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:

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:

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:

Population of trial subjects

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:

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
Arm title	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

Arm title	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

Number of subjects in period 1	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
Protocol deviation	12	15
Lack of efficacy	3	-

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:	
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	

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:	
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:	
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[1]	217[2]		
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:	
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-pitiutary-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: Double-blind Treatment Period	FFNS 110 mcg: Double-blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168[3]	172[4]		
Units: Micrograms per 24 hours (mcg/24 hours)				
arithmetic mean (standard deviation)				
End of 16-week Baseline Period, n=168, 172	9.771 (± 6.0479)	9.242 (± 5.5821)		
End of 52-week DB Treatment Period, n=163, 169	11.34 (± 9.6775)	11.125 (± 9.2195)		
End of 8-week Follow-up Period, n=161, 167	10.615 (± 6.6903)	10.311 (± 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 (>=1 nostril) to absent (both nostrils); Worsened=shift from absent (both nostrils) to present (>=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 (>=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: Double-blind Treatment Period	FFNS 110 mcg: Double-blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191[5]	188[6]		
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 >=1 dose of study medication

[6] - ITT Population: participants who had been randomized to and received >=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: Double-blind Treatment Period	FFNS 110 mcg: Double-blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231[7]	234[8]		
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: Double-blind Treatment Period	FFNS 110 mcg: Double-blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231[9]	234[10]		
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: Double-blind Treatment Period	FFNS 110 mcg: Double-blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231[11]	234[12]		
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 (± 8.34)	44.6 (± 8.16)		
Creatinine, Follow-up Period, n=175, 175	44.5 (± 7.38)	45 (± 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: Double-blind Treatment Period	FFNS 110 mcg: Double-blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231[13]	234[14]		
Units: Millimoles (mmol)/L				
arithmetic mean (standard deviation)				
Glucose, Baseline Period, n=230, 231	4.83 (± 0.683)	4.86 (± 0.69)		
Glucose, DB Treatment Period, n=184, 182	4.82 (± 0.782)	4.78 (± 0.72)		
Glucose, Follow-up Period, n=175, 175	4.87 (± 0.84)	4.85 (± 0.7)		
Calcium, Baseline Period, n=229, 232	2.441 (± 0.0786)	2.435 (± 0.0993)		
Calcium, DB Treatment Period, n=175, 179	2.437 (± 0.0776)	2.44 (± 0.0847)		
Calcium, Follow-up Period, n=169, 173	2.438 (± 0.0769)	2.436 (± 0.082)		
Potassium, Baseline Period, n=229, 232	4.3 (± 0.404)	4.31 (± 0.437)		
Potassium, DB Treatment Period, n=175, 179	4.3 (± 0.373)	4.3 (± 0.345)		
Potassium, Follow-up Period, n=169, 173	4.28 (± 0.362)	4.32 (± 0.409)		
Sodium, Baseline Period, n=231, 234	139.4 (± 1.9)	139.3 (± 1.83)		
Sodium, DB Treatment Period, n=184, 182	139.1 (± 1.65)	139.2 (± 1.58)		
Sodium, Follow-up Period, n=175, 175	139.3 (± 1.89)	139.4 (± 2.19)		
Urea/BUN, Baseline Period, n=231, 235	4.99 (± 1.897)	4.77 (± 1.195)		
Urea/BUN, DB Treatment Period, n=184, 182	4.82 (± 1.315)	4.82 (± 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: Double-blind Treatment Period	FFNS 110 mcg: Double-blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228[15]	231[16]		
Units: Giga (10^9) 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: Double-blind Treatment Period	FFNS 110 mcg: Double-blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231[17]	231[18]		
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:

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:

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: Double-blind Treatment Period	FFNS 110 mcg: Double-blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231[19]	231[20]		
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:

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:

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: Double-blind Treatment Period	FFNS 110 mcg: Double-blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231[21]	231[22]		
Units: Trillion (10^12) 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: Double-blind Treatment Period	FFNS 110 mcg: Double-blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233[23]	229[24]		
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: Double-blind Treatment Period	FFNS 110 mcg: Double-blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233[25]	229[26]		
Units: ratio				
arithmetic mean (standard deviation)				
Baseline Period, n=233, 229	1.024 (± 0.00718)	1.0234 (± 0.00673)		
DB Treatment Period, n=182, 181	1.0244 (± 0.00695)	1.0234 (± 0.00649)		
Follow-up Period, n=180, 186	1.0237 (± 0.00642)	1.0242 (± 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: Double-blind Treatment Period	FFNS 110 mcg: Double-blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233[27]	229[28]		
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: Double-blind Treatment Period	FFNS 110 mcg: Double-blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233[29]	229[30]		
Units: Participants				
Urine Glucose-Neg, Baseline Period, n=233, 229	233	229		
Urine Glucose-Neg, DB Treatment Period, n=182, 181	181	181		
Urine Glucose-Tr, DB Treatment Period, n=182, 181	1	0		
Urine Glucose-Neg, Follow-up Period, n=180, 186	179	186		
Urine Glucose-1+, Follow-up Period, n=180, 186	1	0		
Urine Ketones-Neg, Baseline Period, n=233, 229	231	227		
Urine Ketones-Tr, Baseline Period, n=233, 229	0	1		
Urine Ketones-1+, Baseline Period, n=233, 229	2	1		
Urine Ketones-Neg, DB Treatment Period, n=182, 181	179	176		
Urine Ketones-Tr, DB Treatment Period, n=182, 181	3	5		
Urine Ketones-Neg, Follow-up Period, n=180, 186	180	184		
Urine Ketones-Tr, Follow-up Period, n=180, 186	0	1		
Urine Ketones-1+, Follow-up Period, n=180, 186	0	1		
Urine Protein-Neg, Baseline Period, n=233, 229	218	207		
Urine Protein-Tr, Baseline Period, n=233, 229	11	18		
Urine Protein-1+, Baseline Period, n=233, 229	2	4		
Urine Protein-2+, Baseline Period, n=233, 229	2	0		
Urine Protein-Neg, DB Treatment Period, n=182, 181	145	152		
Urine Protein-Tr, DB Treatment Period, n=182, 181	20	20		
Urine Protein-1+, DB Treatment Period, n=182, 181	14	7		
Urine Protein-2+, DB Treatment Period, n=182, 181	2	2		
Urine Protein-3+, DB Treatment Period, n=182, 181	1	0		
Urine Protein-Neg, Follow-up Period, n=180, 186	156	155		
Urine Protein-Tr, Follow-up Period, n=180, 186	16	22		
Urine Protein-1+, Follow-up Period, n=180, 186	6	8		
Urine Ketones-2+, Follow-up Period, n=180, 186	1	1		
Urine Ketones-3+, Follow-up Period, 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: Double-blind Treatment Period	FFNS 110 mcg: Double-blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233[31]	229[32]		
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: Double-blind Treatment Period	FFNS 110 mcg: Double-blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233[33]	229[34]		
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

Serious adverse events	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	
Infections and infestations			
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 %

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

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

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported