Clinical trial results:
A prospective, randomized, open, multi-centre study to assess safety of PURETHAL Birch given with a rush up-dosing regimen to patients with allergic rhinitis/rhinoconjunctivitis.

Summary

EudraCT number	2013-000086-36
Trial protocol	PL
Global end of trial date	28 March 2014

Results information

Result version number	v1
This version publication date	30 June 2016
First version publication date	18 June 2015

Trial information

Trial identification

Sponsor protocol code	PB/0040

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01918956
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	HAL Allergy BV
Sponsor organisation address	J.H. Oortweg 15-17, Leiden, Netherlands, NL-2333 CH
Public contact	Clinical Trial Supervisor, HAL Allergy BV, +31 (0)88 1959 093, jvdwerf@hal-allergy.com
Scientific contact	Clinical Trial Supervisor, HAL Allergy BV, +31 (0)88 1959 093, jvdwerf@hal-allergy.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	28 March 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 February 2014
Global end of trial reached?	Yes
Global end of trial date	28 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of the study is to show that reaching the maintenance dose of 0.5 ml PURETHAL Birch following a rush regimen of three injections in weekly intervals is as safe as a conventional regimen of six injections in weekly intervals.

Protection of trial subjects:

In the conventional up-dosing arm the common clinical protocol was followed for immunotherapy with this preparation. On site monitoring during the first 30 minutes after injection and the direct availability of emergency medication are standard. In the rush up-dosing arm, except for the up-dosing, the same clinical protocol was followed. No specific additional protection measures were taken in either arm.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 August 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: 123
Worldwide total number of subjects	123
EEA total number of subjects	123

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)	42
Adults (18-64 years)	81
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Enrollment from 03SEP2013 till 28OCT2013

Pre-assignment

Screening details:

Outpatients consulting (paediatric) allergists or other specialists for their complaints related to birch pollen allergy and that fulfilled the more general in- and exclusion criteria, like age, symptoms, SPT results and/or ssIgE level or positive provocation test, were informed about the study and requested to participate.

Period 1

Period 1 title	treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	conventional

Arm description:

Up-dosing according to conventional (= registered) regimen: 0.05, 0.1, 0.2, 0.3, 0.4 and 0.5 ml PURETHAL Birch at weekly intervals.
Maintenance dosing : three doses of 0.5 ml PURETHAL Birch biweekly

Arm type	Active comparator
Investigational medicinal product name	PURETHAL Birch
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Up-dosing: sequential steps of 0.05, 0.1, 0,2, 0.3, 0.4 and 0.5 ml PURETHAL Birch at weekly time intervals
Maintenance dosing: three doses of 0.5 ml PURETHAL Birch biweekly

Arm title	rush up-dosing

Arm description:

Up-dosing according to a rush regimen: 0.1, 0.3 and 0.5 ml PURETHAL Birch at weekly intervals.
Maintenance dosing : three doses of 0.5 ml PURETHAL Birch biweekly

Arm type	Experimental
Investigational medicinal product name	PURETHAL Birch
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Up-dosing: sequential steps of 0.1, 0.3 and 0.5 ml PURETHAL Birch at weekly time intervals
Maintenance dosing: three doses of 0.5 ml PURETHAL Birch biweekly

Number of subjects in period 1	conventional	rush up-dosing
Started	61	62
maintenance phase succesfully reached	59 [1]	61
Completed	60	61
Not completed	1	1
Consent withdrawn by subject	1	-
Adverse event, non-fatal	-	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: 2 patients did not fulfil the criterion set for 'successful reaching maintenance phase' (intermediate milestone), 1 of these because of discontinuation. The other patient continued and completed the study, but due to too many up-dosing injections/adverse reactions 'did not successfully reach the maintenance dose'.

Baseline characteristics

Reporting groups	
Reporting group title	conventional
Reporting group description:	
Up-dosing according to conventional (= registered) regimen: 0.05, 0.1, 0.2, 0.3, 0.4 and 0.5 ml PURETHAL Birch at weekly intervals. Maintenance dosing : three doses of 0.5 ml PURETHAL Birch biweekly	
Reporting group title	rush up-dosing
Reporting group description:	
Up-dosing according to a rush regimen: 0.1, 0.3 and 0.5 ml PURETHAL Birch at weekly intervals. Maintenance dosing : three doses of 0.5 ml PURETHAL Birch biweekly	

Reporting group values	conventional	rush up-dosing	Total
Number of subjects	61	62	123
Age categorical			
Units: Subjects			
Adolescents (12-17 years)	21	21	42
Adults (18-64 years)	40	41	81
Age continuous			
Units: years			
arithmetic mean	26.6	27.9	
full range (min-max)	12 to 59	12 to 59	-
Gender categorical			
Units: Subjects			
Female	29	30	59
Male	32	32	64

End points

End points reporting groups

Reporting group title	conventional
Reporting group description:	
Up-dosing according to conventional (= registered) regimen: 0.05, 0.1, 0.2, 0.3, 0.4 and 0.5 ml PURETHAL Birch at weekly intervals. Maintenance dosing : three doses of 0.5 ml PURETHAL Birch biweekly	
Reporting group title	rush up-dosing
Reporting group description:	
Up-dosing according to a rush regimen: 0.1, 0.3 and 0.5 ml PURETHAL Birch at weekly intervals. Maintenance dosing : three doses of 0.5 ml PURETHAL Birch biweekly	

Primary: proportion of patients succesfully reaching the maintenance dose

End point title	proportion of patients succesfully reaching the maintenance dose
End point description:	
End point type	Primary
End point timeframe:	
milestone during treatment	

End point values	conventional	rush up-dosing		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	62		
Units: subjects				
Maintenance phase reached succesfully (Y/N)	59	61		

Statistical analyses

Statistical analysis title	non-inferiority testing
Comparison groups	conventional v rush up-dosing
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk difference (RD)
Point estimate	0.017
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.038
upper limit	0.071

Adverse events

Adverse events information

Timeframe for reporting adverse events:

treatment

Adverse event reporting additional description:

During 30 minutes after injection adverse event monitoring under supervision at site, during 24 hrs after injection by use of patient diary (focus on local reactions). Other general adverse events reported by patient at visit for next injection.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	conventional

Reporting group description:

up-dosing according to conventional (= registered) regimen

Reporting group title	rush up-dosing

Reporting group description:

up-dosing according to a rush regimen

Serious adverse events	conventional	rush up-dosing	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 61 (0.00%)	1 / 62 (1.61%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 61 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	conventional	rush up-dosing	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 61 (63.93%)	38 / 62 (61.29%)	
Nervous system disorders			
Headache			

subjects affected / exposed	4 / 61 (6.56%)	5 / 62 (8.06%)	
occurrences (all)	4	10	
Dizziness			
subjects affected / exposed	0 / 61 (0.00%)	2 / 62 (3.23%)	
occurrences (all)	0	2	
Somnolence			
subjects affected / exposed	0 / 61 (0.00%)	2 / 62 (3.23%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	5 / 61 (8.20%)	6 / 62 (9.68%)	
occurrences (all)	9	8	
Injection site pruritus			
subjects affected / exposed	5 / 61 (8.20%)	8 / 62 (12.90%)	
occurrences (all)	10	12	
Injection site swelling			
subjects affected / exposed	5 / 61 (8.20%)	5 / 62 (8.06%)	
occurrences (all)	8	5	
Injection site hypersensitivity			
subjects affected / exposed	4 / 61 (6.56%)	2 / 62 (3.23%)	
occurrences (all)	8	4	
Local swelling			
subjects affected / exposed	2 / 61 (3.28%)	2 / 62 (3.23%)	
occurrences (all)	2	3	
Injection site erythema			
subjects affected / exposed	1 / 61 (1.64%)	2 / 62 (3.23%)	
occurrences (all)	1	3	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	1 / 61 (1.64%)	3 / 62 (4.84%)	
occurrences (all)	1	3	
Eye irritation			
subjects affected / exposed	0 / 61 (0.00%)	2 / 62 (3.23%)	
occurrences (all)	0	2	
Eye pruritus			

subjects affected / exposed	0 / 61 (0.00%)	2 / 62 (3.23%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 61 (0.00%)	2 / 62 (3.23%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Sneezing			
subjects affected / exposed	5 / 61 (8.20%)	2 / 62 (3.23%)	
occurrences (all)	6	2	
Oropharyngeal pain			
subjects affected / exposed	3 / 61 (4.92%)	2 / 62 (3.23%)	
occurrences (all)	4	2	
Rhinorrhoea			
subjects affected / exposed	1 / 61 (1.64%)	3 / 62 (4.84%)	
occurrences (all)	1	4	
Dyspnoea			
subjects affected / exposed	1 / 61 (1.64%)	2 / 62 (3.23%)	
occurrences (all)	1	2	
Nasal discomfort			
subjects affected / exposed	0 / 61 (0.00%)	2 / 62 (3.23%)	
occurrences (all)	0	3	
Nasal oedema			
subjects affected / exposed	0 / 61 (0.00%)	2 / 62 (3.23%)	
occurrences (all)	0	3	
Throat irritation			
subjects affected / exposed	0 / 61 (0.00%)	2 / 62 (3.23%)	
occurrences (all)	0	3	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	2 / 61 (3.28%)	1 / 62 (1.61%)	
occurrences (all)	3	2	
Erythema			
subjects affected / exposed	2 / 61 (3.28%)	0 / 62 (0.00%)	
occurrences (all)	2	0	
Rash			

subjects affected / exposed	2 / 61 (3.28%)	0 / 62 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 61 (8.20%)	4 / 62 (6.45%)	
occurrences (all)	7	5	
Upper respiratory tract infection			
subjects affected / exposed	6 / 61 (9.84%)	5 / 62 (8.06%)	
occurrences (all)	7	5	
Pharyngitis			
subjects affected / exposed	5 / 61 (8.20%)	5 / 62 (8.06%)	
occurrences (all)	5	5	
Rhinitis			
subjects affected / exposed	2 / 61 (3.28%)	3 / 62 (4.84%)	
occurrences (all)	2	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported