Clinical trial results:
A multi-centre, double-blind dose-ranging study to evaluate the efficacy and safety/tolerability of Birch Modified Allergen Tyrosine-adsorbed + MPL (POLLINEX Quattro® Birch) in Subjects with seasonal allergic rhinoconjunctivitis due to birch pollen

Summary

EudraCT number	2012-004336-28
Trial protocol	DE AT PL
Global end of trial date	27 June 2014

Results information

Result version number	v1 (current)
This version publication date	25 March 2016
First version publication date	25 March 2016

Trial information

Trial identification

Sponsor protocol code	PQBirch203

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Allergy Therapeutics (UK) Ltd.
Sponsor organisation address	Dominion Way, Worthing, West Sussex, United Kingdom, BN14 8SA
Public contact	Head of Clinical Operations, Clinical Research Management, Bencard Allergie GmbH , +49 (0)893681198, denise.lee@allergytherapeutics.com
Scientific contact	Head of Clinical Operations, Clinical Research Management, Bencard Allergie GmbH , +49 (0)893681198, denise.lee@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	10 February 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 June 2014
Global end of trial reached?	Yes
Global end of trial date	27 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the differences in change (baseline to post-treatment) in total symptom scores (TSS) recorded following Conjunctival Provocation Tests (CPT), between four POLLINEX Quattro® Birch treatment arms of 600SU, 1550SU, 5100SU and 13600SU (cumulative doses). The purpose of this was to identify the most appropriate dose for POLLINEX Quattro® Birch for clinical development. Defining the most appropriate dose was to be based on clinical judgement as to balance of efficacy and safety/ tolerability outcomes of the different doses, taking into account the consistency of patterns, the extent of differences in individual parameters and the achievement of or approach towards statistical significance.

Protection of trial subjects:

This study was conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Patients, as adopted by the General Assembly of the World Medical Association in 1996 in South Africa. Furthermore, the study was compliant with the current version of the German Drug Law (”Arzneimittelgesetz”), other national legal requirements in participating countries (Germany, Austria, and Poland) and all applicable amendments laid down by the World Medical Assemblies and the International Conference on Harmonization (ICH) guidelines for Good Clinical Practice (GCP). A written approval and/or favorable opinion of the responsible Ethics Committee (EC) as well as approval from the Competent Authority (CA) for each country was obtained before the study was initiated.

Subjects gave their informed consent prior to admission to a clinical study and before any protocol specified procedures were carried out. The written consent document embodied the elements of informed consent as described in the Declaration of Helsinki and also complied with local regulations. Subjects were informed that they were free to withdraw from the study at any time at their own discretion.

Background therapy:

The following medication washout periods were to be adhered to prior to screening.

- Oral or parenteral corticosteroids (7 days);
- Ocular corticosteroids (7 days);
- Inhaled or intranasal corticosteroids (1 day);
- Mast cell stabilizers, e.g. Nedocromil, Lodoxamide (5 days);
- Intranasal or systemic decongestants, including cold preparations (1 day);
- Leukotriene modifiers, e.g. Montelukast, Zafirlukast, Zileuton (1 day);
- Afrin (oxymetazoline hydrochloride) (14 days);
- Antihistamines:
  - Once-daily or twice-daily antihistamines, e.g. Desloratadine (7 days);
  - Short-acting (3 or 4 times a day) antihistamines, e.g. Dimetindene (Fenistil®) (3 days);
  - Hydroxyzine (7 days);
  - H2-blockers, e.g. Ranitidine (1 day)

Other anti-inflammatory, anti-allergy and any other medications (e.g. anticholinergic agents and tricyclic antidepressants) which in the opinion of the Investigator could interfere with the study objectives were to be considered on a case-by-case basis. Subjects were to refrain from using any topical skin medication on the forearms within 7 days prior to skin testing.

During the course of the study, none of the prior medications listed above were to be used for the relief of allergy symptoms. Subjects with mild asthma were permitted to use beta2-agonists as needed and Budesonide (or equivalent) up to 400 µg once daily.

Other medications that had no known effect on allergy symptom relief were allowed during the study if they were taken chronically (i.e. not "as needed") and if the medication dose had been stable for at least 30 days prior to screening. Examples of these medications included contraceptives, hormone replacement therapy, e.g. levothyroxine. Acetaminophen, non-steroidal anti-inflammatory drugs and other drugs that did not impact study participation or outcomes were allowed if taken "as needed". Ketotifen was provided to treat any symptoms remaining after CPT.

Evidence for comparator:

N/A

Actual start date of recruitment	09 September 2013
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	Poland: 19
Country: Number of subjects enrolled	Austria: 30
Country: Number of subjects enrolled	Germany: 100
Worldwide total number of subjects	149
EEA total number of subjects	149

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)	149
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 16 investigational sites in three different countries: Austria (3), Germany (10) and Poland (3). Overall, 174 subjects were screened and 149 were randomized to receive study medication.

Pre-assignment

Screening details:

Male and female subjects (not of child-bearing potential or using adequate contraception) were included in the study aged, 18 to 60 with an allergy to birch pollen. Subjects were not included in the study if they had any acute, chronic and/or infectious ocular disorder (other than allergic conjunctivitis) or moderate/severe asthma.

Pre-assignment period milestones

Number of subjects started	149
Number of subjects completed	149

Period 1

Period 1 title	Treatment
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. The treatment blind was not broken until the database was locked and unblinding was authorized in writing. The blind of an individual subject could have been broken if specific knowledge of the study medication administered was necessary for determination of appropriate emergency treatment required for the subject.

Arms

Are arms mutually exclusive?	Yes
Arm title	13600SU

Arm description:

Received 300, 800, 2000, 3500, 3500, and 3500 SU given sequentially at weekly intervals

Arm type	Experimental
Investigational medicinal product name	POLLINEX Quattro Birch Plus 1.0 ml 100%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Investigator or trained study site personnel (a physician or nurse under the supervision of a physician) as subcutaneous injections to eligible subjects in the lateral/posterior aspect of the upper arm. Each randomized subject was scheduled to receive 6 injections from Visit 2 to Visit 7, with a 7 day (+/-1 day) interval between each injection. The arms were to be alternated between injections, e.g. 1st, 3rd and 5th injection right arm, 2nd, 4th and 6th injection left arm.

Arm title	5100SU

Arm description:

placebo, placebo, 300SU, 800SU, 2000SU and 2000SU given sequentially at weekly intervals

Arm type	Experimental

Investigational medicinal product name	POLLINEX Quattro Birch Plus 1.0 ml 100%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Investigator or trained study site personnel (a physician or nurse under the supervision of a physician) as subcutaneous injections to eligible subjects in the lateral/posterior aspect of the upper arm. Each randomized subject was scheduled to receive 6 injections from Visit 2 to Visit 7, with a 7 day (+/-1 day) interval between each injection. The arms were to be alternated between injections, e.g. 1st, 3rd and 5th injection right arm, 2nd, 4th and 6th injection left arm.

Arm title	1550SU

Arm description:

placebo, placebo, 150SU, 300SU, 300SU and 800SU given sequentially at weekly intervals

Arm type	Experimental
Investigational medicinal product name	POLLINEX Quattro Birch Plus 1.0 ml 100%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Investigator or trained study site personnel (a physician or nurse under the supervision of a physician) as subcutaneous injections to eligible subjects in the lateral/posterior aspect of the upper arm. Each randomized subject was scheduled to receive 6 injections from Visit 2 to Visit 7, with a 7 day (+/-1 day) interval between each injection. The arms were to be alternated between injections, e.g. 1st, 3rd and 5th injection right arm, 2nd, 4th and 6th injection left arm.

Arm title	600SU

Arm description:

placebo, placebo, 150SU, 150SU, 150SU and 150SU given sequentially at weekly intervals

Arm type	Experimental
Investigational medicinal product name	POLLINEX Quattro Birch Plus 1.0 ml 100%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Investigator or trained study site personnel (a physician or nurse under the supervision of a physician) as subcutaneous injections to eligible subjects in the lateral/posterior aspect of the upper arm. Each randomized subject was scheduled to receive 6 injections from Visit 2 to Visit 7, with a 7 day (+/-1 day) interval between each injection. The arms were to be alternated between injections, e.g. 1st, 3rd and 5th injection right arm, 2nd, 4th and 6th injection left arm.

Number of subjects in period 1	13600SU	5100SU	1550SU
Started	37	37	36
Completed	36	36	35
Not completed	1	1	1
Adverse event, non-fatal	1	1	-
Lost to follow-up	-	-	1

Number of subjects in period 1	600SU
Started	39
Completed	38
Not completed	1
Adverse event, non-fatal	1
Lost to follow-up	-

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

Blinding implementation details:

As in the treatment period.

Arms

Are arms mutually exclusive?	Yes
Arm title	13600SU

Arm description:

As in treament period

Arm type	Experimental
Investigational medicinal product name	POLLINEX Quattro Birch Plus 1.0 ml 100%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Investigator or trained study site personnel (a physician or nurse under the supervision of a physician) as subcutaneous injections to eligible subjects in the lateral/posterior aspect of the upper arm. Each randomized subject was scheduled to receive 6 injections from Visit 2 to Visit 7, with a 7 day (+/-1 day) interval between each injection. The arms were to be alternated between injections, e.g. 1st, 3rd and 5th injection right arm, 2nd, 4th and 6th injection left arm.

Arm title	5100SU

Arm description:

As in treatment period

Arm type	Experimental
Investigational medicinal product name	POLLINEX Quattro Birch Plus 1.0 ml 100%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Investigator or trained study site personnel (a physician or nurse under the supervision of a physician) as subcutaneous injections to eligible subjects in the lateral/posterior aspect of the upper arm. Each randomized subject was scheduled to receive 6 injections from Visit 2 to Visit 7, with a 7 day (+/-1 day) interval between each injection. The arms were to be alternated between injections, e.g. 1st, 3rd and 5th injection right arm, 2nd, 4th and 6th injection left arm.

Arm title	1550SU

Arm description:

As in treatment period

Arm type	Experimental
Investigational medicinal product name	POLLINEX Quattro Birch Plus 1.0 ml 100%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Investigator or trained study site personnel (a physician or nurse under the supervision of a physician) as subcutaneous injections to eligible subjects in the lateral/posterior aspect of the upper arm. Each randomized subject was scheduled to receive 6 injections from Visit 2 to Visit 7, with a 7 day (+/-1 day) interval between each injection. The arms were to be alternated between injections, e.g. 1st, 3rd and 5th injection right arm, 2nd, 4th and 6th injection left arm.

Arm title	600SU

Arm description:

As in treatment period

Arm type	Experimental
Investigational medicinal product name	POLLINEX Quattro Birch Plus 1.0 ml 100%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Investigator or trained study site personnel (a physician or nurse under the supervision of a physician) as subcutaneous injections to eligible subjects in the lateral/posterior aspect of the upper arm. Each randomized subject was scheduled to receive 6 injections from Visit 2 to Visit 7, with a 7 day (+/-1 day) interval between each injection. The arms were to be alternated between injections, e.g. 1st, 3rd and 5th injection right arm, 2nd, 4th and 6th injection left arm.

Number of subjects in period 2	13600SU	5100SU	1550SU
Started	36	36	35
Completed	36	36	35

Number of subjects in period 2	600SU
Started	38
Completed	38

Period 3

Period 3 title	Follow up (6-month phone call)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

As in the treatment period

Arms

Are arms mutually exclusive?	Yes
Arm title	13600SU

Arm description:

As in the treatement period

Arm type	Experimental
Investigational medicinal product name	POLLINEX Quattro Birch Plus 1.0 ml 100%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Investigator or trained study site personnel (a physician or nurse under the supervision of a physician) as subcutaneous injections to eligible subjects in the lateral/posterior aspect of the upper arm. Each randomized subject was scheduled to receive 6 injections from Visit 2 to Visit 7, with a 7 day (+/-1 day) interval between each injection. The arms were to be alternated between injections, e.g. 1st, 3rd and 5th injection right arm, 2nd, 4th and 6th injection left arm.

Arm title	5100SU

Arm description:

As in the treatment period

Arm type	Experimental
Investigational medicinal product name	POLLINEX Quattro Birch Plus 1.0 ml 100%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Investigator or trained study site personnel (a physician or nurse under the supervision of a physician) as subcutaneous injections to eligible subjects in the lateral/posterior aspect of the upper arm. Each randomized subject was scheduled to receive 6 injections from Visit 2 to Visit 7, with a 7 day (+/-1 day) interval between each injection. The arms were to be alternated between injections, e.g. 1st, 3rd and 5th injection right arm, 2nd, 4th and 6th injection left arm.

Arm title	1550SU

Arm description:

As in the treatment period

Arm type	Experimental
Investigational medicinal product name	POLLINEX Quattro Birch Plus 1.0 ml 100%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Investigator or trained study site personnel (a physician or nurse under the supervision of a physician) as subcutaneous injections to eligible subjects in the lateral/posterior aspect of the upper arm. Each randomized subject was scheduled to receive 6 injections from Visit 2 to Visit 7, with a 7 day (+/-1 day)

interval between each injection. The arms were to be alternated between injections, e.g. 1st, 3rd and 5th injection right arm, 2nd, 4th and 6th injection left arm.

Investigational medicinal product name	POLLINEX Quattro Birch Plus 1.0 ml 100%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Investigator or trained study site personnel (a physician or nurse under the supervision of a physician) as subcutaneous injections to eligible subjects in the lateral/posterior aspect of the upper arm. Each randomized subject was scheduled to receive 6 injections from Visit 2 to Visit 7, with a 7 day (+/-1 day) interval between each injection. The arms were to be alternated between injections, e.g. 1st, 3rd and 5th injection right arm, 2nd, 4th and 6th injection left arm.

Arm title	600SU

Arm description:

As in the treatment period

Arm type	Experimental
Investigational medicinal product name	POLLINEX Quattro Birch Plus 1.0 ml 100%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Investigator or trained study site personnel (a physician or nurse under the supervision of a physician) as subcutaneous injections to eligible subjects in the lateral/posterior aspect of the upper arm. Each randomized subject was scheduled to receive 6 injections from Visit 2 to Visit 7, with a 7 day (+/-1 day) interval between each injection. The arms were to be alternated between injections, e.g. 1st, 3rd and 5th injection right arm, 2nd, 4th and 6th injection left arm.

Number of subjects in period 3	13600SU	5100SU	1550SU
Started	36	36	35
Completed	37	36	35
Not completed	0	0	0
Lost to follow-up	-	-	-
Joined	1	0	0
Joining telephone FU after AE	1	-	-

Number of subjects in period 3	600SU
Started	38
Completed	37
Not completed	1
Lost to follow-up	1
Joined	0
Joining telephone FU after AE	-

Baseline characteristics

Reporting groups	
Reporting group title	13600SU
Reporting group description:	
Received 300, 800, 2000, 3500, 3500, and 3500 SU given sequentially at weekly intervals	
Reporting group title	5100SU
Reporting group description:	
placebo, placebo, 300SU, 800SU, 2000SU and 2000SU given sequentially at weekly intervals	
Reporting group title	1550SU
Reporting group description:	
placebo, placebo, 150SU, 300SU, 300SU and 800SU given sequentially at weekly intervals	
Reporting group title	600SU
Reporting group description:	
placebo, placebo, 150SU, 150SU, 150SU and 150SU given sequentially at weekly intervals	

Reporting group values	13600SU	5100SU	1550SU
Number of subjects	37	37	36
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	35.6	36.2	34.3
standard deviation	± 12.23	± 10.9	± 9.66
Gender categorical Units: Subjects			
Female	23	22	19
Male	14	15	17

Reporting group values	600SU	Total	
Number of subjects	39	149	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	32.5		
standard deviation	± 10	-	
Gender categorical			
Units: Subjects			
Female	21	85	
Male	18	64	

Subject analysis sets

Subject analysis set title	Modified full analysisi set
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Modified Full Analysis Set (mFAS): all subjects from the Full Aanalysis (FAS) Set who received the full dose to which they are randomized and without missing values with respect to the TSS at baseline or post-treatment. FAS defined as all subjects that reported at least a baseline TSS and were treated at least once with study medication. For efficacy, subjects were analysed according to the randomised treatment regardless of whether the cumulative dose that a subject received during the course of the study was equal to the treatment group to which they were randomised.

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

Subject analysis set description:

All subjects who received at least one dose of study medication. Subjects not receiving the cumulative treatment as assigned were allocated to the treatment group most closely resembling the cumulative dose aactulally received as follows: ≤600SU = 600SU, >600SY and ≤1550SU = 1550SU, >1550SU and ≤5100SU = 5100SU, >5100SU - 13600SU

Reporting group values	Modified full analysisi set	Safety set	
Number of subjects	143	149	
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	34.3		
standard deviation	± 10.73	±	

Gender categorical Units: Subjects			
Female	81		
Male	62		

End points

End points reporting groups

Reporting group title	13600SU
Reporting group description:	
Received 300, 800, 2000, 3500, 3500, and 3500 SU given sequentially at weekly intervals	
Reporting group title	5100SU
Reporting group description:	
placebo, placebo, 300SU, 800SU, 2000SU and 2000SU given sequentially at weekly intervals	
Reporting group title	1550SU
Reporting group description:	
placebo, placebo, 150SU, 300SU, 300SU and 800SU given sequentially at weekly intervals	
Reporting group title	600SU
Reporting group description:	
placebo, placebo, 150SU, 150SU, 150SU and 150SU given sequentially at weekly intervals	
Reporting group title	13600SU
Reporting group description:	
As in treament period	
Reporting group title	5100SU
Reporting group description:	
As in treatment period	
Reporting group title	1550SU
Reporting group description:	
As in treatment period	
Reporting group title	600SU
Reporting group description:	
As in treatment period	
Reporting group title	13600SU
Reporting group description:	
As in the treatement period	
Reporting group title	5100SU
Reporting group description:	
As in the treatment period	
Reporting group title	1550SU
Reporting group description:	
As in the treatment period	
Reporting group title	600SU
Reporting group description:	
As in the treatment period	
Subject analysis set title	Modified full analysisi set
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Modified Full Analysis Set (mFAS): all subjects from the Full Aanalysis (FAS) Set who received the full dose to which they are randomized and without missing values with respect to the TSS at baseline or post-treatment. FAS defined as all subjects that reported at least a baseline TSS and were treated at least once with study medication. For efficacy, subjects were analysed according to the randomised treatment regardless of whether the cumulative dose that a subject received during the course of the study was equal to the treatment group to which they were randomised.	
Subject analysis set title	Safety set
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects who received at least one dose of study medication. Subjects not receiving the cumulative	

treatment as assigned were allocated to the treatment group most closely resembling the cumulative dose aactulally received as follows: ≤600SU = 600SU, >600SY and ≤1550SU = 1550SU, >1550SU and ≤5100SU = 5100SU, >5100SU - 13600SU

Primary: Total symptom score (TSS) at conjuntival provocation test (CPT

End point title	Total symptom score (TSS) at conjuntival provocation test (CPT

End point description:

The primary efficacy variable was the change from baseline to post treatment TSS at Visit 8 recorded following CPT (with the allergen concentration eliciting TSS ≥ 6, adjusted for reference eye score, at the confirmatory CPT). The baseline value was the TSS recorded during the confirmatory CPT prior to first administration of study medication.

End point type	Primary

End point timeframe:

Baseline (Visit 2 or 2a) to Visit 8. Approximately 8 weeks from beginning of treatment.

End point values	13600SU	5100SU	1550SU	600SU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	36	35	34	38
Units: Score				
arithmetic mean (standard deviation)				
Baseline	7.4 (± 1.18)	7.3 (± 1.32)	7.6 (± 1.5)	7.6 (± 1.39)
Visit 8	4.2 (± 2.4)	5 (± 2.58)	4.9 (± 2.71)	6.1 (± 2.51)
Baseline - Visit 8	-3.2 (± 2.81)	-2.3 (± 2.51)	-2.7 (± 2.96)	-1.5 (± 2.51)

Attachments (see zip file)	Predicted change from baseline TSS /Chart 1.png

Statistical analyses

Statistical analysis title	Predefined first primary comparison

Statistical analysis description:

A strict semi-hierarchical test procedure was applied to the hypotheses. The first two hypotheses were considered as the most important and were tested in parallel, using a Bonferroni adjustment for the significance level.

1. H01: Mean change TSS (13600SU) = Mean change TSS (600SU) vs.
   H11: Mean change TSS (13600SU) ≠ Mean change TSS (600SU)
2. H02: Mean change TSS (5100SU) = Mean change TSS (600SU) vs.
   H12: Mean change TSS (5100SU) ≠ Mean change TSS

Comparison groups	13600SU v 600SU
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	≥ 0.025 [2]
Method	ANCOVA
Parameter estimate	Least square means
Point estimate	1.88

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.54
upper limit	3.22
Variability estimate	Standard error of the mean
Dispersion value	0.59

Notes:

[1] - If both null hypotheses (H01 and H02) could be rejected at a significance level of 0.025, only then were further comparisons tested. The test procedure ensured that the overall significance level of 0.05 was strictly maintained for all comparisons.
[2] - p = 0.0019

Statistical analysis title	Predefined second primary comparison

Statistical analysis description:

A strict semi-hierarchical test procedure was applied to the hypotheses. The first two hypotheses were considered as the most important and were tested in parallel, using a Bonferroni adjustment for the significance level.

1. H01: Mean change TSS (13600SU) = Mean change TSS (600SU) vs.
   H11: Mean change TSS (13600SU) ≠ Mean change TSS (600SU)
2. H02: Mean change TSS (5100SU) = Mean change TSS (600SU) vs.
   H12: Mean change TSS (5100SU) ≠ Mean change TSS

Comparison groups	5100SU v 600SU
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	≥ 0.025 [4]
Method	ANCOVA
Parameter estimate	Least square mean
Point estimate	1.01
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.34
upper limit	2.36
Variability estimate	Standard error of the mean
Dispersion value	0.6

Notes:

[3] - If both null hypotheses (H01 and H02) could be rejected at a significance level of 0.025, only then were further comparisons tested. The test procedure ensured that the overall significance level of 0.05 was strictly maintained for all comparisons.
[4] - p = 0.0919

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Treatment period i.e. from first injection (Visit 2) to 3 weeks after last injection (Visit 8)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups	
Reporting group title	13600SU
Reporting group description:	
Received 300, 800, 2000, 3500, 3500, and 3500 SU given sequentially at weekly intervals	
Reporting group title	5100SU
Reporting group description:	
placebo, placebo, 300SU, 800SU, 2000SU and 2000SU given sequentially at weekly intervals	
Reporting group title	1550SU
Reporting group description:	
placebo, placebo, 150SU, 300SU, 300SU AND 800SU given sequentially at weekly intervals	
Reporting group title	600SU
Reporting group description:	
placebo, placebo, 150SU, 150SU, 150SU AND 150SU at weekly intervals	

Serious adverse events	13600SU	5100SU	1550SU
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 36 (2.78%)	0 / 37 (0.00%)	0 / 36 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	0 / 36 (0.00%)	0 / 37 (0.00%)	0 / 36 (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
Nervous system disorders			
Lumbar radiculopathy			
subjects affected / exposed	1 / 36 (2.78%)	0 / 37 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			

subjects affected / exposed	0 / 36 (0.00%)	0 / 37 (0.00%)	0 / 36 (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	600SU		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 40 (5.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Lumbar radiculopathy			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	13600SU	5100SU	1550SU
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 36 (72.22%)	26 / 37 (70.27%)	28 / 36 (77.78%)
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 36 (8.33%)	2 / 37 (5.41%)	1 / 36 (2.78%)
occurrences (all)	4	3	1
General disorders and administration site conditions			

Injection site swelling			
subjects affected / exposed	19 / 36 (52.78%)	19 / 37 (51.35%)	16 / 36 (44.44%)
occurrences (all)	53	43	30
Injection site erythema			
subjects affected / exposed	17 / 36 (47.22%)	19 / 37 (51.35%)	14 / 36 (38.89%)
occurrences (all)	48	47	33
Injection site pruritus			
subjects affected / exposed	7 / 36 (19.44%)	7 / 37 (18.92%)	5 / 36 (13.89%)
occurrences (all)	21	9	9
Injection site pain			
subjects affected / exposed	4 / 36 (11.11%)	4 / 37 (10.81%)	1 / 36 (2.78%)
occurrences (all)	6	6	1
Injection site induration			
subjects affected / exposed	2 / 36 (5.56%)	2 / 37 (5.41%)	3 / 36 (8.33%)
occurrences (all)	2	3	3
Injection site nodule			
subjects affected / exposed	1 / 36 (2.78%)	2 / 37 (5.41%)	2 / 36 (5.56%)
occurrences (all)	1	3	3
Injection site urticaria			
subjects affected / exposed	0 / 36 (0.00%)	0 / 37 (0.00%)	3 / 36 (8.33%)
occurrences (all)	0	0	5
Injection site warmth			
subjects affected / exposed	2 / 36 (5.56%)	0 / 37 (0.00%)	0 / 36 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 36 (0.00%)	0 / 37 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	1 / 36 (2.78%)	0 / 37 (0.00%)	2 / 36 (5.56%)
occurrences (all)	1	0	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 36 (5.56%)	2 / 37 (5.41%)	4 / 36 (11.11%)
occurrences (all)	2	2	4

Gastroenteritis			
subjects affected / exposed	0 / 36 (0.00%)	1 / 37 (2.70%)	0 / 36 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	600SU		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 40 (82.50%)		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
General disorders and administration site conditions			
Injection site swelling			
subjects affected / exposed	15 / 40 (37.50%)		
occurrences (all)	37		
Injection site erythema			
subjects affected / exposed	14 / 40 (35.00%)		
occurrences (all)	27		
Injection site pruritus			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	7		
Injection site pain			
subjects affected / exposed	7 / 40 (17.50%)		
occurrences (all)	9		
Injection site induration			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Injection site nodule			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Injection site urticaria			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Injection site warmth			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal			

disorders Cough subjects affected / exposed occurrences (all)	 2 / 40 (5.00%) 2		
Renal and urinary disorders Urinary tract infection subjects affected / exposed occurrences (all)	 0 / 40 (0.00%) 0		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Gastroenteritis subjects affected / exposed occurrences (all)	 5 / 40 (12.50%) 5 2 / 40 (5.00%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 September 2013	To complete the set of procedures performed at post-treatment visit (Visit 8). For women of childbearing potential a pregnancy test was integrated, to be performed prior to the CPT. In addition, re-consent was to be given by subjects prior to the procedure via the associated updated ICF.

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: