Clinical trial results:
A phase 2, randomised, double-blind, placebo-controlled, crossover study to evaluate the effects of a topical pentosan polysulphate sodium (PPS) formulation in subjects with seasonal allergic rhinitis

Summary

EudraCT number	2016-003341-28
Trial protocol	SE
Global end of trial date	22 March 2017

Results information

Result version number	v1 (current)
This version publication date	07 April 2018
First version publication date	07 April 2018

Trial information

Trial identification

Sponsor protocol code	PARA_003

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Paradigm Biopharmaceuticals
Sponsor organisation address	Level 2, 517 Flinders Lane, Melbourne, Australia,
Public contact	Claire Kaufman, Chief Operations Officer, Paradigm Biopharmaceuticals, +61 413 421 160, ckaufman@paradigmbiopharma.com
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Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 November 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the effect of a topical Pentosan polysulphate sodium formulation on post-challenge nasal symptoms using an allergen challenge model in subjects with seasonal allergic rhinitis.

Protection of trial subjects:

Subjects attended a follow-up visit 1 to 2 weeks after the last day of the second treatment period. Additional physical and nasal examinations and measurements of vital signs could be performed if clinically indicated.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 November 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	40
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All subjects were recruited at a single site. Informed consent and screening were on the same day. The first subject provided informed consent and was screened on 21 November 2016. The last subject provided informed consent and was screened on 18 January 2017.

Pre-assignment

Screening details:

Forty-five (45) subjects were screened, of whom 40 were randomized to one of the two treatment arms. There were 5 screening failures, all of which were because exclusion criterion #13 (APTT value outside the normal range at screening) was met.

Period 1

Period 1 title	Baseline period (screening to day -1)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

The Sponsor was also blinded to treatment arm allocation.

Arms

Arm title	Baseline period

Arm description:

All enrolled subjects

Arm type	No intervention
Investigational medicinal product name	Pentosan polysulphate sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Intranasal use

Dosage and administration details:

Pentosan polysulphate sodium was provided in a 20 mL silicone lined class 1 glass bottle, closed with a cartridge pump system nasal pump device. NOTE: Pentosan polysulphate sodium was not administered during the baseline period.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Intranasal use

Dosage and administration details:

The placebo formulation consisted of the Pentosan polysulphate sodium formulation vehicle, adjusted to isotonicity with NaCl. Placebo was provided in a 20 mL silicone lined class 1 glass bottle, closed with a cartridge pump system nasal pump device. NOTE: Placebo was not administered during the baseline period.

Number of subjects in period 1	Baseline period
Started	40
Completed	40

Period 2

Period 2 title	Treatment period (days 1 to 14)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

The Sponsor was also blinded to treatment arm allocation.
The placebo and formulations were identical in appearance and nasal feel. The study site was given envelopes (one per subject) containing each subject's treatment allocation. These envelopes were held in a secure location. In a medical emergency requiring knowledge of the study drug, the envelope for that subject could be opened to determine their treatment allocation (while maintaining the blinding for all other subjects).

Arms

Are arms mutually exclusive?	Yes
Arm title	Pentosan polysulphate sodium then Placebo

Arm description:

Subjects received Pentosan polysulphate sodium (80 mg/day) during treatment period 1 and Placebo during treatment period 2. Subjects received IMP using 2 sprays per nostril twice daily. Nasal symptoms and PNIF (Peak Nasal Inspiratory Flow) were assessed before each dose. During the last 7 days of each treatment period, an individualised allergen challenge was administered after the morning dose of IMP. Nasal symptoms were assessed 10 minutes after the allergen challenge.

Arm type	Experimental and Placebo
Investigational medicinal product name	Pentosan polysulphate sodium
Investigational medicinal product code	
Other name	PPS, Rhinosul®
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Intranasal use

Dosage and administration details:

Pentosan polysulphate sodium was provided in a 20 mL silicone lined class 1 glass bottle, closed with a cartridge pump system nasal pump device. Subjects received Pentosan polysulphate sodium as 2 equal daily doses for 14 days. They self-administered Pentosan polysulphate sodium each morning and evening. For each morning or evening dose, subjects administered 1 spray (100 µL) of Pentosan polysulphate sodium to each nostril, waited 2 minutes, and then administered a second spray to each nostril. The concentration of Pentosan polysulphate sodium was 100 mg/mL and the total dose per day was 80 mg.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Intranasal use

Dosage and administration details:

The placebo formulation consisted of the Pentosan polysulphate sodium formulation vehicle, adjusted to isotonicity with NaCl. Placebo was provided in a 20 mL silicone lined class 1 glass bottle, closed with a cartridge pump system nasal pump device. Subjects received Placebo for 14 days. They self-administered Placebo each morning and evening. For each morning or evening dose, subjects administered 1 spray (100 µL) of Placebo to each nostril, waited 2 minutes, and then administered a second spray to each nostril.

Arm title	Placebo then Pentosan polysulphate sodium

Arm description:

Subjects received Placebo during treatment period 1 and Pentosan polysulphate sodium (80 mg/day) during treatment period 2. Subjects received IMP using 2 sprays per nostril twice daily. Nasal symptoms and PNIF (Peak Nasal Inspiratory Flow) were assessed before each dose. During the last 7 days of each treatment period, an individualised allergen challenge was administered after the morning dose of IMP. Nasal symptoms were assessed 10 minutes after the allergen challenge.

Arm type	Experimental and Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Intranasal use

Dosage and administration details:

See description for Pentosan polysulphate sodium then Placebo arm

Investigational medicinal product name	Pentosan polysulphate sodium
Investigational medicinal product code	
Other name	PPS, Rhinosul®
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Intranasal use

Dosage and administration details:

See description for Pentosan polysulphate sodium then Placebo arm

Number of subjects in period 2	Pentosan polysulphate sodium then Placebo	Placebo then Pentosan polysulphate sodium
Started	20	20
Completed	19	20
Not completed	1	0
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Baseline period
Reporting group description:	
All enrolled subjects	

Reporting group values	Baseline period	Total	
Number of subjects	40	40	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	40	40	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	25.8		
standard deviation	± 4.8	-	
Gender categorical			
Units: Subjects			
Female	8	8	
Male	32	32	
Ethnicity			
Units: Subjects			
Asian	1	1	
Black	1	1	
White	38	38	
Weight			
Units: kg			
arithmetic mean	74.9		
standard deviation	± 13.0	-	
Height			
Units: cm			
arithmetic mean	179.2		
standard deviation	± 9.4	-	

Subject analysis sets	
Subject analysis set title	PPROT, Pentosan polysulphate sodium
Subject analysis set type	Per protocol

Subject analysis set description:

Pentosan polysulphate sodium data for all randomised subjects who (i) were deemed to have no major protocol violations that could interfere with the primary objective of the study and (ii) took at least 22 of 28 full doses of the study drug, including all 3 morning doses and the first 2 evening doses during the last 3 days of allergen challenge (treatment days 12 to 14), according to the diary cards, during both treatment periods

Subject analysis set title	PPROT, Placebo
Subject analysis set type	Per protocol

Subject analysis set description:

Placebo data for all randomised subjects who (i) were deemed to have no major protocol violations that could interfere with the primary objective of the study and (ii) took at least 22 of 28 full doses of the study drug, including all 3 morning doses and the first 2 evening doses during the last 3 days of allergen challenge (treatment days 12 to 14), according to the diary cards, during both treatment periods

Subject analysis set title	FAS, Pentosan polysulphate sodium
Subject analysis set type	Full analysis

Subject analysis set description:

Pentosan polysulphate sodium data for all randomised subjects who (i) took at least 1 dose of study drug, (ii) received at least 1 allergen challenge and (iii) had at least 1 post-baseline assessment of any efficacy variable

Subject analysis set title	FAS, Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Placebo data for all randomised subjects who (i) took at least 1 dose of study drug, (ii) received at least 1 allergen challenge and (iii) had at least 1 post-baseline assessment of any efficacy variable

Subject analysis set title	Safety Set, Pentosan polysulphate sodium then Placebo arm
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised subjects in the Pentosan polysulphate sodium then Placebo arm who received at least 1 dose of study drug

Subject analysis set title	Safety Set, Placebo then Pentosan polysulphate sodium arm
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised subjects in the Placebo then Pentosan polysulphate sodium arm who received at least 1 dose of study drug

Reporting group values	PPROT, Pentosan polysulphate sodium	PPROT, Placebo	FAS, Pentosan polysulphate sodium
Number of subjects	37	37	40
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	37	37	40
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	25.7	25.7	25.8
standard deviation	± 4.8	± 4.8	± 4.8

Gender categorical Units: Subjects			
Female	8	8	8
Male	29	29	32
Ethnicity Units: Subjects			
Asian	1	1	1
Black	1	1	1
White	35	35	38
Weight Units: kg			
arithmetic mean	74.8	74.8	74.9
standard deviation	± 13.4	± 13.4	± 13.0
Height Units: cm			
arithmetic mean	178.1	178.1	179.2
standard deviation	± 8.9	± 8.9	± 9.4

Reporting group values	FAS, Placebo	Safety Set, Pentosan polysulphate sodium then Placebo arm	Safety Set, Placebo then Pentosan polysulphate sodium arm
Number of subjects	40	20	20
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	40	20	20
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	25.8	25.7	25.9
standard deviation	± 4.8	± 3.6	± 5.8
Gender categorical Units: Subjects			
Female	8	3	5
Male	32	17	15
Ethnicity Units: Subjects			
Asian	1	1	0
Black	1	1	0
White	38	18	20
Weight Units: kg			
arithmetic mean	74.9	77.2	72.7
standard deviation	± 13.0	± 14.2	± 11.5

Height			
Units: cm			
arithmetic mean	179.2	179.4	178.9
standard deviation	± 9.4	± 9.1	± 9.9

End points

End points reporting groups

Reporting group title	Baseline period

Reporting group description:

All enrolled subjects

Reporting group title	Pentosan polysulphate sodium then Placebo

Reporting group description:

Subjects received Pentosan polysulphate sodium (80 mg/day) during treatment period 1 and Placebo during treatment period 2. Subjects received IMP using 2 sprays per nostril twice daily. Nasal symptoms and PNIF (Peak Nasal Inspiratory Flow) were assessed before each dose. During the last 7 days of each treatment period, an individualised allergen challenge was administered after the morning dose of IMP. Nasal symptoms were assessed 10 minutes after the allergen challenge.

Reporting group title	Placebo then Pentosan polysulphate sodium

Reporting group description:

Subjects received Placebo during treatment period 1 and Pentosan polysulphate sodium (80 mg/day) during treatment period 2. Subjects received IMP using 2 sprays per nostril twice daily. Nasal symptoms and PNIF (Peak Nasal Inspiratory Flow) were assessed before each dose. During the last 7 days of each treatment period, an individualised allergen challenge was administered after the morning dose of IMP. Nasal symptoms were assessed 10 minutes after the allergen challenge.

Subject analysis set title	PPROT, Pentosan polysulphate sodium
Subject analysis set type	Per protocol

Subject analysis set description:

Pentosan polysulphate sodium data for all randomised subjects who (i) were deemed to have no major protocol violations that could interfere with the primary objective of the study and (ii) took at least 22 of 28 full doses of the study drug, including all 3 morning doses and the first 2 evening doses during the last 3 days of allergen challenge (treatment days 12 to 14), according to the diary cards, during both treatment periods

Subject analysis set title	PPROT, Placebo
Subject analysis set type	Per protocol

Subject analysis set description:

Placebo data for all randomised subjects who (i) were deemed to have no major protocol violations that could interfere with the primary objective of the study and (ii) took at least 22 of 28 full doses of the study drug, including all 3 morning doses and the first 2 evening doses during the last 3 days of allergen challenge (treatment days 12 to 14), according to the diary cards, during both treatment periods

Subject analysis set title	FAS, Pentosan polysulphate sodium
Subject analysis set type	Full analysis

Subject analysis set description:

Pentosan polysulphate sodium data for all randomised subjects who (i) took at least 1 dose of study drug, (ii) received at least 1 allergen challenge and (iii) had at least 1 post-baseline assessment of any efficacy variable

Subject analysis set title	FAS, Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Placebo data for all randomised subjects who (i) took at least 1 dose of study drug, (ii) received at least 1 allergen challenge and (iii) had at least 1 post-baseline assessment of any efficacy variable

Subject analysis set title	Safety Set, Pentosan polysulphate sodium then Placebo arm
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised subjects in the Pentosan polysulphate sodium then Placebo arm who received at least 1 dose of study drug

Subject analysis set title	Safety Set, Placebo then Pentosan polysulphate sodium arm
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised subjects in the Placebo then Pentosan polysulphate sodium arm who received at least 1 dose of study drug

Primary: Mean post-challenge TNSS over the last 3 days of allergen challenge

End point title	Mean post-challenge TNSS over the last 3 days of allergen challenge

End point description:

Nasal symptoms were monitored approximately 10 minutes after allergen challenge. TNSS (total nasal symptom score) was calculated as the sum of the scores for the following nasal symptoms, each scored on a scale from 1 to 3: (i) nasal secretion, (ii) nasal congestion and (iii) sneezing or nasal itching (whichever was more severe). TNSS has a value of 0 to 9.

End point type	Primary

End point timeframe:

Last 3 days of allergen challenge (treatment days 12 to 14)

End point values	PPROT, Pentosan polysulphate sodium	PPROT, Placebo	FAS, Pentosan polysulphate sodium	FAS, Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	37	40	39
Units: no units				
arithmetic mean (standard deviation)	5.3 (± 1.7)	5.1 (± 1.6)	5.1 (± 1.7)	5.1 (± 1.6)

Statistical analyses

Statistical analysis title	ANOVA, PPROT

Statistical analysis description:

ANOVA model with subject, treatment period and treatment as fixed effects

Comparison groups	PPROT, Pentosan polysulphate sodium v PPROT, Placebo
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.5759 [2]
Method	ANOVA

Notes:

[1] - Comparison of Pentosan polysulphate sodium versus Placebo in the 37 subjects with data for both Pentosan polysulphate sodium and Placebo. Note: Number of subjects included in analysis = 37.
[2] - Not significant

Statistical analysis title	ANOVA, FAS

Statistical analysis description:

ANOVA model with subject, treatment period and treatment as fixed effects

Comparison groups	FAS, Pentosan polysulphate sodium v FAS, Placebo

Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.6083 [4]
Method	ANOVA

Notes:

[3] - Comparison of Pentosan polysulphate sodium versus Placebo in the 39 subjects with data for both Pentosan polysulphate sodium and Placebo. Note: Number of subjects included in analysis = 39.
[4] - Not significant

Secondary: Mean morning TNSS over the last 3 days of allergen challenge

End point title	Mean morning TNSS over the last 3 days of allergen challenge

End point description:

Nasal symptoms were monitored within 30 minutes of waking. TNSS was calculated as the sum of the scores for (i) nasal secretion, (ii) nasal congestion and (iii) sneezing or nasal itching (whichever was more severe).

End point type	Secondary

End point timeframe:

Last 3 days of allergen challenge (treatment days 12 to 14)

End point values	PPROT, Pentosan polysulphate sodium	PPROT, Placebo	FAS, Pentosan polysulphate sodium	FAS, Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	37	40	39
Units: no units				
arithmetic mean (standard deviation)	1.55 (± 1.18)	1.52 (± 1.34)	1.55 (± 1.18)	1.59 (± 1.48)

Statistical analyses

Statistical analysis title	ANOVA, PPROT

Statistical analysis description:

ANOVA model with subject, treatment period and treatment as fixed effects

Comparison groups	PPROT, Pentosan polysulphate sodium v PPROT, Placebo
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.8953 [6]
Method	ANOVA

Notes:

[5] - Comparison of Pentosan polysulphate sodium versus Placebo in the 37 subjects with data for both Pentosan polysulphate sodium and Placebo. Note: Number of subjects included in analysis = 37.
[6] - Not significant

Statistical analysis title	ANOVA, FAS

Statistical analysis description:

ANOVA model with subject, treatment period and treatment as fixed effects

Comparison groups	FAS, Pentosan polysulphate sodium v FAS, Placebo

Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.7166 [8]
Method	ANOVA

Notes:

[7] - Comparison of Pentosan polysulphate sodium versus Placebo in the 39 subjects with data for both Pentosan polysulphate sodium and Placebo. Note: Number of subjects included in analysis = 39.
[8] - Not significant

Secondary: Mean evening TNSS over the last 3 days of allergen challenge

End point title	Mean evening TNSS over the last 3 days of allergen challenge

End point description:

Nasal symptoms were monitored between 20:00 and 24:00. TNSS was calculated as the sum of the scores for (i) nasal secretion, (ii) nasal congestion and (iii) sneezing or nasal itching (whichever was more severe).

End point type	Secondary

End point timeframe:

Last 3 days of allergen challenge (treatment days 12 to 14)

End point values	PPROT, Pentosan polysulphate sodium	PPROT, Placebo	FAS, Pentosan polysulphate sodium	FAS, Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	37	40	39
Units: no units				
arithmetic mean (standard deviation)	1.76 (± 1.41)	1.40 (± 1.46)	1.79 (± 1.38)	1.48 (± 1.62)

Statistical analyses

Statistical analysis title	ANOVA, PPROT

Statistical analysis description:

ANOVA model with subject, treatment period and treatment as fixed effects

Comparison groups	PPROT, Pentosan polysulphate sodium v PPROT, Placebo
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.1526 [10]
Method	ANOVA

Notes:

[9] - Comparison of Pentosan polysulphate sodium versus Placebo in the 37 subjects with data for both Pentosan polysulphate sodium and Placebo. Note: Number of subjects included in analysis = 37.
[10] - Not significant

Statistical analysis title	ANOVA, FAS

Statistical analysis description:

ANOVA model with subject, treatment period and treatment as fixed effects

Comparison groups	FAS, Pentosan polysulphate sodium v FAS, Placebo

Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.2075 [12]
Method	ANOVA

Notes:

[11] - Comparison of Pentosan polysulphate sodium versus Placebo in the 39 subjects with data for both Pentosan polysulphate sodium and Placebo. Note: Number of subjects included in analysis = 39.
[12] - Not significant

Secondary: Mean post-challenge PNIF over the last 3 days of allergen challenge

End point title	Mean post-challenge PNIF over the last 3 days of allergen challenge

End point description:

Subjects measured PNIF (peak nasal inspiratory flow) using a flow meter equipped with a facial mask immediately after post-allergen challenge monitoring of nasal symptoms. Subjects recorded 3 PNIF measurements, the highest of which was used in the analyses.

End point type	Secondary

End point timeframe:

Last 3 days of allergen challenge (treatment days 12 to 14)

End point values	PPROT, Pentosan polysulphate sodium	PPROT, Placebo	FAS, Pentosan polysulphate sodium	FAS, Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	37	40	39
Units: L/min				
arithmetic mean (standard deviation)	133.2 (± 42.8)	136.4 (± 36.9)	131.3 (± 42.6)	135.7 (± 36.8)

Statistical analyses

Statistical analysis title	ANOVA, PPROT

Statistical analysis description:

ANOVA model with subject, treatment period and treatment as fixed effects

Comparison groups	PPROT, Placebo v PPROT, Pentosan polysulphate sodium
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.3467 [14]
Method	ANOVA

Notes:

[13] - Comparison of Pentosan polysulphate sodium versus Placebo in the 37 subjects with data for both Pentosan polysulphate sodium and Placebo. Note: Number of subjects included in analysis = 37.
[14] - Not significant

Statistical analysis title	ANOVA, FAS

Statistical analysis description:

ANOVA model with subject, treatment period and treatment as fixed effects

Comparison groups	FAS, Pentosan polysulphate sodium v FAS, Placebo
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.2687 [16]
Method	ANOVA

Notes:

[15] - Comparison of Pentosan polysulphate sodium versus Placebo in the 39 subjects with data for both Pentosan polysulphate sodium and Placebo. Note: Number of subjects included in analysis = 39.
[16] - Not significant

Secondary: Mean morning PNIF over the last 3 days of allergen challenge

End point title	Mean morning PNIF over the last 3 days of allergen challenge

End point description:

Subjects measured PNIF immediately after morning monitoring of nasal symptoms. Subjects recorded 3 PNIF measurements, the highest of which was used in the analyses.

End point type	Secondary

End point timeframe:

Last 3 days of allergen challenge (treatment days 12 to 14)

End point values	PPROT, Pentosan polysulphate sodium	PPROT, Placebo	FAS, Pentosan polysulphate sodium	FAS, Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	37	40	39
Units: L/min				
arithmetic mean (standard deviation)	155.41 (± 39.00)	156.49 (± 37.43)	152.17 (± 41.21)	155.38 (± 39.11)

Statistical analyses

Statistical analysis title	ANOVA, PPROT

Statistical analysis description:

ANOVA model with subject, treatment period and treatment as fixed effects

Comparison groups	PPROT, Placebo v PPROT, Pentosan polysulphate sodium
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.7048 [18]
Method	ANOVA

Notes:

[17] - Comparison of Pentosan polysulphate sodium versus Placebo in the 37 subjects with data for both Pentosan polysulphate sodium and Placebo. Note: Number of subjects included in analysis = 37.
[18] - Not significant

Statistical analysis title	ANOVA, FAS

Statistical analysis description:

ANOVA model with subject, treatment period and treatment as fixed effects

Comparison groups	FAS, Placebo v FAS, Pentosan polysulphate sodium
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.5238 [20]
Method	ANOVA

Notes:

[19] - Comparison of Pentosan polysulphate sodium versus Placebo in the 39 subjects with data for both Pentosan polysulphate sodium and Placebo. Note: Number of subjects included in analysis = 39.
[20] - Not significant

Secondary: Mean evening PNIF over the last 3 days of allergen challenge

End point title	Mean evening PNIF over the last 3 days of allergen challenge

End point description:

Subjects measured PNIF immediately after evening monitoring of nasal symptoms. Subjects recorded 3 PNIF measurements, the highest of which was used in the analyses.

End point type	Secondary

End point timeframe:

Last 3 days of allergen challenge (treatment days 12 to 14)

End point values	PPROT, Pentosan polysulphate sodium	PPROT, Placebo	FAS, Pentosan polysulphate sodium	FAS, Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	37	40	39
Units: L/min				
arithmetic mean (standard deviation)	159.23 (± 37.93)	169.23 (± 42.12)	156.46 (± 39.34)	167.31 (± 43.10)

Statistical analyses

Statistical analysis title	ANOVA, PPROT

Statistical analysis description:

ANOVA model with subject, treatment period and treatment as fixed effects

Comparison groups	PPROT, Placebo v PPROT, Pentosan polysulphate sodium
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.0262 [22]
Method	ANOVA

Notes:

[21] - Comparison of Pentosan polysulphate sodium versus Placebo in the 37 subjects with data for both Pentosan polysulphate sodium and Placebo. Note: Number of subjects included in analysis = 37.
[22] - Significant difference in favour of Placebo

Statistical analysis title	ANOVA, FAS

Statistical analysis description:

ANOVA model with subject, treatment period and treatment as fixed effects

Comparison groups	FAS, Placebo v FAS, Pentosan polysulphate sodium
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.0177 [24]
Method	ANOVA

Notes:

[23] - Comparison of Pentosan polysulphate sodium versus Placebo in the 39 subjects with data for both Pentosan polysulphate sodium and Placebo. Note: Number of subjects included in analysis = 39.
[24] - Significant difference in favour of Placebo

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing of informed consent at Visit 1 (screening) to completion of the final study visit

Adverse event reporting additional description:

AEs elicited with non-leading questions or directly observed or spontaneously volunteered by subjects were reported. Subjects were asked to telephone the study site to report any AEs that occurred in the week following Visit 1, and to record AEs occurring between visits on diary cards.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Pentosan polysulphate sodium treatment

Reporting group description:

Adverse events that occurred in the Safety Set in relation to Pentosan polysulphate sodium treatment

Reporting group title	Placebo treatment

Reporting group description:

Adverse events that occurred in the Safety Set in relation to Placebo treatment

Serious adverse events	Pentosan polysulphate sodium treatment	Placebo treatment	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Head injury	Additional description: Subject was hit by a car when cycling during treatment period 1 (Pentosan polysulphate sodium). He sustained a head injury, was hospitalised and discontinued the study. The Investigator judged no causal relationship with study treatment,		
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (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: 0 %

Non-serious adverse events	Pentosan polysulphate sodium treatment	Placebo treatment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 40 (80.00%)	24 / 39 (61.54%)	

Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 40 (0.00%)	3 / 39 (7.69%)	
occurrences (all)	0	3	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Malaise			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	0 / 40 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	27 / 40 (67.50%)	8 / 39 (20.51%)	
occurrences (all)	52	13	
Nasal crusting			
subjects affected / exposed	11 / 40 (27.50%)	6 / 39 (15.38%)	
occurrences (all)	12	6	
Nasal discomfort			
subjects affected / exposed	8 / 40 (20.00%)	3 / 39 (7.69%)	
occurrences (all)	9	3	
Nasal dryness			
subjects affected / exposed	1 / 40 (2.50%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Nasal pruritus			
subjects affected / exposed	2 / 40 (5.00%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
Nasal septum disorder			

subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Nasal ulcer			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Rhinalgia			
subjects affected / exposed	1 / 40 (2.50%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	2	
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 40 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	2 / 40 (5.00%)	7 / 39 (17.95%)	
occurrences (all)	2	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 March 2017	A preliminary review of blinded data (prior to finalisation of the statistical analysis plan and database lock) revealed that 15/40 subjects would be excluded from the per-protocol set, as defined in the study protocol, because they failed to take "all 6 doses [of IMP] during the last 3 days of allergen challenge (treatment days 12 to 14; according to the diary cards), during both treatment periods". With one exception, all subjects who failed to take all of these 6 doses of IMP failed to take the very last dose and only that dose. This last dose was scheduled to be taken after the final assessments (of nasal symptoms and peak nasal inspiratory flow) on the last day of the treatment period. Therefore, failure to take the final evening dose had no implications for the efficacy analyses. To increase the validity of the efficacy analyses, which use the per-protocol set as the primary analysis population, the per-protocol set was redefined as: "All randomised subjects who (i) are deemed to have no major protocol violations that could interfere with the primary objective of this study and (ii) took at least 22 of the 28 doses of the study medication, including all 3 morning doses and the first 2 evening doses during the last 3 days of allergen challenge (treatment days 12 to 14) according to the diary cards, during both treatment periods." NOTE: The actual date of the amendment is 24 April 2017 (i.e. after 22 March 2017, the global end of trial date).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported