Clinical trial results:
A multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of intraseasonal specific short-term immunotherapy with depigmented glutaraldehyde polymerized birch pollen allergenic extract (Depiquick® Birch) in patients with allergic rhinitis and/or rhinoconjunctivitis with or without intermittent asthma.

Summary

EudraCT number	2011-004185-14
Trial protocol	DE
Global end of trial date	16 July 2012

Results information

Result version number	v1 (current)
This version publication date	15 April 2016
First version publication date	15 April 2016

Trial information

Trial identification

Sponsor protocol code	CDPG103ADE01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01902992
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111 ,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111 ,

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	16 July 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 July 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of the study was to assess the efficacy and safety of a depigmented and polymerized allergenic extract of 100% birch pollen in subjects suffering from tree pollen-induced allergic rhinitis and/or rhinoconjunctivitis with or without intermittent asthma when specific immunotherapy (SIT) started intra-seasonally.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial. Subjects were allowed to take rescue medication such as antihistamines, corticosteroids and beta-2 agonist on an as-needed basis for symptoms of birch pollen allergic rhinitis and/or rhinoconjunctivitis, asthma between study visits.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 March 2012
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	Germany: 202
Worldwide total number of subjects	202
EEA total number of subjects	202

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)	6
Adults (18-64 years)	185

From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 35 active centres in Germany.

Pre-assignment

Screening details:

A total of 325 subjects were screened, of which 202 were randomized while 123 were screen failures and excluded from the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Data analyst, Assessor, Subject

Blinding implementation details:

The identity of the treatments was concealed by the use of study drugs that were identical in packaging, labeling, schedule of administration, appearance, taste and odor. Unblinding was allowed only in case of subjects emergencies and at the conclusion of the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Birch allergen extract

Arm description:

Birch allergen extract aqueous solution (0.5 ml) was administered weekly via subcutaneous (s.c.) route for 5 weeks.

Arm type	Experimental
Investigational medicinal product name	Birch allergen extract
Investigational medicinal product code	DPG103
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Birch allergen extract aqueous solution (0.5 ml) was administered weekly via s.c. route for 5 weeks.

Arm title	Placebo

Arm description:

Placebo matched to birch allergen extract aqueous solution (0.5 ml) was administered weekly via s.c. route for 5 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo matched to birch allergen extract aqueous solution (0.5 ml) was administered weekly via s.c. route for 5 weeks.

Number of subjects in period 1	Birch allergen extract	Placebo
Started	100	102
Completed	98	99
Not completed	2	3
Consent withdrawn by subject	1	2
Adverse event, non-fatal	1	-
Medical or ethical reasons, including compliance	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Birch allergen extract
Reporting group description:	
Birch allergen extract aqueous solution (0.5 ml) was administered weekly via subcutaneous (s.c.) route for 5 weeks.	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to birch allergen extract aqueous solution (0.5 ml) was administered weekly via s.c. route for 5 weeks.	

Reporting group values	Birch allergen extract	Placebo	Total
Number of subjects	100	102	202
Age categorical Units: Subjects			
Adolescents and adults (12-70 years)	100	102	202
Age continuous Units: years			
arithmetic mean	42.3	41.6	
standard deviation	± 13.82	± 13.23	-
Gender categorical Units: Subjects			
Female	65	53	118
Male	35	49	84

End points

End points reporting groups

Reporting group title	Birch allergen extract
Reporting group description:	
Birch allergen extract aqueous solution (0.5 ml) was administered weekly via subcutaneous (s.c.) route for 5 weeks.	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to birch allergen extract aqueous solution (0.5 ml) was administered weekly via s.c. route for 5 weeks.	

Primary: Combined Symptom and Medication Score for rhinitis/rhinoconjunctivitis (SMSrhi) in full analysis set

End point title	Combined Symptom and Medication Score for rhinitis/rhinoconjunctivitis (SMSrhi) in full analysis set
End point description:	
The combined SMS represented the sum of symptom severity and rescue medication score. The symptom severity score consisted of 6 items measured on a 4-point scale (0: absent symptoms to 3-severe symptoms) and rescue medication score was derived from average of daily rescue medication scores during the pollen season. The combined score for SMS ranged from 0 to 36 (symptom severity score range 0 to 18 and rescue medication score range 0 to 18). A lower score indicated an improvement in the allergic condition. The analysis was performed in full analysis set (FAS) population, defined as all randomized subjects who received at least one dose of study drug and had a baseline and at least one post-baseline assessment for the primary efficacy parameter.	
End point type	Primary
End point timeframe:	
From Day 1 to end of relevant pollen exposition time	

End point values	Birch allergen extract	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	102		
Units: Units on a scale				
arithmetic mean (standard deviation)	6.65 (± 2.719)	6.66 (± 2.72)		

Statistical analyses

Statistical analysis title	Treatment comparisons for SMSrhi
Comparison groups	Birch allergen extract v Placebo
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8878
Method	ANOVA
Parameter estimate	Least square mean difference
Point estimate	0.06

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.73
upper limit	0.84

Secondary: Combined SMS for rhinitis/rhinoconjunctivitis with a certain median symptom score

End point title	Combined SMS for rhinitis/rhinoconjunctivitis with a certain median symptom score

End point description:

The combined SMS represented the sum of symptom severity and rescue medication score. The symptom severity score consisted of 6 items measured on a 4-point scale (0: absent symptoms to 3-severe symptoms) and a median cut-off score was defined after the pollen season on the basis of blinded data. Rescue medication score was derived from average of daily rescue medication scores during the pollen season. The combined score for SMS ranged from 0 to 36 (symptom severity score range 0 to 18 and rescue medication score range 0 to 18). A lower score indicated an improvement in the allergic condition. The analysis was performed in FAS population.

End point type	Secondary

End point timeframe:

From Day 1 to end of relevant pollen exposition time

End point values	Birch allergen extract	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	102		
Units: Units on a scale				
arithmetic mean (standard deviation)	5.82 (± 2.506)	6.1 (± 2.507)		

Statistical analyses

No statistical analyses for this end point

Secondary: Symptom score for rhinitis/rhinoconjunctivitis (Srhi) and for asthma (Sast) based on pollen grain count

End point title	Symptom score for rhinitis/rhinoconjunctivitis (Srhi) and for asthma (Sast) based on pollen grain count

End point description:

The symptom severity score (Srhi and Sast) was derived from subject diaries with ratings for 6 symptoms of rhinitis/rhinoconjunctivits (nasal itching, nasal sneezing, rhinorrhea, nasal obstruction, ocular itching/grittiness/redness, and ocular tearing) and 4 asthma symptoms (chest tightness, shortness of breath, cough, and wheezing). Subjects rated the symptoms on a 4-point scale: 0 - absent symptoms (no sign/symptom evident), 1: mild symptoms (sign/symptom clearly present, but minimal awareness; easily, tolerated), 2: moderate symptoms (definite awareness of, sign/symptom that is bothersome but, tolerable), 3: severe symptoms (sign/symptom hard to tolerate; causes interference with, activities of daily living and/or sleeping). The symptom severity score ranged from 0 to 18. A lower score indicated an improvement in the allergic condition. The analysis was performed on FAS population.

End point type	Secondary

End point timeframe:

From Day 1 to end of relevant pollen exposition time

End point values	Birch allergen extract	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	102		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Srhi	5.56 (± 2.27)	5.54 (± 2.27)		
Sast	1.24 (± 1.437)	1.32 (± 1.437)		

Statistical analyses

No statistical analyses for this end point

Secondary: Symptom score for rhinitis/rhinoconjunctivitis (Srhi) and for asthma (Sast) based on median symptom score

End point title	Symptom score for rhinitis/rhinoconjunctivitis (Srhi) and for asthma (Sast) based on median symptom score

End point description:

The symptom severity score (Srhi and Sast) was derived from subject diaries with ratings for 6 symptoms of rhinitis/rhinoconjunctivits and 4 asthma symptoms. Subjects rated the symptoms on a 4-point scale: 0 - absent symptoms, 1: mild symptoms, 2: moderate symptoms and 3: severe symptoms. The symptom severity and asthma score ranged from 0 to 18. Symptom severity scores were analyzed on the basis of all days with a median symptom score of at least 3. The analysis was performed on FAS population.

End point type	Secondary

End point timeframe:

From Day 1 to end of relevant pollen exposition time

End point values	Birch allergen extract	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	102		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Srhi	4.9 (± 2.097)	5.08 (± 2.097)		
Sast	1.03 (± 1.364)	1.22 (± 1.364)		

Statistical analyses

No statistical analyses for this end point

Secondary: Medication score for rhinitis/rhinoconjunctivitis (Mrhi) and for asthma

End point title	Medication score for rhinitis/rhinoconjunctivitis (Mrhi) and for asthma

End point description:

The rescue medication score was defined as mean score of daily rescue medication utilized for relief from rhinitis/rhinoconjuctivitis (Mrhi) and asthma symptoms (Mast) during the pollen season. The improvement in symptoms post administration of any rescue medication were rated by subjects on a 4-point scale: 0- no improvement, 1- slight improvement, 2- good improvement and 3- vast improvement. The rescue medication score ranged from 0 to 18. A lower score indicated an improvement in the allergic condition. Analysis was performed in FAS population.

End point type	Secondary

End point timeframe:

From Day 1 to end of relevant pollen exposition time

End point values	Birch allergen extract	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	102		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Mrhi	1.1 (± 1.063)	1.11 (± 1.063)		
Mast	0.3 (± 0.666)	0.4 (± 0.666)		

Statistical analyses

No statistical analyses for this end point

Secondary: Medication score for rhinitis/rhinoconjunctivitis (Mrhi) and for asthma (Mast) based on median symptom score

End point title	Medication score for rhinitis/rhinoconjunctivitis (Mrhi) and for asthma (Mast) based on median symptom score

End point description:

The rescue medication score was defined as mean score of daily rescue medication utilized for relief from rhinitis/rhinoconjuctivitis (Mrhi) and asthma symptoms (Mast) during the pollen season. The improvement in symptoms post administration of any rescue medication were rated by subjects on a 4-point scale: 0- no improvement, 1- slight improvement, 2- good improvement and 3- vast improvement. The rescue medication score ranged from 0 to 18. Rescue medication scores were analyzed on the basis of all days with a median symptom score of at least 3. A lower score indicated an improvement in the allergic condition. Analysis was performed in FAS population.

End point type	Secondary

End point timeframe:

From Day 1 to end of relevant pollen exposition time

End point values	Birch allergen extract	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	102		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Mrhi	0.92 (± 1.004)	1.02 (± 1.004)		
Mast	0.27 (± 0.613)	0.41 (± 0.613)		

Statistical analyses

No statistical analyses for this end point

Secondary: Subject's assessed time to onset of action

End point title	Subject's assessed time to onset of action

End point description:

The time to onset of action was defined as the time from date of randomization to the date of event defined as the first documented onset of action. The subjects documented the onset of action as response to the following question: Do you have the feeling that your allergy symptoms are better today due to the injections (immunotherapy)? If a subject had no event, time to onset of action was censored at the date of last adequate assessment of the SMS for rhinitis/rhinoconjunctivitis. Analysis was performed in FAS population.

End point type	Secondary

End point timeframe:

Day 1 up to Day 92

End point values	Birch allergen extract	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	102		
Units: Days				
median (full range (min-max))	7.5 (4 to 9)	4 (2 to 6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of well days

End point title	Percentage of well days

End point description:

Well days during the tree pollen season were defined as the days with a symptom score less than 2 and no rescue medication intake. Analysis was performed in FAS population.

End point type	Secondary

End point timeframe:

From Day 1 to end of relevant pollen exposition time

End point values	Birch allergen extract	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	102		
Units: Percentage of days				
arithmetic mean (standard deviation)	6.757 (± 12.0854)	6.012 (± 12.7633)		

Statistical analyses

No statistical analyses for this end point

Secondary: Subject’s and investigator's assessment of global efficacy of treatment

End point title	Subject’s and investigator's assessment of global efficacy of treatment

End point description:

The subjects and investigators assessed the overall impression of the therapy efficacy as excellent/ good/ moderate/ poor or unacceptable. Analysis was performed on FAS population.

End point type	Secondary

End point timeframe:

Day 92

End point values	Birch allergen extract	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	102		
Units: Participants				
Subject’s assessment (Excellent)	28	27		
Subject’s assessment (Good)	47	52		
Subject’s assessment (Moderate)	15	14		
Subject’s assessment (Poor)	3	6		
Subject’s assessment (Unacceptable)	5	0		
Investigator’s assessment (Excellent)	35	33		
Investigator’s assessment (Good)	50	50		
Investigator’s assessment (Moderate)	8	11		
Investigator’s assessment (Poor)	4	5		
Investigator’s assessment (Unacceptable)	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in health related quality of life (HRQoL) total score at Week 7

End point title	Change from baseline in health related quality of life (HRQoL) total score at Week 7

End point description:

HRQoL was assessed in adults and adolescent subjects by the rhinitis/rhinoconjunctivitis quality of life questionnaire (RQLQ) and adolescent rhinoconjunctivitis quality of life questionnaire (AdolRQLQ) respectively. The RQLQ, a 28-item disease-specific questionnaire and AdolRQLQ comprising of 25 item disease specific questionnaire measured the functional impairments on a 6-point scale for each item. The overall score of a questionnaire was the mean response of all 28 or 25 items, respectively. Changes in scores of 0.5 to 1.0 were considered clinically meaningful; 1.0 to 1.5 as moderate and greater than (>) 1.5 as marked clinically important differences for overall summary score. Analysis was performed in FAS population.

End point type	Secondary

End point timeframe:

Baseline to Week 7

End point values	Birch allergen extract	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	102		
Units: Units on a scale				
arithmetic mean (standard deviation)	-1.123 (± 1.107)	-0.98 (± 1.1836)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in health related quality of life (HRQoL) domain scores at Week 7

End point title	Change from baseline in health related quality of life (HRQoL) domain scores at Week 7

End point description:

HRQoL was assessed in adults and adolescent subjects by the RQLQ and AdolRQLQ respectively. The RQLQ, a 28-item disease-specific questionnaire and AdolRQLQ comprising of 25 item disease specific questionnaire measured the functional impairments divided in 7 domains (activities, sleep, common complaints, practical problems, nasal symptoms, ocular symptoms and emotions) on a 6-point scale for each item. Each domain score was the mean response to all the items in that domain. Changes in scores of 0.5 to 1.0 were considered clinically meaningful; 1.0 to 1.5 as moderate and >1.5 as marked clinically important differences for overall summary score. Analysis was performed in FAS population.

End point type	Secondary

End point timeframe:

Baseline to Week 7

End point values	Birch allergen extract	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	102		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Activities	-1.308 (± 1.6326)	-1.255 (± 1.7353)		
Sleep	-1.103 (± 1.3788)	-0.896 (± 1.5496)		
Common complaints	-0.933 (± 1.2165)	-0.753 (± 1.3039)		
Practical problems	-1.531 (± 1.5609)	-1.515 (± 1.5616)		
Nasal symptoms	-1.222 (± 1.4748)	-1.015 (± 1.4916)		
Ocular symptoms	-1.144 (± 1.4855)	-1.028 (± 1.2499)		
Emotions	-0.874 (± 1.1969)	-0.788 (± 1.1625)		

Statistical analyses

No statistical analyses for this end point

Secondary: Subject's assessed medication scores for rhinitis/rhinoconjuctivitis (M-sub-rhi) and asthma (M-sub-ast)

End point title	Subject's assessed medication scores for rhinitis/rhinoconjuctivitis (M-sub-rhi) and asthma (M-sub-ast)

End point description:

Subjects self-assessed the improvement in the allergic symptoms of rhinitis/rhinoconjuctivitis (M-sub-rhi) and asthma (M-sub-ast) post administration of rescue medication. The medication score assessment was based on Likert scale, 0--no improvement, 1--mild improvement, 2--good improvement and 3--enormous improvement. The range of the medication score for rhinitis/ rhinoconjunctivitis complaints was 0–15 (five possible rescue medications with a score from 0–3) and for asthma synptoms was 0-9 (3 possible medications with a score from 0-3). The range of the rescue medication by intake for rhintis/rhinoconjuctivitis and asthma was 0–18 and 0-12, respectively. M-sub-rhi and M-sub-ast was determined as: medication score/ intake scores. A higher medication score indicated improvement in allergic condition. The analysis was performed in FAS population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

From Day 1 to end of secondary pollen exposition time

End point values	Birch allergen extract	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	102		
Units: Units on a scale				
arithmetic mean (standard deviation)				
M-sub-rhi (n= 100, 102)	1.209 (± 1.3814)	1.29 (± 1.4865)		

M-sub-ast (n= 98, 100)	0.147 (± 0.5633)	0.261 (± 0.6164)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Birch allergen extract

Reporting group description:

Birch allergen extract aqueous solution (0.5 ml) was administered weekly via subcutaneous (s.c.) route for 5 weeks.

Reporting group title	Placebo

Reporting group description:

Placebo matched to birch allergen extract aqueous solution (0.5 ml) was administered weekly via s.c. route for 5 weeks.

Serious adverse events	Birch allergen extract	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 100 (0.00%)	0 / 102 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Birch allergen extract	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 100 (16.00%)	25 / 102 (24.51%)	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 100 (1.00%)	6 / 102 (5.88%)	
occurrences (all)	1	9	
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed	1 / 100 (1.00%)	6 / 102 (5.88%)	
occurrences (all)	1	6	
Injection site reaction			
subjects affected / exposed	11 / 100 (11.00%)	11 / 102 (10.78%)	
occurrences (all)	39	34	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 100 (5.00%)	7 / 102 (6.86%)	
occurrences (all)	5	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2012	To implement changes concerning the selection of study population, the protocol version 00, dated 23-Jan-2012, was amended and resulted in study protocol version 01, dated 01-Feb-2012.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported