 (± 3.83)                                        |  |  |

Notes:

[9] - ITT Population

[10] - ITT Population

### Statistical analyses

No statistical analyses for this end point

### Secondary: Mean values for the laboratory parameters of Total Bilirubin and Creatinine

|                 |                                                                             |
|-----------------|-----------------------------------------------------------------------------|
| End point title | Mean values for the laboratory parameters of Total Bilirubin and Creatinine |
|-----------------|-----------------------------------------------------------------------------|

End point description:

Participants in the study were evaluated for the following clinical laboratory parameters at the indicated time points: Total Bilirubin and Creatinine. Only those participants remaining in the study and contributing viable samples at the various time points were analyzed.

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

End point timeframe:

Baseline Period (Weeks -16 to 0), DB Treatment Period (Weeks 1 to 52), and Follow-up Period (Weeks 53 to 60)

| End point values                                 | Placebo:<br>Double-blind<br>Treatment<br>Period | FFNS 110 mcg:<br>Double-blind<br>Treatment<br>Period |  |  |
|--------------------------------------------------|-------------------------------------------------|------------------------------------------------------|--|--|
| Subject group type                               | Reporting group                                 | Reporting group                                      |  |  |
| Number of subjects analysed                      | 231 <sup>[11]</sup>                             | 234 <sup>[12]</sup>                                  |  |  |
| Units: Micromoles (µmol)/L                       |                                                 |                                                      |  |  |
| arithmetic mean (standard deviation)             |                                                 |                                                      |  |  |
| Total Bilirubin, Baseline Period, n=231, 234     | 6.9 (± 2.43)                                    | 7.2 (± 3.4)                                          |  |  |
| Total Bilirubin, DB Treatment Period, n=184, 182 | 7.2 (± 2.69)                                    | 7.7 (± 3.56)                                         |  |  |
| Total Bilirubin, Follow-up Period, n=175, 175    | 7 (± 2.72)                                      | 7.1 (± 3.14)                                         |  |  |
| Creatinine, Baseline Period, n=231, 234          | 43.3 (± 7.98)                                   | 43.6 (± 7.96)                                        |  |  |

|                                             |                    |                    |  |  |
|---------------------------------------------|--------------------|--------------------|--|--|
| Creatinine, DB Treatment Period, n=184, 182 | 45 ( $\pm$ 8.34)   | 44.6 ( $\pm$ 8.16) |  |  |
| Creatinine, Follow-up Period, n=175, 175    | 44.5 ( $\pm$ 7.38) | 45 ( $\pm$ 7.72)   |  |  |

Notes:

[11] - ITT Population

[12] - ITT Population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean values for the laboratory parameters of Glucose, Calcium, Potassium, Sodium, and Urea/Blood Urea Nitrogen (BUN)

|                 |                                                                                                                      |
|-----------------|----------------------------------------------------------------------------------------------------------------------|
| End point title | Mean values for the laboratory parameters of Glucose, Calcium, Potassium, Sodium, and Urea/Blood Urea Nitrogen (BUN) |
|-----------------|----------------------------------------------------------------------------------------------------------------------|

End point description:

Participants in the study were evaluated for the following clinical laboratory parameters at the indicated time points: Glucose, Calcium, Potassium, Sodium, and Urea/BUN. Only those participants remaining in the study and contributing viable samples at the various time points were analyzed.

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

End point timeframe:

Baseline Period (Weeks -16 to 0), DB Treatment Period (Weeks 1 to 52), and Follow-up Period (Weeks 53 to 60)

| End point values                           | Placebo:<br>Double-blind<br>Treatment<br>Period | FFNS 110 mcg:<br>Double-blind<br>Treatment<br>Period |  |  |
|--------------------------------------------|-------------------------------------------------|------------------------------------------------------|--|--|
| Subject group type                         | Reporting group                                 | Reporting group                                      |  |  |
| Number of subjects analysed                | 231 <sup>[13]</sup>                             | 234 <sup>[14]</sup>                                  |  |  |
| Units: Millimoles (mmol)/L                 |                                                 |                                                      |  |  |
| arithmetic mean (standard deviation)       |                                                 |                                                      |  |  |
| Glucose, Baseline Period, n=230, 231       | 4.83 ( $\pm$ 0.683)                             | 4.86 ( $\pm$ 0.69)                                   |  |  |
| Glucose, DB Treatment Period, n=184, 182   | 4.82 ( $\pm$ 0.782)                             | 4.78 ( $\pm$ 0.72)                                   |  |  |
| Glucose, Follow-up Period, n=175, 175      | 4.87 ( $\pm$ 0.84)                              | 4.85 ( $\pm$ 0.7)                                    |  |  |
| Calcium, Baseline Period, n=229, 232       | 2.441 ( $\pm$ 0.0786)                           | 2.435 ( $\pm$ 0.0993)                                |  |  |
| Calcium, DB Treatment Period, n=175, 179   | 2.437 ( $\pm$ 0.0776)                           | 2.44 ( $\pm$ 0.0847)                                 |  |  |
| Calcium, Follow-up Period, n=169, 173      | 2.438 ( $\pm$ 0.0769)                           | 2.436 ( $\pm$ 0.082)                                 |  |  |
| Potassium, Baseline Period, n=229, 232     | 4.3 ( $\pm$ 0.404)                              | 4.31 ( $\pm$ 0.437)                                  |  |  |
| Potassium, DB Treatment Period, n=175, 179 | 4.3 ( $\pm$ 0.373)                              | 4.3 ( $\pm$ 0.345)                                   |  |  |
| Potassium, Follow-up Period, n=169, 173    | 4.28 ( $\pm$ 0.362)                             | 4.32 ( $\pm$ 0.409)                                  |  |  |
| Sodium, Baseline Period, n=231, 234        | 139.4 ( $\pm$ 1.9)                              | 139.3 ( $\pm$ 1.83)                                  |  |  |
| Sodium, DB Treatment Period, n=184, 182    | 139.1 ( $\pm$ 1.65)                             | 139.2 ( $\pm$ 1.58)                                  |  |  |
| Sodium, Follow-up Period, n=175, 175       | 139.3 ( $\pm$ 1.89)                             | 139.4 ( $\pm$ 2.19)                                  |  |  |
| Urea/BUN, Baseline Period, n=231, 235      | 4.99 ( $\pm$ 1.897)                             | 4.77 ( $\pm$ 1.195)                                  |  |  |
| Urea/BUN, DB Treatment Period, n=184, 182  | 4.82 ( $\pm$ 1.315)                             | 4.82 ( $\pm$ 1.294)                                  |  |  |

|                                        |                |                |  |  |
|----------------------------------------|----------------|----------------|--|--|
| Urea/BUN, Follow-up Period, n=175, 175 | 4.93 (± 1.219) | 4.75 (± 1.274) |  |  |
|----------------------------------------|----------------|----------------|--|--|

Notes:

[13] - ITT Population

[14] - ITT Population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean hematology values for Basophil, Eosinophil, Lymphocyte, White Blood Cell (WBC), Monocyte, Segmented Neutrophil (Neu), and Platelet counts

|                 |                                                                                                                                                |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Mean hematology values for Basophil, Eosinophil, Lymphocyte, White Blood Cell (WBC), Monocyte, Segmented Neutrophil (Neu), and Platelet counts |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Participants in the study were evaluated for the following hematology laboratory parameters at the indicated time points: Basophil, Eosinophil, Lymphocyte, White Blood Cell (WBC), Monocyte, Segmented Neutrophil (Neu), and Platelet counts. Only those participants remaining in the study and contributing viable samples at the various time points were analyzed.

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

End point timeframe:

Baseline Period (Weeks -16 to 0), DB Treatment Period (Weeks 1 to 52), and Follow-up Period (Weeks 53 to 60)

| End point values                            | Placebo:<br>Double-blind<br>Treatment<br>Period | FFNS 110 mcg:<br>Double-blind<br>Treatment<br>Period |  |  |
|---------------------------------------------|-------------------------------------------------|------------------------------------------------------|--|--|
| Subject group type                          | Reporting group                                 | Reporting group                                      |  |  |
| Number of subjects analysed                 | 228 <sup>[15]</sup>                             | 231 <sup>[16]</sup>                                  |  |  |
| Units: Giga (10 <sup>9</sup> ) cells (Gi)/L |                                                 |                                                      |  |  |
| arithmetic mean (standard deviation)        |                                                 |                                                      |  |  |
| Basophil, Baseline Period, n=228, 231       | 0.026 (± 0.0176)                                | 0.025 (± 0.0151)                                     |  |  |
| Basophil, DB Treatment Period, n=186, 188   | 0.026 (± 0.0198)                                | 0.027 (± 0.0184)                                     |  |  |
| Basophil, Follow-up Period, n=177, 179      | 0.026 (± 0.0172)                                | 0.025 (± 0.0165)                                     |  |  |
| Eosinophil, Baseline Period, n=228, 231     | 0.395 (± 0.3292)                                | 0.455 (± 0.3859)                                     |  |  |
| Eosinophil, DB Treatment Period, n=186, 188 | 0.442 (± 0.3505)                                | 0.394 (± 0.3577)                                     |  |  |
| Eosinophil, Follow-up Period, n=177, 179    | 0.419 (± 0.3337)                                | 0.409 (± 0.3296)                                     |  |  |
| Lymphocyte, Baseline Period, n=228, 231     | 3.046 (± 0.9686)                                | 2.987 (± 0.9158)                                     |  |  |
| Lymphocyte, DB Treatment Period, n=177, 179 | 2.779 (± 0.8038)                                | 2.82 (± 0.8424)                                      |  |  |
| Lymphocyte, Follow-up Period, n=169, 173    | 2.871 (± 0.8784)                                | 2.841 (± 0.8107)                                     |  |  |
| WBC, Baseline Period, n=228, 231            | 7.71 (± 2.077)                                  | 7.36 (± 1.818)                                       |  |  |
| WBC, DB Treatment Period, n=186, 188        | 7.14 (± 1.899)                                  | 6.98 (± 1.896)                                       |  |  |
| WBC, Follow-up Period, n=177, 179           | 7.18 (± 1.945)                                  | 6.96 (± 1.894)                                       |  |  |

|                                                |                  |                  |  |  |
|------------------------------------------------|------------------|------------------|--|--|
| Monocyte, Baseline Period, n=228, 231          | 0.348 (± 0.1655) | 0.373 (± 0.187)  |  |  |
| Monocyte, DB Treatment Period, n=186, 188      | 0.32 (± 0.1393)  | 0.343 (± 0.1598) |  |  |
| Monocyte, Follow-up Period, n=177, 179         | 0.334 (± 0.1471) | 0.326 (± 0.1592) |  |  |
| Segmented Neu, Baseline Period, n=228, 231     | 3.892 (± 1.6722) | 3.517 (± 1.5347) |  |  |
| Segmented Neu, DB Treatment Period, n=186, 188 | 3.572 (± 1.5407) | 3.391 (± 1.4828) |  |  |
| Segmented Neu, Follow-up Period, n=177, 179    | 3.527 (± 1.5623) | 3.354 (± 1.4379) |  |  |
| Platelet, Baseline Period, n=230, 230          | 313.8 (± 70.19)  | 314.1 (± 59.46)  |  |  |
| Platelet, DB Treatment Period, n=187, 187      | 278.6 (± 55.58)  | 279.5 (± 49.51)  |  |  |
| Platelet, Follow-up Period, n=175, 180         | 276.4 (± 49.27)  | 283.6 (± 59.5)   |  |  |

Notes:

[15] - ITT Population

[16] - ITT Population

### Statistical analyses

No statistical analyses for this end point

### Secondary: Mean values for hemoglobin

|                                                                                                                                                                                                |                            |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| End point title                                                                                                                                                                                | Mean values for hemoglobin |
| End point description:                                                                                                                                                                         |                            |
| Hemoglobin was assessed in participants at the indicated time points. Only those participants remaining in the study and contributing viable samples at the various time points were analyzed. |                            |
| End point type                                                                                                                                                                                 | Secondary                  |
| End point timeframe:                                                                                                                                                                           |                            |
| Baseline Period (Weeks -16 to 0), DB Treatment Period (Weeks 1 to 52), and Follow-up Period (Weeks 53 to 60)                                                                                   |                            |

| End point values                     | Placebo:<br>Double-blind<br>Treatment<br>Period | FFNS 110 mcg:<br>Double-blind<br>Treatment<br>Period |  |  |
|--------------------------------------|-------------------------------------------------|------------------------------------------------------|--|--|
| Subject group type                   | Reporting group                                 | Reporting group                                      |  |  |
| Number of subjects analysed          | 231 <sup>[17]</sup>                             | 231 <sup>[18]</sup>                                  |  |  |
| Units: g/L                           |                                                 |                                                      |  |  |
| arithmetic mean (standard deviation) |                                                 |                                                      |  |  |
| Baseline Period, n=231, 231          | 129.5 (± 7.87)                                  | 128.4 (± 8)                                          |  |  |
| DB Treatment Period, n=186, 188      | 131.8 (± 7.32)                                  | 130.8 (± 7.77)                                       |  |  |
| Follow-up Period, n=177, 180         | 132.1 (± 7.43)                                  | 130 (± 7.9)                                          |  |  |

Notes:

[17] - ITT Population

[18] - ITT Population

### Statistical analyses

No statistical analyses for this end point

### Secondary: Mean values for hematocrit

|                                                                                                                                                                                                                                                                                                                        |                            |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| End point title                                                                                                                                                                                                                                                                                                        | Mean values for hematocrit |
| End point description:<br>Hematocrit was assessed in participants at indicated the time points. Hematocrit is the percentage of blood volume (BV) that is occupied by red blood cells (RBCs). Only those participants remaining in the study and contributing viable samples at the various time points were analyzed. |                            |
| End point type                                                                                                                                                                                                                                                                                                         | Secondary                  |
| End point timeframe:<br>Baseline Period (Weeks -16 to 0), DB Treatment Period (Weeks 1 to 52), and Follow-up Period (Weeks 53 to 60)                                                                                                                                                                                   |                            |

| End point values                         | Placebo:<br>Double-blind<br>Treatment<br>Period | FFNS 110 mcg:<br>Double-blind<br>Treatment<br>Period |  |  |
|------------------------------------------|-------------------------------------------------|------------------------------------------------------|--|--|
| Subject group type                       | Reporting group                                 | Reporting group                                      |  |  |
| Number of subjects analysed              | 231 <sup>[19]</sup>                             | 231 <sup>[20]</sup>                                  |  |  |
| Units: Percentage of BV occupied by RBCs |                                                 |                                                      |  |  |
| arithmetic mean (standard deviation)     |                                                 |                                                      |  |  |
| Baseline Period, n=231, 231              | 0.3823 (± 0.02296)                              | 0.3783 (± 0.0248)                                    |  |  |
| DB Treatment Period, n=186, 188          | 0.3904 (± 0.02291)                              | 0.3873 (± 0.02481)                                   |  |  |
| Follow-up Period, n=177, 180             | 0.3906 (± 0.02227)                              | 0.3844 (± 0.02416)                                   |  |  |

Notes:

[19] - ITT Population

[20] - ITT Population

### Statistical analyses

No statistical analyses for this end point

### Secondary: Mean hematology values for red blood cells (RBCs)

|                                                                                                                                                                                                                    |                                                   |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| End point title                                                                                                                                                                                                    | Mean hematology values for red blood cells (RBCs) |
| End point description:<br>RBCs was assessed in participants at the indicated time points. Only those participants remaining in the study and contributing viable samples at the various time points were analyzed. |                                                   |
| End point type                                                                                                                                                                                                     | Secondary                                         |
| End point timeframe:<br>Baseline Period (Weeks -16 to 0), DB Treatment Period (Weeks 1 to 52), and Follow-up Period (Weeks 53 to 60)                                                                               |                                                   |



| End point values                                 | Placebo:<br>Double-blind<br>Treatment<br>Period | FFNS 110 mcg:<br>Double-blind<br>Treatment<br>Period |  |  |
|--------------------------------------------------|-------------------------------------------------|------------------------------------------------------|--|--|
| Subject group type                               | Reporting group                                 | Reporting group                                      |  |  |
| Number of subjects analysed                      | 231 <sup>[21]</sup>                             | 231 <sup>[22]</sup>                                  |  |  |
| Units: Trillion (10 <sup>12</sup> ) cells (Ti)/L |                                                 |                                                      |  |  |
| arithmetic mean (standard deviation)             |                                                 |                                                      |  |  |
| Baseline Period, n=231, 231                      | 4.59 (± 0.312)                                  | 4.54 (± 0.327)                                       |  |  |
| DB Treatment Period, n=186, 188                  | 4.56 (± 0.303)                                  | 4.53 (± 0.319)                                       |  |  |
| Follow-up Period, n=177, 180                     | 4.57 (± 0.306)                                  | 4.5 (± 0.314)                                        |  |  |

Notes:

[21] - ITT Population

[22] - ITT Population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean values for urine pH

|                 |                          |
|-----------------|--------------------------|
| End point title | Mean values for urine pH |
|-----------------|--------------------------|

End point description:

Urine pH is an acid-base measurement. pH is measured on a numeric scale ranging from 0 to 14; values on the scale refer to the degree of alkalinity or acidity. A pH of 7 is neutral. A pH less than 7 is acidic, and a pH greater than 7 is basic. Normal urine has a slightly acid pH (5.0 - 6.0). Only those participants remaining in the study and contributing viable samples at the various time points were analyzed.

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

End point timeframe:

Baseline Period (Weeks -16 to 0), DB Treatment Period (Weeks 1 to 52), and Follow-up Period (Weeks 53 to 60)

| End point values                     | Placebo:<br>Double-blind<br>Treatment<br>Period | FFNS 110 mcg:<br>Double-blind<br>Treatment<br>Period |  |  |
|--------------------------------------|-------------------------------------------------|------------------------------------------------------|--|--|
| Subject group type                   | Reporting group                                 | Reporting group                                      |  |  |
| Number of subjects analysed          | 233 <sup>[23]</sup>                             | 229 <sup>[24]</sup>                                  |  |  |
| Units: scores on a scale             |                                                 |                                                      |  |  |
| arithmetic mean (standard deviation) |                                                 |                                                      |  |  |
| Baseline Period, n=233, 229          | 6.02 (± 0.477)                                  | 6 (± 0.536)                                          |  |  |
| DB Treatment Period, n=182, 181      | 6.02 (± 0.547)                                  | 6.05 (± 0.507)                                       |  |  |
| Follow-up Period, n=180, 186         | 6.05 (± 0.538)                                  | 6.05 (± 0.524)                                       |  |  |

Notes:

[23] - ITT Population

[24] - ITT Population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean values for urine specific gravity

|                 |                                        |
|-----------------|----------------------------------------|
| End point title | Mean values for urine specific gravity |
|-----------------|----------------------------------------|

End point description:

Specific gravity is a measure of the amount of material dissolved in the urine. Specific gravity is the ratio of the density (mass of a unit volume) of a substance to the density (mass of the same unit volume) of a reference substance. Normal urine has a specific gravity between 1.010 and 1.020. Only those participants remaining in the study and contributing viable samples at the various time points were analyzed.

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

End point timeframe:

Baseline Period (Weeks -16 to 0), DB Treatment Period (Weeks 1 to 52), and Follow-up Period (Weeks 53 to 60)

| End point values                     | Placebo:<br>Double-blind<br>Treatment<br>Period | FFNS 110 mcg:<br>Double-blind<br>Treatment<br>Period |  |  |
|--------------------------------------|-------------------------------------------------|------------------------------------------------------|--|--|
| Subject group type                   | Reporting group                                 | Reporting group                                      |  |  |
| Number of subjects analysed          | 233 <sup>[25]</sup>                             | 229 <sup>[26]</sup>                                  |  |  |
| Units: ratio                         |                                                 |                                                      |  |  |
| arithmetic mean (standard deviation) |                                                 |                                                      |  |  |
| Baseline Period, n=233, 229          | 1.024 (±<br>0.00718)                            | 1.0234 (±<br>0.00673)                                |  |  |
| DB Treatment Period, n=182, 181      | 1.0244 (±<br>0.00695)                           | 1.0234 (±<br>0.00649)                                |  |  |
| Follow-up Period, n=180, 186         | 1.0237 (±<br>0.00642)                           | 1.0242 (±<br>0.00672)                                |  |  |

Notes:

[25] - ITT Population

[26] - ITT Population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with the indicated urinalysis results for urine bilirubin and urine nitrite

|                 |                                                                                                    |
|-----------------|----------------------------------------------------------------------------------------------------|
| End point title | Number of participants with the indicated urinalysis results for urine bilirubin and urine nitrite |
|-----------------|----------------------------------------------------------------------------------------------------|

End point description:

Bilirubin is a normal body by-product (bile), and nitrite is a by-product of bacterial growth. Participants were categorized as Negative (Neg.) or Positive (Pos.) based on the absence or presence, respectively, of urine bilirubin (UB) and urine nitrate. Only those participants remaining in the study and contributing viable samples at the various time points were analyzed.

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

End point timeframe:

Baseline Period (Weeks -16 to 0), DB Treatment Period (Weeks 1 to 52), and Follow-up Period (Weeks 53 to 60)

| End point values                                   | Placebo:<br>Double-blind<br>Treatment<br>Period | FFNS 110 mcg:<br>Double-blind<br>Treatment<br>Period |  |  |
|----------------------------------------------------|-------------------------------------------------|------------------------------------------------------|--|--|
| Subject group type                                 | Reporting group                                 | Reporting group                                      |  |  |
| Number of subjects analysed                        | 233 <sup>[27]</sup>                             | 229 <sup>[28]</sup>                                  |  |  |
| Units: Participants                                |                                                 |                                                      |  |  |
| UB-Neg, Baseline Period, n=233, 229                | 233                                             | 229                                                  |  |  |
| UB-Pos, Baseline Period, n=233, 229                | 0                                               | 0                                                    |  |  |
| UB-Neg, DB Treatment Period, n=182, 181            | 182                                             | 181                                                  |  |  |
| UB-Pos, DB Treatment Period, n=182, 181            | 0                                               | 0                                                    |  |  |
| UB-Neg, Follow-up Period, n=180, 186               | 180                                             | 186                                                  |  |  |
| UB-Pos, Follow-up Period, n=180, 186               | 0                                               | 0                                                    |  |  |
| Urine Nitrite-Neg, Baseline Period, n=233, 229     | 232                                             | 228                                                  |  |  |
| Urine Nitrite-Pos, Baseline Period, n=233, 229     | 1                                               | 1                                                    |  |  |
| Urine Nitrite-Neg, DB Treatment Period, n=182, 181 | 178                                             | 176                                                  |  |  |
| Urine Nitrite-Pos, DB Treatment Period, n=182, 181 | 4                                               | 5                                                    |  |  |
| Urine Nitrite-Neg, Follow-up Period, n=180, 186    | 179                                             | 183                                                  |  |  |
| Urine Nitrite-Pos, Follow-up Period, n=180, 186    | 1                                               | 3                                                    |  |  |

Notes:

[27] - ITT Population

[28] - ITT Population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with the indicated urinalysis results for urine glucose, urine ketones, and urine proteins

|                 |                                                                                                                   |
|-----------------|-------------------------------------------------------------------------------------------------------------------|
| End point title | Number of participants with the indicated urinalysis results for urine glucose, urine ketones, and urine proteins |
|-----------------|-------------------------------------------------------------------------------------------------------------------|

End point description:

Urine glucose, urine ketones, and urine proteins were measured in participants using a dipstick (qualitative) test at the indicated time points. In this dipstick test, the level of glucose, ketones, and protein in urine samples was recorded as negative (Neg), trace (tr), 1+, 2+, and 3+ (the plus sign increases with a higher level of glucose, ketones, or proteins in the urine: 1+=slightly positive, 2+=positive, 3+=high positive). Participants were categorized as negative or positive based on the absence or presence, respectively, of glucose, ketones, and proteins in the urine. Only those participants remaining in the study and contributing viable samples at the various time points were analyzed.

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

End point timeframe:

Baseline Period (Weeks -16 to 0), DB Treatment Period (Weeks 1 to 52), and Follow-up Period (Weeks 53 to 60)

| End point values                                      | Placebo:<br>Double-blind<br>Treatment<br>Period | FFNS 110 mcg:<br>Double-blind<br>Treatment<br>Period |  |  |
|-------------------------------------------------------|-------------------------------------------------|------------------------------------------------------|--|--|
| Subject group type                                    | Reporting group                                 | Reporting group                                      |  |  |
| Number of subjects analysed                           | 233 <sup>[29]</sup>                             | 229 <sup>[30]</sup>                                  |  |  |
| Units: Participants                                   |                                                 |                                                      |  |  |
| Urine Glucose-Neg, Baseline Period,<br>n=233, 229     | 233                                             | 229                                                  |  |  |
| Urine Glucose-Neg, DB Treatment<br>Period, n=182, 181 | 181                                             | 181                                                  |  |  |
| Urine Glucose-Tr, DB Treatment Period,<br>n=182, 181  | 1                                               | 0                                                    |  |  |
| Urine Glucose-Neg, Follow-up Period,<br>n=180, 186    | 179                                             | 186                                                  |  |  |
| Urine Glucose-1+, Follow-up Period,<br>n=180, 186     | 1                                               | 0                                                    |  |  |
| Urine Ketones-Neg, Baseline Period,<br>n=233, 229     | 231                                             | 227                                                  |  |  |
| Urine Ketones-Tr, Baseline Period,<br>n=233, 229      | 0                                               | 1                                                    |  |  |
| Urine Ketones-1+, Baseline Period,<br>n=233, 229      | 2                                               | 1                                                    |  |  |
| Urine Ketones-Neg, DB Treatment<br>Period, n=182, 181 | 179                                             | 176                                                  |  |  |
| Urine Ketones-Tr, DB Treatment Period,<br>n=182, 181  | 3                                               | 5                                                    |  |  |
| Urine Ketones-Neg, Follow-up Period,<br>n=180, 186    | 180                                             | 184                                                  |  |  |
| Urine Ketones-Tr, Follow-up Period,<br>n=180, 186     | 0                                               | 1                                                    |  |  |
| Urine Ketones-1+, Follow-up Period,<br>n=180, 186     | 0                                               | 1                                                    |  |  |
| Urine Protein-Neg, Baseline Period,<br>n=233, 229     | 218                                             | 207                                                  |  |  |
| Urine Protein-Tr, Baseline Period,<br>n=233, 229      | 11                                              | 18                                                   |  |  |
| Urine Protein-1+, Baseline Period,<br>n=233, 229      | 2                                               | 4                                                    |  |  |
| Urine Protein-2+, Baseline Period,<br>n=233, 229      | 2                                               | 0                                                    |  |  |
| Urine Protein-Neg, DB Treatment Period,<br>n=182, 181 | 145                                             | 152                                                  |  |  |
| Urine Protein-Tr, DB Treatment Period,<br>n=182, 181  | 20                                              | 20                                                   |  |  |
| Urine Protein-1+, DB Treatment Period,<br>n=182, 181  | 14                                              | 7                                                    |  |  |
| Urine Protein-2+, DB Treatment Period,<br>n=182, 181  | 2                                               | 2                                                    |  |  |
| Urine Protein-3+, DB Treatment Period,<br>n=182, 181  | 1                                               | 0                                                    |  |  |
| Urine Protein-Neg, Follow-up Period,<br>n=180, 186    | 156                                             | 155                                                  |  |  |
| Urine Protein-Tr, Follow-up Period,<br>n=180, 186     | 16                                              | 22                                                   |  |  |
| Urine Protein-1+, Follow-up Period,<br>n=180, 186     | 6                                               | 8                                                    |  |  |
| Urine Ketones-2+, Follow-up Period,<br>n=180, 186     | 1                                               | 1                                                    |  |  |
| Urine Ketones-3+, Follow-up Period,<br>n=180, 186     | 1                                               | 0                                                    |  |  |

Notes:

[29] - ITT Population

[30] - ITT Population

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of participants with the indicated urinalysis results for urine occult blood (OB) and the urine leukocyte esterase test (LET)

|                 |                                                                                                                                      |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of participants with the indicated urinalysis results for urine occult blood (OB) and the urine leukocyte esterase test (LET) |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Occult blood (OB) is blood that cannot be seen without a microscope. Normal urine does not contain any red blood cells. Leukocyte esterase is an enzyme and is not found in normal urine. In the dipstick (qualitative) test, the level of OB and leukocyte esterase in urine samples was recorded as negative (Neg), small, moderate, large, trace, 1+ (slightly positive), 2+ (positive), and 3+ (high positive). Participants were categorized as negative or positive based on the absence or presence, respectively, of OB and urine leukocyte esterase. Only those participants remaining in the study and contributing viable samples at the various time points were analyzed.

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

End point timeframe:

Baseline Period (Weeks -16 to 0), DB Treatment Period (Weeks 1 to 52), and Follow-up Period (Weeks 53 to 60)

| End point values                                | Placebo:<br>Double-blind<br>Treatment<br>Period | FFNS 110 mcg:<br>Double-blind<br>Treatment<br>Period |  |  |
|-------------------------------------------------|-------------------------------------------------|------------------------------------------------------|--|--|
| Subject group type                              | Reporting group                                 | Reporting group                                      |  |  |
| Number of subjects analysed                     | 233 <sup>[31]</sup>                             | 229 <sup>[32]</sup>                                  |  |  |
| Units: Participants                             |                                                 |                                                      |  |  |
| Urine OB-Neg, Baseline Period, n=233, 229       | 226                                             | 226                                                  |  |  |
| Urine OB-Small, Baseline Period, n=233, 229     | 1                                               | 0                                                    |  |  |
| Urine OB-Moderate, Baseline Period, n=233, 229  | 1                                               | 0                                                    |  |  |
| Urine OB-Trace, Baseline Period, n=233, 229     | 4                                               | 3                                                    |  |  |
| Urine OB-1+, Baseline Period, n=233, 229        | 1                                               | 0                                                    |  |  |
| Urine OB-Neg, DB Treatment Period, n=182, 181   | 178                                             | 178                                                  |  |  |
| Urine OB-Trace, DB Treatment Period, n=182, 181 | 4                                               | 1                                                    |  |  |
| Urine OB-1+, DB Treatment Period, n=182, 181    | 0                                               | 1                                                    |  |  |
| Urine OB-3+, DB Treatment Period, n=182, 181    | 0                                               | 1                                                    |  |  |
| Urine OB-Neg, Follow-up Period, n=180, 186      | 177                                             | 184                                                  |  |  |

|                                                  |     |     |  |  |
|--------------------------------------------------|-----|-----|--|--|
| Urine OB-Trace, Follow-up Period, n=180, 186     | 1   | 1   |  |  |
| Urine OB-1+, Follow-up Period, n=180, 186        | 2   | 0   |  |  |
| Urine OB-2+, Follow-up Period, n=180, 186        | 0   | 1   |  |  |
| Urine LET-Neg, Baseline Period, n=233, 229       | 220 | 219 |  |  |
| Urine LET-Small, Baseline Period, n=233, 229     | 1   | 2   |  |  |
| Urine LET-Moderate, Baseline Period, n=233, 229  | 0   | 1   |  |  |
| Urine LET-Large, Baseline Period, n=233, 229     | 0   | 1   |  |  |
| Urine LET-Trace, Baseline Period, n=233, 229     | 7   | 0   |  |  |
| Urine LET-1+, Baseline Period, n=233, 229        | 3   | 2   |  |  |
| Urine LET-2+, Baseline Period, n=233, 229        | 0   | 2   |  |  |
| Urine LET-3+, Baseline Period, n=233, 229        | 2   | 2   |  |  |
| Urine LET-Neg, DB Treatment Period, n=182, 181   | 170 | 163 |  |  |
| Urine LET-Trace, DB Treatment Period, n=182, 181 | 5   | 4   |  |  |
| Urine LET-1+, DB Treatment Period, n=182, 181    | 5   | 6   |  |  |
| Urine LET-2+, DB Treatment Period, n=182, 181    | 2   | 7   |  |  |
| Urine LET-3+, DB Treatment Period, n=182, 181    | 0   | 1   |  |  |
| Urine LET-Neg, Follow-up Period, n=180, 186      | 162 | 167 |  |  |
| Urine LET-Trace, Follow-up Period, n=180, 186    | 5   | 5   |  |  |
| Urine LET-1+, Follow-up Period, n=180, 186       | 2   | 8   |  |  |
| Urine LET-2+, Follow-up Period, n=180, 186       | 8   | 4   |  |  |
| Urine LET-3+, Follow-up Period, n=180, 186       | 3   | 2   |  |  |

Notes:

[31] - ITT Population

[32] - ITT Population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with the indicated urinalysis results for urine appearance (App.)/clarity and color

|                 |                                                                                                            |
|-----------------|------------------------------------------------------------------------------------------------------------|
| End point title | Number of participants with the indicated urinalysis results for urine appearance (App.)/clarity and color |
|-----------------|------------------------------------------------------------------------------------------------------------|

End point description:

Participants were assessed for their urine appearance, which was categorized as clear (normal), cloudy (presence of crystals, blood cells, or bacteria), of turbid. Also, participants were categorized by the color of urine: straw, yellow (normal urine), and dark yellow (DY) (which may be the result of bile in the urine). Only those participants remaining in the study and contributing viable samples at the various time points were analyzed.

|                                                                                                              |           |
|--------------------------------------------------------------------------------------------------------------|-----------|
| End point type                                                                                               | Secondary |
| End point timeframe:                                                                                         |           |
| Baseline Period (Weeks -16 to 0), DB Treatment Period (Weeks 1 to 52), and Follow-up Period (Weeks 53 to 60) |           |

| End point values                                    | Placebo:<br>Double-blind<br>Treatment<br>Period | FFNS 110 mcg:<br>Double-blind<br>Treatment<br>Period |  |  |
|-----------------------------------------------------|-------------------------------------------------|------------------------------------------------------|--|--|
| Subject group type                                  | Reporting group                                 | Reporting group                                      |  |  |
| Number of subjects analysed                         | 233 <sup>[33]</sup>                             | 229 <sup>[34]</sup>                                  |  |  |
| Units: Participants                                 |                                                 |                                                      |  |  |
| Urine App.-Clear, Baseline Period, n=233, 229       | 188                                             | 197                                                  |  |  |
| Urine App.-Cloudy, Baseline Period, n=233, 229      | 23                                              | 21                                                   |  |  |
| Urine App.-Turbid, Baseline Period, n=233, 229      | 22                                              | 11                                                   |  |  |
| Urine App.-Clear, DB Treatment Period, n=182, 181   | 134                                             | 139                                                  |  |  |
| Urine App.-Cloudy, DB Treatment Period, n=182, 181  | 31                                              | 33                                                   |  |  |
| Urine App.-Turbid, DB Treatment Period, n=182, 181  | 17                                              | 9                                                    |  |  |
| Urine App.-Clear, Follow-up Period, n=180, 186      | 139                                             | 137                                                  |  |  |
| Urine App.-Cloudy, Follow-up Period, n=180, 186     | 25                                              | 35                                                   |  |  |
| Urine App.-Turbid, Follow-up Period, n=180, 186     | 16                                              | 14                                                   |  |  |
| Urine Color-Straw, Baseline Period, n=233, 229      | 8                                               | 8                                                    |  |  |
| Urine Color-Yellow, Baseline Period, n=233, 229     | 214                                             | 213                                                  |  |  |
| Urine Color-DY, Baseline Period, n=233, 229         | 11                                              | 8                                                    |  |  |
| Urine Color-Straw, DB Treatment Period, n=182, 181  | 6                                               | 7                                                    |  |  |
| Urine Color-Yellow, DB Treatment Period, n=182, 181 | 154                                             | 155                                                  |  |  |
| Urine Color-DY, DB Treatment Period, n=182, 181     | 22                                              | 19                                                   |  |  |
| Urine Color-Straw, Follow-up Period, n=180, 186     | 6                                               | 7                                                    |  |  |
| Urine Color-Yellow, Follow-up Period, n=180, 186    | 156                                             | 160                                                  |  |  |
| Urine Color-DY, Follow-up Period, n=180, 186        | 18                                              | 19                                                   |  |  |

Notes:

[33] - ITT Population

[34] - ITT Population

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Post-randomization adverse events include those that occurred on or after the randomization date.

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

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 13.1 |
|--------------------|------|

### Reporting groups

|                       |                                        |
|-----------------------|----------------------------------------|
| Reporting group title | Placebo: Double-blind Treatment Period |
|-----------------------|----------------------------------------|

Reporting group description:

Participants were randomized to receive matching placebo nasal spray OD as 2 sprays per nostril during the 52-week Double-blind Treatment Period

|                       |                                             |
|-----------------------|---------------------------------------------|
| Reporting group title | FFNS 110 mcg: Double-blind Treatment Period |
|-----------------------|---------------------------------------------|

Reporting group description:

Participants were randomized to receive fluticasone furoate nasal spray (FFNS) 110 micrograms (mcg) OD as 2 sprays per nostril during the 52-week Double-blind Treatment Period

| <b>Serious adverse events</b>                     | Placebo: Double-blind Treatment Period | FFNS 110 mcg: Double-blind Treatment Period |  |
|---------------------------------------------------|----------------------------------------|---------------------------------------------|--|
| Total subjects affected by serious adverse events |                                        |                                             |  |
| subjects affected / exposed                       | 4 / 237 (1.69%)                        | 2 / 237 (0.84%)                             |  |
| number of deaths (all causes)                     | 0                                      | 0                                           |  |
| number of deaths resulting from adverse events    | 0                                      | 0                                           |  |
| Injury, poisoning and procedural complications    |                                        |                                             |  |
| Head injury                                       |                                        |                                             |  |
| subjects affected / exposed                       | 1 / 237 (0.42%)                        | 0 / 237 (0.00%)                             |  |
| occurrences causally related to treatment / all   | 0 / 1                                  | 0 / 0                                       |  |
| deaths causally related to treatment / all        | 0 / 0                                  | 0 / 0                                       |  |
| Respiratory, thoracic and mediastinal disorders   |                                        |                                             |  |
| Asthma                                            |                                        |                                             |  |
| subjects affected / exposed                       | 1 / 237 (0.42%)                        | 0 / 237 (0.00%)                             |  |
| occurrences causally related to treatment / all   | 0 / 1                                  | 0 / 0                                       |  |
| deaths causally related to treatment / all        | 0 / 0                                  | 0 / 0                                       |  |
| Musculoskeletal and connective tissue disorders   |                                        |                                             |  |
| Myositis                                          |                                        |                                             |  |



|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 237 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Infections and infestations</b>              |                 |                 |  |
| Appendicitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 237 (0.00%) | 1 / 237 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 237 (0.00%) | 1 / 237 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteomyelitis                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 237 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia primary atypical                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 237 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory tract infection viral               |                 |                 |  |
| subjects affected / exposed                     | 1 / 237 (0.42%) | 0 / 237 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

Frequency threshold for reporting non-serious adverse events: 2 %

| <b>Non-serious adverse events</b>                     | Placebo: Double-blind Treatment Period | FFNS 110 mcg: Double-blind Treatment Period |  |
|-------------------------------------------------------|----------------------------------------|---------------------------------------------|--|
| Total subjects affected by non-serious adverse events |                                        |                                             |  |
| subjects affected / exposed                           | 147 / 237 (62.03%)                     | 140 / 237 (59.07%)                          |  |
| Nervous system disorders                              |                                        |                                             |  |
| Headache                                              |                                        |                                             |  |

|                                                                                                                                                                                                                                                                                                                                      |                                                                                                                 |                                                                                                              |  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                     | 6 / 237 (2.53%)<br>20                                                                                           | 8 / 237 (3.38%)<br>11                                                                                        |  |
| General disorders and administration<br>site conditions<br>Pyrexia<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                               | 15 / 237 (6.33%)<br>21                                                                                          | 23 / 237 (9.70%)<br>25                                                                                       |  |
| Ear and labyrinth disorders<br>Ear pain<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                          | 5 / 237 (2.11%)<br>6                                                                                            | 2 / 237 (0.84%)<br>2                                                                                         |  |
| Gastrointestinal disorders<br>Vomiting<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                           | 4 / 237 (1.69%)<br>4                                                                                            | 5 / 237 (2.11%)<br>5                                                                                         |  |
| Respiratory, thoracic and mediastinal<br>disorders<br>Asthma<br>subjects affected / exposed<br>occurrences (all)<br><br>Cough<br>subjects affected / exposed<br>occurrences (all)<br><br>Epistaxis<br>subjects affected / exposed<br>occurrences (all)<br><br>Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all) | 10 / 237 (4.22%)<br>13<br><br>16 / 237 (6.75%)<br>25<br><br>24 / 237 (10.13%)<br>34<br><br>6 / 237 (2.53%)<br>8 | 7 / 237 (2.95%)<br>8<br><br>14 / 237 (5.91%)<br>20<br><br>17 / 237 (7.17%)<br>22<br><br>7 / 237 (2.95%)<br>8 |  |
| Infections and infestations<br>Acute sinusitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Acute tonsillitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Bronchitis                                                                                                                                    | 13 / 237 (5.49%)<br>15<br><br>7 / 237 (2.95%)<br>9                                                              | 3 / 237 (1.27%)<br>3<br><br>8 / 237 (3.38%)<br>10                                                            |  |

|                                   |                   |                   |
|-----------------------------------|-------------------|-------------------|
| subjects affected / exposed       | 28 / 237 (11.81%) | 36 / 237 (15.19%) |
| occurrences (all)                 | 48                | 64                |
| Ear infection                     |                   |                   |
| subjects affected / exposed       | 2 / 237 (0.84%)   | 7 / 237 (2.95%)   |
| occurrences (all)                 | 2                 | 7                 |
| Gastroenteritis                   |                   |                   |
| subjects affected / exposed       | 4 / 237 (1.69%)   | 9 / 237 (3.80%)   |
| occurrences (all)                 | 4                 | 10                |
| Gastroenteritis viral             |                   |                   |
| subjects affected / exposed       | 9 / 237 (3.80%)   | 3 / 237 (1.27%)   |
| occurrences (all)                 | 9                 | 3                 |
| Influenza                         |                   |                   |
| subjects affected / exposed       | 9 / 237 (3.80%)   | 15 / 237 (6.33%)  |
| occurrences (all)                 | 10                | 16                |
| Nasopharyngitis                   |                   |                   |
| subjects affected / exposed       | 45 / 237 (18.99%) | 37 / 237 (15.61%) |
| occurrences (all)                 | 75                | 62                |
| Otitis media                      |                   |                   |
| subjects affected / exposed       | 8 / 237 (3.38%)   | 6 / 237 (2.53%)   |
| occurrences (all)                 | 8                 | 6                 |
| Otitis media acute                |                   |                   |
| subjects affected / exposed       | 7 / 237 (2.95%)   | 5 / 237 (2.11%)   |
| occurrences (all)                 | 7                 | 8                 |
| Pharyngitis                       |                   |                   |
| subjects affected / exposed       | 19 / 237 (8.02%)  | 12 / 237 (5.06%)  |
| occurrences (all)                 | 22                | 16                |
| Sinusitis                         |                   |                   |
| subjects affected / exposed       | 14 / 237 (5.91%)  | 12 / 237 (5.06%)  |
| occurrences (all)                 | 16                | 14                |
| Tonsillitis                       |                   |                   |
| subjects affected / exposed       | 7 / 237 (2.95%)   | 8 / 237 (3.38%)   |
| occurrences (all)                 | 7                 | 8                 |
| Upper respiratory tract infection |                   |                   |
| subjects affected / exposed       | 12 / 237 (5.06%)  | 15 / 237 (6.33%)  |
| occurrences (all)                 | 14                | 18                |
| Urinary tract infection           |                   |                   |

|                                         |                  |                  |  |
|-----------------------------------------|------------------|------------------|--|
| subjects affected / exposed             | 3 / 237 (1.27%)  | 7 / 237 (2.95%)  |  |
| occurrences (all)                       | 4                | 7                |  |
| Viral pharyngitis                       |                  |                  |  |
| subjects affected / exposed             | 5 / 237 (2.11%)  | 3 / 237 (1.27%)  |  |
| occurrences (all)                       | 6                | 3                |  |
| Viral upper respiratory tract infection |                  |                  |  |
| subjects affected / exposed             | 6 / 237 (2.53%)  | 3 / 237 (1.27%)  |  |
| occurrences (all)                       | 6                | 3                |  |
| Respiratory tract infection viral       |                  |                  |  |
| subjects affected / exposed             | 16 / 237 (6.75%) | 13 / 237 (5.49%) |  |
| occurrences (all)                       | 21               | 13               |  |
| Respiratory tract infection             |                  |                  |  |
| subjects affected / exposed             | 7 / 237 (2.95%)  | 4 / 237 (1.69%)  |  |
| occurrences (all)                       | 8                | 4                |  |
| H1N1 influenza                          |                  |                  |  |
| subjects affected / exposed             | 6 / 237 (2.53%)  | 3 / 237 (1.27%)  |  |
| occurrences (all)                       | 6                | 3                |  |

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported