Clinical trial results:
A multi-centre, double-blind, placebo-controlled study to explore the safety and efficacy of Birch Modified Allergen Tyrosine adsorbed + MPL (POLLINEX® Quattro Plus 1.0 mL Birch [PQ Birch]) in subjects with seasonal allergic rhinoconjunctivitis due to birch pollen.

Summary

EudraCT number	2015-000984-15
Trial protocol	DE AT
Global end of trial date	08 February 2016

Results information

Result version number	v1 (current)
This version publication date	24 February 2017
First version publication date	24 February 2017

Trial information

Trial identification

Sponsor protocol code	PQBirch204

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Allergy Therapeutic (UK) Ltd. (ATL)
Sponsor organisation address	Dominion Way, Worthing, West Sussex, United Kingdom, BN14 8SA
Public contact	Research and Development, Allergy Therapeutics, +44 19038440, ClinicalOperations@allergytherapeutics.com
Scientific contact	Research and Development, Allergy Therapeutics, +44 1903844700, ClinicalOperations@allergytherapeutics.com

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	12 August 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 February 2016
Global end of trial reached?	Yes
Global end of trial date	08 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study was designed to evaluate the safety and efficacy of different cumulative doses of POLLINEX® Quattro Plus 1.0 mL Birch 100% (PQ Birch) treatment as assessed with conjunctival provocation test (CPT).

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization (ICH) guideline E6: Good Clinical Practice (GCP). An informed consent form explaining the procedures of the study including the potential hazards was reviewed and approved by the responsible IEC/IRB before its use.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 September 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 51
Country: Number of subjects enrolled	Germany: 319
Worldwide total number of subjects	370
EEA total number of subjects	370

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)	370
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 28 investigational sites in two countries: Austria and Germany.
Overall, 461 subjects were screened, 371 were randomized and 370 patients received study medication.
One patient was randomized by mistake despite being a screening failure. This patient was not treated.

Pre-assignment

Screening details:

Male or female aged 18 to 60 with a positive history of moderate to severe seasonal allergic rhinoconjunctivitis ascribed to birch pollen exposure requiring treatment for at least the last 2 years (i.e., pollen seasons) prior to study and severe symptoms of allergic rhinoconjunctivitis in the past birch pollen season as determined by DSQ (score ≥5)

Pre-assignment period milestones

Number of subjects started	370
Number of subjects completed	370

Period 1

Period 1 title	Visit 2-7 (Visit 1=Screening)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The identity of study medication administered was not known by the subjects, investigators or other persons directly involved in the conduct of the clinical study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

6 injections of Placebo given sequentially at weekly intervals

Arm type	Placebo
Investigational medicinal product name	Placebo (2% L-Tyrosine)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Trained site personnel administered 6 subcutaneous injections of 1.0 mL each in eligible subjects in the lateral/posterior aspect of the upper arm.

Arm title	5100 SU

Arm description:

2 injections of Placebo and 4 active injections of PQ Birch achieving 5100 SU cumulative dose

Arm type	Experimental
Investigational medicinal product name	POLLINEX® Quattro Plus 1.0 mL Birch; Placebo (2 % L-Tyrosine)
Investigational medicinal product code	
Other name	PQ Birch
Pharmaceutical forms	Suspension for injection

Routes of administration	Subcutaneous use

Dosage and administration details:

6 subcutaneous injections of 1.0 mL each, with 2 Placebo injections followed by active formulation at dose strenghts 300, 800, 2000 and 2000 SU/mL given sequentially at weekly intervals.

Arm title	5000 SU

Arm description:

6 active injections of PQ Birch achieving 5000 SU cumulative dose

Arm type	Experimental
Investigational medicinal product name	POLLINEX® Quattro Plus 1.0 mL Birch
Investigational medicinal product code	
Other name	PQ Birch
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

6 subcutaneous injections of 1.0 mL each, at dose strengths 300, 300, 800, 800, 800, 2000 SU/mL given sequentially at weekly intervals.

Arm title	15300 SU

Arm description:

2 injections of Placebo and 4 active injections of PQ Birch achieving 15300 SU cumulative dose

Arm type	Experimental
Investigational medicinal product name	POLLINEX® Quattro Plus 1.0 mL Birch, Placebo (2 % L-Tyrosine)
Investigational medicinal product code	
Other name	PQ Birch
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

6 subcutaneous injections of 1.0 mL each with 2 Placebo injections followed by active formulation at dose strengths 900, 2400, 6000 and 6000 SU/mL given sequentially at weekly intervals.

Arm title	15000 SU

Arm description:

6 active injections of PQ Birch achieving 15000 SU cumulative dose

Arm type	Experimental
Investigational medicinal product name	POLLINEX® Quattro Plus 1.0 mL Birch
Investigational medicinal product code	
Other name	PQ Birch
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

6 subcutaneous injections of 1.0 mL each, at dose strengths 900, 900, 2400, 2400, 2400, 6000 SU/mL given sequentially at weekly intervals.

Arm title	20100 SU

Arm description:

6 active injections of PQ Birch achieving 20100 SU cumulative dose

Arm type	Experimental

Investigational medicinal product name	POLLINEX® Quattro Plus 1.0 mL Birch
Investigational medicinal product code	
Other name	PQ Birch
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

6 subcutaneous injections of 1.0 mL each, at dose strengths 900, 2400, 2400, 2400, 6000 and 6000 SU/mL given sequentially at weekly intervals.

Arm title	27300 SU

Arm description:

6 active injections of PQ Birch achieving 27300 SU cumulative dose

Arm type	Experimental
Investigational medicinal product name	POLLINEX® Quattro Plus 1.0 mL Birch
Investigational medicinal product code	
Other name	PQ Birch
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

6 subcutaneous injections of 1.0 mL each, at dose strengths 900, 2400, 6000, 6000, 6000, 6000 SU/mL given sequentially at weekly intervals.

Number of subjects in period 1	Placebo	5100 SU	5000 SU
Started	53	49	53
Completed	49	44	50
Not completed	4	5	3
Consent withdrawn by subject	1	2	-
Adverse event, non-fatal	2	2	1
Pregnancy	1	-	-
Lost to follow-up	-	-	1
Protocol deviation	-	1	1

Number of subjects in period 1	15300 SU	15000 SU	20100 SU
Started	53	55	51
Completed	52	52	48
Not completed	1	3	3
Consent withdrawn by subject	-	1	2
Adverse event, non-fatal	1	2	-
Pregnancy	-	-	-
Lost to follow-up	-	-	1
Protocol deviation	-	-	-

Number of subjects in period 1	27300 SU
Started	56

Completed	54
Not completed	2
Consent withdrawn by subject	-
Adverse event, non-fatal	2
Pregnancy	-
Lost to follow-up	-
Protocol deviation	-

Period 2

Period 2 title	Follow-up (Visit 8)
Is this the baseline period?	No
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

Arm description:

6 injections of Placebo given sequentially at weekly intervals

Arm type	Experimental
Investigational medicinal product name	Placebo (2 % L-Tyrosine)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Trained site personnel administered 6 subcutaneous injections of 1.0 mL each in eligible subjects in lateral/posterior aspect of the upper arm.

Arm title	5100 SU

Arm description:

2 injections of Placebo and 4 active injections of PQ Birch achieving 5100 SU cumulative dose

Arm type	Experimental
Investigational medicinal product name	POLLINEX® Quattro Plus 1.0 mL Birch, Placebo (2 % L-Tyrosine)
Investigational medicinal product code	
Other name	PQ Birch
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

6 subcutaneous injections of 1.0 mL each, with 2 placebo injections followed by active formulation at dose strengths 300, 800, 2000 and 2000 SU/mL given sequentially at weekly intervals.

Arm title	5000 SU

Arm description:

6 active injections of PQ Birch achieving 5000 SU cumulative dose

Arm type	Experimental

Investigational medicinal product name	POLLINEX® Quattro Plus 1.0 mL Birch
Investigational medicinal product code	
Other name	PQ Birch
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

6 subcutaneous injections of 1.0 mL each, at dose strengths 300, 300, 800, 800, 800, 2000 SU/mL given sequentially at weekly intervals.

Arm title	15300 SU

Arm description:

2 injections of Placebo and 4 active injections of PQ birch Birch achieving 15300 SU cumulative dose

Arm type	Experimental
Investigational medicinal product name	POLLINEX® Quattro Plus 1.0 mL Birch, Placebo (2 % L-Tyrosine)
Investigational medicinal product code	
Other name	PQ Birch
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

6 subcutaneous injections of 1.0 mL each, with 2 placebo injections followed by active formulation at dose strengths 900, 2400, 6000 and 6000 SU/mL given sequentially at weekly intervals.

Arm title	15000 SU

Arm description:

6 active injections of PQ Birch achieving 15000 SU cumulative dose

Arm type	Experimental
Investigational medicinal product name	POLLINEX® Quattro Plus 1.0 mL Birch
Investigational medicinal product code	
Other name	PQ Birch
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

6 subcutaneous injections of 1.0 mL each, at dose strengths 900, 900, 2400, 2400, 2400, 6000 SU/mL given sequentially at weekly intervals.

Arm title	20100 SU

Arm description:

6 active injections of PQ Birch achieving 20100 SU cumulative dose

Arm type	Experimental
Investigational medicinal product name	POLLINEX® Quattro Plus 1.0 mL Birch
Investigational medicinal product code	
Other name	PQ Birch
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

6 subcutaneous injections of 1.0 mL each, at dose strengths 900, 2400, 2400, 2400, 6000, 6000 SU/mL given sequentially at weekly intervals.

Arm title	27300 SU

Arm description:

6 active injections of PQ Birch achieving 27300 SU cumulative dose

Arm type	Experimental

Investigational medicinal product name	POLLINEX® Quattro Plus 1.0 mL Birch
Investigational medicinal product code	
Other name	PQ Birch
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

6 subcutaneous injections of 1.0 mL each, at dose strengths 900, 2400, 6000, 6000, 6000, 6000 SU/mL given sequentially at weekly intervals.

Number of subjects in period 2	Placebo	5100 SU	5000 SU
Started	49	44	50
Completed	49	44	50
Not completed	0	0	0
Terminated after treatment period	-	-	-

Number of subjects in period 2	15300 SU	15000 SU	20100 SU
Started	52	52	48
Completed	51	51	48
Not completed	1	1	0
Terminated after treatment period	1	1	-

Number of subjects in period 2	27300 SU
Started	54
Completed	54
Not completed	0
Terminated after treatment period	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
6 injections of Placebo given sequentially at weekly intervals	
Reporting group title	5100 SU
Reporting group description:	
2 injections of Placebo and 4 active injections of PQ Birch achieving 5100 SU cumulative dose	
Reporting group title	5000 SU
Reporting group description:	
6 active injections of PQ Birch achieving 5000 SU cumulative dose	
Reporting group title	15300 SU
Reporting group description:	
2 injections of Placebo and 4 active injections of PQ Birch achieving 15300 SU cumulative dose	
Reporting group title	15000 SU
Reporting group description:	
6 active injections of PQ Birch achieving 15000 SU cumulative dose	
Reporting group title	20100 SU
Reporting group description:	
6 active injections of PQ Birch achieving 20100 SU cumulative dose	
Reporting group title	27300 SU
Reporting group description:	
6 active injections of PQ Birch achieving 27300 SU cumulative dose	

Reporting group values	Placebo	5100 SU	5000 SU
Number of subjects	53	49	53
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)	53	49	53
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	37.5	36.4	35.2
standard deviation	± 12.19	± 11.95	± 11.35
Gender categorical Units: Subjects			
Female	23	34	29
Male	30	15	24

Reporting group values	15300 SU	15000 SU	20100 SU
Number of subjects	53	55	51
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)	53	55	51
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	35.9	36.1	34.6
standard deviation	± 12.4	± 12.63	± 12.02
Gender categorical			
Units: Subjects			
Female	25	30	21
Male	28	25	30

Reporting group values	27300 SU	Total	
Number of subjects	56	370	
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)	56	370	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	35.7		
standard deviation	± 12.48	-	
Gender categorical			
Units: Subjects			
Female	31	193	
Male	25	177	

Subject analysis sets

Subject analysis set title	Safety Set
Subject analysis set type	Full analysis

Subject analysis set description:

All patients who received at least one dose of study medication. Subjects were analyzed according to the treatment that they received.

Subject analysis set title	mFAS
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subset of the Full Analysis Set that excluded all patients who did not receive the full cumulative dose they were randomized to or who had missing values with respect to the post-treatment TSS.

Reporting group values	Safety Set	mFAS	
Number of subjects	370	346	
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)	370	346	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	35.9	35.7	
standard deviation	± 12.09	± 12.07	
Gender categorical Units: Subjects			
Female	193	177	
Male	177	169	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
6 injections of Placebo given sequentially at weekly intervals	
Reporting group title	5100 SU
Reporting group description:	
2 injections of Placebo and 4 active injections of PQ Birch achieving 5100 SU cumulative dose	
Reporting group title	5000 SU
Reporting group description:	
6 active injections of PQ Birch achieving 5000 SU cumulative dose	
Reporting group title	15300 SU
Reporting group description:	
2 injections of Placebo and 4 active injections of PQ Birch achieving 15300 SU cumulative dose	
Reporting group title	15000 SU
Reporting group description:	
6 active injections of PQ Birch achieving 15000 SU cumulative dose	
Reporting group title	20100 SU
Reporting group description:	
6 active injections of PQ Birch achieving 20100 SU cumulative dose	
Reporting group title	27300 SU
Reporting group description:	
6 active injections of PQ Birch achieving 27300 SU cumulative dose	
Reporting group title	Placebo
Reporting group description:	
6 injections of Placebo given sequentially at weekly intervals	
Reporting group title	5100 SU
Reporting group description:	
2 injections of Placebo and 4 active injections of PQ Birch achieving 5100 SU cumulative dose	
Reporting group title	5000 SU
Reporting group description:	
6 active injections of PQ Birch achieving 5000 SU cumulative dose	
Reporting group title	15300 SU
Reporting group description:	
2 injections of Placebo and 4 active injections of PQ birch Birch achieving 15300 SU cumulative dose	
Reporting group title	15000 SU
Reporting group description:	
6 active injections of PQ Birch achieving 15000 SU cumulative dose	
Reporting group title	20100 SU
Reporting group description:	
6 active injections of PQ Birch achieving 20100 SU cumulative dose	
Reporting group title	27300 SU
Reporting group description:	
6 active injections of PQ Birch achieving 27300 SU cumulative dose	
Subject analysis set title	Safety Set
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients who received at least one dose of study medication. Subjects were analyzed according to the treatment that they received.	
Subject analysis set title	mFAS

Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subset of the Full Analysis Set that excluded all patients who did not receive the full cumulative dose they were randomized to or who had missing values with respect to the post-treatment TSS.

Primary: Total Symptom Score reported during CPTs

End point title	Total Symptom Score reported during CPTs

End point description:

The primary efficacy variable was the change from baseline to post-treatment in TSS (comprising the categories eye redness, tearing, itching and irritation).
The MCP-Mod methodology (multiple comparison procedure - modelling) was used to test for a dose-response and to estimate the dose-response shape.

End point type	Primary

End point timeframe:

Approximately four weeks after the last injection.

End point values	Placebo	5100 SU	5000 SU	15300 SU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	49	44	50	50
Units: Score				
arithmetic mean (standard deviation)				
Post-treatment - Baseline	-2.2 (± 2.8)	-3.2 (± 2.9)	-2.9 (± 2.5)	-3.6 (± 3.2)

End point values	15000 SU	20100 SU	27300 SU	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51	48	54	
Units: Score				
arithmetic mean (standard deviation)				
Post-treatment - Baseline	-3.1 (± 2.8)	-2.8 (± 2.1)	-3.5 (± 2.8)	

Attachments (see zip file)	Primary Endpoint/Attachment Primary Endpoint.pdf

Statistical analyses

Statistical analysis title	MCP-Mod
Comparison groups	Placebo v 5100 SU v 5000 SU v 15300 SU v 15000 SU v 20100 SU v 27300 SU
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.004 [1]
Method	MCP-Mod

Notes:

[1] - Three candidate models were used to analyze the data using the MCP-Mod and the dose response curve is presented in the Appendix.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Within the time period from the first injection of study medication until Visit 8a

Adverse event reporting additional description:

AEs were summarized by treatment group and primary SOC, preferred term, additionally by causality assessment and intensity.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

6 subcutaneous injections of 1.0 mL each given sequentially at weekly intervals

Reporting group title	5100 SU

Reporting group description:

6 subcutaneous injections of 1.0 mL each, with 2 placebo injections followed by active formulation at dose strengths 300, 800, 2000 and 2000 SU/mL given sequentially at weekly intervals.

Reporting group title	5000 SU

Reporting group description:

6 subcutaneous injections of 1.0 mL each, at dose strengths 300, 300, 800, 800, 800, 2000 SU/mL given sequentially at weekly intervals.

Reporting group title	15300 SU

Reporting group description:

6 subcutaneous injections of 1.0 mL each, with 2 placebo injections followed by active formulation at dose strengths 900, 2400, 6000 and 6000 SU/mL given sequentially at weekly intervals.

Reporting group title	15000 SU

Reporting group description:

6 subcutaneous injections of 1.0 mL each, at dose strengths 900, 900, 2400, 2400, 2400, 6000 SU/mL given sequentially at weekly intervals.

Reporting group title	20100 SU

Reporting group description:

6 subcutaneous injections of 1.0 mL each, at dose strengths 900, 2400, 2400, 2400, 6000, 6000 SU/mL given sequentially at weekly intervals.

Reporting group title	27300 SU

Reporting group description:

6 subcutaneous injections of 1.0 mL each, at dose strengths 900, 2400, 6000, 6000, 6000, 6000 SU/mL given sequentially at weekly intervals.

Serious adverse events	Placebo	5100 SU	5000 SU
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 53 (1.89%)	1 / 49 (2.04%)	0 / 53 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Hepatobiliary disorders			

Hyperbilirubinaemia	Additional description: Reported adverse event was assessed as non-related to study medication.		
subjects affected / exposed	0 / 53 (0.00%)	0 / 49 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Diverticulitis	Additional description: Reported adverse event was assessed as non-related to study medication.		
subjects affected / exposed	1 / 53 (1.89%)	0 / 49 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis	Additional description: Reported adverse event was assessed as non-related to study medication.		
subjects affected / exposed	0 / 53 (0.00%)	1 / 49 (2.04%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	15300 SU	15000 SU	20100 SU
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 53 (0.00%)	0 / 55 (0.00%)	0 / 51 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Hepatobiliary disorders			
Hyperbilirubinaemia	Additional description: Reported adverse event was assessed as non-related to study medication.		
subjects affected / exposed	0 / 53 (0.00%)	0 / 55 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Diverticulitis	Additional description: Reported adverse event was assessed as non-related to study medication.		
subjects affected / exposed	0 / 53 (0.00%)	0 / 55 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis	Additional description: Reported adverse event was assessed as non-related to study medication.		
subjects affected / exposed	0 / 53 (0.00%)	0 / 55 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	27300 SU		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 56 (1.79%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Hepatobiliary disorders			
Hyperbilirubinaemia	Additional description: Reported adverse event was assessed as non-related to study medication.		
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Diverticulitis	Additional description: Reported adverse event was assessed as non-related to study medication.		
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Appendicitis	Additional description: Reported adverse event was assessed as non-related to study medication.		
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	5100 SU	5000 SU
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 53 (52.83%)	37 / 49 (75.51%)	41 / 53 (77.36%)
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 53 (1.89%)	1 / 49 (2.04%)	1 / 53 (1.89%)
occurrences (all)	2	3	1
General disorders and administration site conditions			
Injection site swelling			
subjects affected / exposed	6 / 53 (11.32%)	24 / 49 (48.98%)	27 / 53 (50.94%)
occurrences (all)	14	50	64
Injection site erythema			

subjects affected / exposed	5 / 53 (9.43%)	21 / 49 (42.86%)	27 / 53 (50.94%)
occurrences (all)	8	46	83
Injection site pruritus			
subjects affected / exposed	2 / 53 (3.77%)	11 / 49 (22.45%)	17 / 53 (32.08%)
occurrences (all)	2	18	34
Injection site pain			
subjects affected / exposed	7 / 53 (13.21%)	8 / 49 (16.33%)	13 / 53 (24.53%)
occurrences (all)	10	12	20
Injection site induration			
subjects affected / exposed	0 / 53 (0.00%)	4 / 49 (8.16%)	2 / 53 (3.77%)
occurrences (all)	0	6	2
Injection site haematoma			
subjects affected / exposed	0 / 53 (0.00%)	3 / 49 (6.12%)	3 / 53 (5.66%)
occurrences (all)	0	7	3
Injection site urticaria			
subjects affected / exposed	0 / 53 (0.00%)	1 / 49 (2.04%)	3 / 53 (5.66%)
occurrences (all)	0	2	3
Injection site nodule			
subjects affected / exposed	1 / 53 (1.89%)	1 / 49 (2.04%)	2 / 53 (3.77%)
occurrences (all)	1	1	4
Injection site warmth			
subjects affected / exposed	0 / 53 (0.00%)	0 / 49 (0.00%)	3 / 53 (5.66%)
occurrences (all)	0	0	6
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 53 (15.09%)	7 / 49 (14.29%)	5 / 53 (9.43%)
occurrences (all)	8	8	6

Non-serious adverse events	15300 SU	15000 SU	20100 SU
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 53 (79.25%)	39 / 55 (70.91%)	36 / 51 (70.59%)
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 53 (1.89%)	1 / 55 (1.82%)	4 / 51 (7.84%)
occurrences (all)	1	2	7
General disorders and administration site conditions			

Injection site swelling			
subjects affected / exposed	31 / 53 (58.49%)	21 / 55 (38.18%)	21 / 51 (41.18%)
occurrences (all)	62	62	62
Injection site erythema			
subjects affected / exposed	24 / 53 (45.28%)	24 / 55 (43.64%)	20 / 51 (39.22%)
occurrences (all)	50	62	63
Injection site pruritus			
subjects affected / exposed	10 / 53 (18.87%)	11 / 55 (20.00%)	7 / 51 (13.73%)
occurrences (all)	21	22	19
Injection site pain			
subjects affected / exposed	9 / 53 (16.98%)	9 / 55 (16.36%)	10 / 51 (19.61%)
occurrences (all)	19	13	16
Injection site induration			
subjects affected / exposed	2 / 53 (3.77%)	0 / 55 (0.00%)	2 / 51 (3.92%)
occurrences (all)	3	0	2
Injection site haematoma			
subjects affected / exposed	2 / 53 (3.77%)	0 / 55 (0.00%)	3 / 51 (5.88%)
occurrences (all)	2	0	3
Injection site urticaria			
subjects affected / exposed	1 / 53 (1.89%)	3 / 55 (5.45%)	1 / 51 (1.96%)
occurrences (all)	2	9	2
Injection site nodule			
subjects affected / exposed	0 / 53 (0.00%)	3 / 55 (5.45%)	2 / 51 (3.92%)
occurrences (all)	0	8	3
Injection site warmth			
subjects affected / exposed	2 / 53 (3.77%)	2 / 55 (3.64%)	1 / 51 (1.96%)
occurrences (all)	2	6	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 53 (9.43%)	7 / 55 (12.73%)	5 / 51 (9.80%)
occurrences (all)	5	8	5

Non-serious adverse events	27300 SU		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 56 (83.93%)		
Nervous system disorders			

Headache subjects affected / exposed occurrences (all)	2 / 56 (3.57%) 2		
General disorders and administration site conditions Injection site swelling subjects affected / exposed occurrences (all) Injection site erythema subjects affected / exposed occurrences (all) Injection site pruritus subjects affected / exposed occurrences (all) Injection site pain subjects affected / exposed occurrences (all) Injection site induration subjects affected / exposed occurrences (all) Injection site haematoma subjects affected / exposed occurrences (all) Injection site urticaria subjects affected / exposed occurrences (all) Injection site nodule subjects affected / exposed occurrences (all) Injection site warmth subjects affected / exposed occurrences (all)	29 / 56 (51.79%) 79 34 / 56 (60.71%) 100 15 / 56 (26.79%) 35 13 / 56 (23.21%) 19 4 / 56 (7.14%) 5 1 / 56 (1.79%) 1 3 / 56 (5.36%) 5 2 / 56 (3.57%) 4 2 / 56 (3.57%) 2		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	6 / 56 (10.71%) 8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 June 2015	To clarify the exact time point of the spirometry pre- and post-injection and further definition of the observation period post injection in case of notable worsening of the spirometry results. To correct error with respect to the top dose available for the use in the study and to change dose rationale and provide additional information on the dose rational of the study. To clarify that only treatment arms using 6 injections (the 5000 SU, 15000 SU, 201000 SU and the 273000 SU treatment arms) and the placebo arm will primarily be used to estimate the dose-response shape.
23 July 2015	To reflect changes in laboratory testing. Exploratory biomarker (lipocalin) assessment will no longer be performed due to filed collaboration with the laboratory selected to perform this specific analysis. This change does not impact any of the main objectives or safety assessments.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None

Notes: