Clinical trial results:
PHASE IIB STUDY ON THE SAFETY AND EFFICACY OF BM32, A RECOMBINANT HYPOALLERGENIC VACCINE FOR IMMUNOTHERAPY OF GRASS POLLEN ALLERGY

Summary

EudraCT number	2012-000442-35
Trial protocol	DE SI AT BE DK NL
Global end of trial date	14 October 2014

Results information

Result version number	v1 (current)
This version publication date	17 November 2018
First version publication date	17 November 2018

Trial information

Trial identification

Sponsor protocol code	CS-BM32-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01538979
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biomay AG
Sponsor organisation address	Lazarettgasse 19, Vienna, Austria, 1090
Public contact	Head of Product Development, Biomay AG, 0043 17966296101, a.neubauer@biomay.com
Scientific contact	Head of Product Development, Biomay AG, 0043 17966296101, a.neubauer@biomay.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	02 July 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the sustained clinical effect of BM32 during 2 consecutive treatment years compared to placebo. The clinical effect of 2 different dose levels of BM32 is evaluated by a combined Symptom-Medication-Score (SMS) which is recorded during the peak of the grass pollen season of each treatment year.

Protection of trial subjects:

This trial was conducted in accordance to the principles of GCP, ensuring that the rights, safety and well-being of patients are protected and in consistency with the the Declaration of Helsinki.
Inclusion and exclusion criteria were carefully defined in order to protect subjects from contraindications, interactions with other medication and risk factors associated with the investigational medicinal product.
Throughout the study safety was assessed, such as occurrence of AEs, safety labs, vital signs and physical examinations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 May 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	Netherlands: 2
Country: Number of subjects enrolled	Slovenia: 24
Country: Number of subjects enrolled	Austria: 52
Country: Number of subjects enrolled	Belgium: 28
Country: Number of subjects enrolled	Denmark: 13
Country: Number of subjects enrolled	Germany: 47
Worldwide total number of subjects	166
EEA total number of subjects	166

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)	166
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was performed over three years including a "baseline year" for screening. The severity of grass pollen allergy was assessed before and approx.two weeks after the end of the grass pollen season and via and electronic diary during the grass pollen season. At the end of the baseline year, subjects were randomized to one of the 3 study arms

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	BM32 low

Arm description:

BM32 0,2mg/mL

Arm type	Experimental
Investigational medicinal product name	BM32 0,2 mg/mL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Three pre-seasonal injections at monthly intervals in year 1. One boost after the grass pollen season of year 1. Three pre-seasonal injections at monthly intervals in year 2.

Arm title	BM32 high

Arm description:

BM32 0,4 mg/mL

Arm type	Experimental
Investigational medicinal product name	BM32 0,4 mg/mL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Three pre-seasonal injections at monthly intervals in year 1. One boost after the grass pollen season of year 1.

Arm title	Placebo

Arm description:

Placebo

Arm type	Experimental

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Three pre-seasonal injections at monthly intervals in year 1. One boost after the grass pollen season of year 1. Three pre-seasonal injections at monthly intervals in year 2.

Number of subjects in period 1	BM32 low	BM32 high	Placebo
Started	53	60	53
Completed	47	49	45
Not completed	6	11	8
Consent withdrawn by subject	4	3	3
Adverse event, non-fatal	-	2	-
Pregnancy	-	1	1
Concomitant disease	-	1	-
Lost to follow-up	2	1	4
non-compliant with study protocol	-	3	-

Baseline characteristics

Reporting groups	
Reporting group title	BM32 low
Reporting group description:	
BM32 0,2mg/mL	
Reporting group title	BM32 high
Reporting group description:	
BM32 0,4 mg/mL	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Reporting group values	BM32 low	BM32 high	Placebo
Number of subjects	53	60	53
Age categorical			
Units: Subjects			
Adults 18-64	53	60	53
Age continuous			
Units: years			
arithmetic mean	28.7	29.8	29.1
full range (min-max)	18 to 53	18 to 52	18 to 58
Gender categorical			
Units: Subjects			
Female	19	24	22
Male	34	36	31

Reporting group values	Total		
Number of subjects	166		
Age categorical			
Units: Subjects			
Adults 18-64	166		
Age continuous			
Units: years			
arithmetic mean			
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	65		
Male	101		

Subject analysis sets	
Subject analysis set title	BM32 Pooled
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients treated with BM32 low and Placebo, who completed diary in treatment year 2 . Patients who previously have been treated with BM32 high dose in year 1 have been switched to BM32 low dose in year 2 and analysed together as Treatment Group "BM32 pooled"

Reporting group values	BM32 Pooled		
Number of subjects	92		
Age categorical Units: Subjects			
Adults 18-64	92		
Age continuous Units: years arithmetic mean full range (min-max)			
Gender categorical Units: Subjects			
Female Male			

End points

End points reporting groups

Reporting group title	BM32 low
Reporting group description: BM32 0,2mg/mL	
Reporting group title	BM32 high
Reporting group description: BM32 0,4 mg/mL	
Reporting group title	Placebo
Reporting group description: Placebo	
Subject analysis set title	BM32 Pooled
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients treated with BM32 low and Placebo, who completed diary in treatment year 2 . Patients who previously have been treated with BM32 high dose in year 1 have been switched to BM32 low dose in year 2 and analysed together as Treatment Group "BM32 pooled"	

Primary: SMS Differences in Treatment Year 1

End point title	SMS Differences in Treatment Year 1
End point description:	
End point type	Primary
End point timeframe: Mean daily SMS during the peak pollen season in Treatment Year 1	

End point values	BM32 low	BM32 high	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	52	47	
Units: score				
least squares mean (confidence interval 95%)	6.480 (5.349 to 7.611)	6.930 (5.931 to 8.132)	7.782 (6.244 to 9.320)	

Statistical analyses

Statistical analysis title	SMS BM32 low vs Placebo (ANOVA)
Comparison groups	BM32 low v Placebo
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.1537
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.28

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.05
upper limit	0.49
Variability estimate	Standard deviation

Notes:

[1] - Comparison of treatment vs placebo

Statistical analysis title	SMS BM32 high vs Placebo (ANOVA)
Comparison groups	BM32 high v Placebo
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.2877
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.63
upper limit	0.79
Variability estimate	Standard deviation

Notes:

[2] - Comparison Treated vs Placebo

Primary: SMS in Treatment Year 2

End point title	SMS in Treatment Year 2[3]

End point description:

End point type	Primary

End point timeframe:

Mean daily SMS during the peak pollen season in Treatment Year 1

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Based on results of the interim analysis patients, who have received high dose (BM32 high) in the first treatment year have been switched to the lower dose (BM32 low) in the second treatment year. Consequently, all patients receiving BM32 in the second year were analysed together as Treatment Group "BM32 pooled"

End point values	Placebo	BM32 Pooled		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	45	88		
Units: Score				
least squares mean (confidence interval 95%)	7.812 (6.602 to 9.422)	6.601 (5.869 to 7.437)		

Statistical analyses

Statistical analysis title	SMS BM32 pooled vs Placebo (ANOVA)
Comparison groups	Placebo v BM32 Pooled
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.0847
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.74
upper limit	0.18
Variability estimate	Standard deviation

Notes:

[4] - Comparison Treatment vs Placebo

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Throughout the whole study from V1 (screeening) up to V17	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Safety Analysis Set (SA)
Reporting group description: -	
Reporting group title	BM32 Low
Reporting group description: BM32 0,2mg/mL	
Reporting group title	BM32 High
Reporting group description: BM32 0,4mg/mL	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Safety Analysis Set (SA)	BM32 Low	BM32 High
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 166 (4.82%)	2 / 53 (3.77%)	5 / 60 (8.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Clavicula fracture			
subjects affected / exposed	1 / 166 (0.60%)	0 / 53 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligamant rupture	Additional description: Skiing accident		
subjects affected / exposed	1 / 166 (0.60%)	0 / 53 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	1 / 166 (0.60%)	0 / 53 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ligament sprain			
subjects affected / exposed	1 / 166 (0.60%)	0 / 53 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration of arm	Additional description: Road traffic accident		
subjects affected / exposed	1 / 166 (0.60%)	0 / 53 (0.00%)	0 / 60 (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
Back injury			
subjects affected / exposed	1 / 166 (0.60%)	0 / 53 (0.00%)	0 / 60 (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
Accident			
subjects affected / exposed	1 / 166 (0.60%)	0 / 53 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road Traffic Accident			
subjects affected / exposed	1 / 166 (0.60%)	0 / 53 (0.00%)	0 / 60 (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
Surgical and medical procedures			
Appendectomy			
subjects affected / exposed	1 / 166 (0.60%)	0 / 53 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Central nervous system inflammation			
subjects affected / exposed	1 / 166 (0.60%)	0 / 53 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			

subjects affected / exposed	1 / 166 (0.60%)	1 / 53 (1.89%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 166 (0.60%)	1 / 53 (1.89%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 166 (0.60%)	0 / 53 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	1 / 166 (0.60%)	0 / 53 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 53 (1.89%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Clavicula fracture			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ligamant rupture	Additional description: Skiing accident		
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Meniscus injury			

subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ligament sprain				
subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Laceration of arm	Additional description: Road traffic accident			
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Back injury				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Accident				
subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Road Traffic Accident				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Appendectomy				
subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Central nervous system inflammation				
subjects affected / exposed	0 / 53 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				

Anaphylactic reaction			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urticaria			
subjects affected / exposed	0 / 53 (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	Safety Analysis Set (SA)	BM32 Low	BM32 High
Total subjects affected by non-serious adverse events			
subjects affected / exposed	153 / 166 (92.17%)	50 / 53 (94.34%)	56 / 60 (93.33%)
Nervous system disorders			
Headache			
subjects affected / exposed	26 / 166 (15.66%)	8 / 53 (15.09%)	10 / 60 (16.67%)
occurrences (all)	53	18	18
General disorders and administration site conditions			
Injection site swelling			
subjects affected / exposed	120 / 166 (72.29%)	41 / 53 (77.36%)	47 / 60 (78.33%)
occurrences (all)	424	144	179
Injection site erythema			
subjects affected / exposed	112 / 166 (67.47%)	39 / 53 (73.58%)	48 / 60 (80.00%)
occurrences (all)	426	151	187

Injection site pruritus			
subjects affected / exposed	77 / 166 (46.39%)	30 / 53 (56.60%)	37 / 60 (61.67%)
occurrences (all)	222	97	110
Injection site discomfort			
subjects affected / exposed	39 / 166 (23.49%)	13 / 53 (24.53%)	13 / 60 (21.67%)
occurrences (all)	103	28	32
Injection site pain			
subjects affected / exposed	36 / 166 (21.69%)	9 / 53 (16.98%)	10 / 60 (16.67%)
occurrences (all)	52	10	17
Injection site urticaria			
subjects affected / exposed	33 / 166 (19.88%)	16 / 53 (30.19%)	17 / 60 (28.33%)
occurrences (all)	59	27	32
Injection site induration			
subjects affected / exposed	25 / 166 (15.06%)	8 / 53 (15.09%)	8 / 60 (13.33%)
occurrences (all)	32	12	8
Injection site reaction			
subjects affected / exposed	18 / 166 (10.84%)	3 / 53 (5.66%)	7 / 60 (11.67%)
occurrences (all)	23	3	9
Injection site nodule			
subjects affected / exposed	16 / 166 (9.64%)	6 / 53 (11.32%)	5 / 60 (8.33%)
occurrences (all)	30	9	11
Injection site warmth			
subjects affected / exposed	16 / 166 (9.64%)	5 / 53 (9.43%)	8 / 60 (13.33%)
occurrences (all)	23	8	11
Injection site oedema			
subjects affected / exposed	14 / 166 (8.43%)	6 / 53 (11.32%)	5 / 60 (8.33%)
occurrences (all)	39	18	13
Pyrexia			
subjects affected / exposed	9 / 166 (5.42%)	2 / 53 (3.77%)	4 / 60 (6.67%)
occurrences (all)	9	2	4
Fatigue			
subjects affected / exposed	5 / 166 (3.01%)	0 / 53 (0.00%)	2 / 60 (3.33%)
occurrences (all)	6	0	2
Immune system disorders			
Seasonal allergy			

subjects affected / exposed	3 / 166 (1.81%)	3 / 53 (5.66%)	0 / 60 (0.00%)
occurrences (all)	4	4	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 166 (4.82%)	3 / 53 (5.66%)	3 / 60 (5.00%)
occurrences (all)	8	3	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 166 (4.22%)	3 / 53 (5.66%)	3 / 60 (5.00%)
occurrences (all)	7	3	3
Oropharyngeal pain			
subjects affected / exposed	7 / 166 (4.22%)	2 / 53 (3.77%)	3 / 60 (5.00%)
occurrences (all)	9	2	5
Dyspnoea			
subjects affected / exposed	6 / 166 (3.61%)	4 / 53 (7.55%)	2 / 60 (3.33%)
occurrences (all)	7	4	3
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	8 / 166 (4.82%)	3 / 53 (5.66%)	3 / 60 (5.00%)
occurrences (all)	9	3	3
Rash			
subjects affected / exposed	6 / 166 (3.61%)	5 / 53 (9.43%)	0 / 60 (0.00%)
occurrences (all)	7	5	0
Eczema			
subjects affected / exposed	4 / 166 (2.41%)	3 / 53 (5.66%)	1 / 60 (1.67%)
occurrences (all)	7	4	3
Musculoskeletal and connective tissue disorders			
Back injury			
subjects affected / exposed	9 / 166 (5.42%)	2 / 53 (3.77%)	4 / 60 (6.67%)
occurrences (all)	10	2	5
Arthralgia			
subjects affected / exposed	3 / 166 (1.81%)	0 / 53 (0.00%)	3 / 60 (5.00%)
occurrences (all)	3	0	3
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed	71 / 166 (42.77%)	20 / 53 (37.74%)	26 / 60 (43.33%)
occurrences (all)	105	33	40
Rhinitis			
subjects affected / exposed	15 / 166 (9.04%)	7 / 53 (13.21%)	6 / 60 (10.00%)
occurrences (all)	18	9	7
Influenza			
subjects affected / exposed	14 / 166 (8.43%)	4 / 53 (7.55%)	6 / 60 (10.00%)
occurrences (all)	17	4	9
Tonsillitis			
subjects affected / exposed	8 / 166 (4.82%)	3 / 53 (5.66%)	2 / 60 (3.33%)
occurrences (all)	8	3	2
Gastroenteritis			
subjects affected / exposed	7 / 166 (4.22%)	2 / 53 (3.77%)	3 / 60 (5.00%)
occurrences (all)	8	2	4
Bronchitis			
subjects affected / exposed	6 / 166 (3.61%)	5 / 53 (9.43%)	0 / 60 (0.00%)
occurrences (all)	6	5	0
Urinary tract infection			
subjects affected / exposed	6 / 166 (3.61%)	2 / 53 (3.77%)	1 / 60 (1.67%)
occurrences (all)	9	4	1
Sinusitis			
subjects affected / exposed	5 / 166 (3.01%)	3 / 53 (5.66%)	1 / 60 (1.67%)
occurrences (all)	6	3	2

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 53 (88.68%)		
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 53 (15.09%)		
occurrences (all)	17		
General disorders and administration site conditions			
Injection site swelling			
subjects affected / exposed	32 / 53 (60.38%)		
occurrences (all)	101		
Injection site erythema			

subjects affected / exposed	25 / 53 (47.17%)		
occurrences (all)	88		
Injection site pruritus			
subjects affected / exposed	10 / 53 (18.87%)		
occurrences (all)	15		
Injection site discomfort			
subjects affected / exposed	13 / 53 (24.53%)		
occurrences (all)	43		
Injection site pain			
subjects affected / exposed	17 / 53 (32.08%)		
occurrences (all)	25		
Injection site urticaria			
subjects affected / exposed	0 / 53 (0.00%)		
occurrences (all)	0		
Injection site induration			
subjects affected / exposed	9 / 53 (16.98%)		
occurrences (all)	12		
Injection site reaction			
subjects affected / exposed	8 / 53 (15.09%)		
occurrences (all)	11		
Injection site nodule			
subjects affected / exposed	5 / 53 (9.43%)		
occurrences (all)	10		
Injection site warmth			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	4		
Injection site oedema			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	8		
Pyrexia			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	3		
Fatigue			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	4		
Immune system disorders			

Seasonal allergy subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	2 / 53 (3.77%) 2		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1 2 / 53 (3.77%) 2 0 / 53 (0.00%) 0		
Skin and subcutaneous tissue disorders Urticaria subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Eczema subjects affected / exposed occurrences (all)	2 / 53 (3.77%) 3 1 / 53 (1.89%) 2 0 / 53 (0.00%) 0		
Musculoskeletal and connective tissue disorders Back injury subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all)	3 / 53 (5.66%) 3 0 / 53 (0.00%) 0		
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	25 / 53 (47.17%)		
occurrences (all)	32		
Rhinitis			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences (all)	2		
Influenza			
subjects affected / exposed	4 / 53 (7.55%)		
occurrences (all)	4		
Tonsillitis			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	3		
Gastroenteritis			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences (all)	2		
Bronchitis			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	4		
Sinusitis			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 February 2012	Amendment 1: Changes requested by the German Authorities (Paul-Ehrlich-Institut) have been implemented: - further details to the Exclusion-Criteria (No. 1, 10, 13,14 and 15) and a new exclusion criterion « patients with nasal polyposis » have been added - further detailed explanations for definitions and procedures have been given - correction of typos have been made
05 July 2013	Amendment 2: - Administrative changes have been done (change in name of Pharmacovigilance). - The background of the study has been revised. - An Interim analysis after the first treatment year has been added. - Some Wordings have been corrected
05 July 2013	Amendment 3: Based of the result of interim analysis the advice of the IDMC was to continue the study but to switch patients, who have received high dose (40 µg per API) in the first treatment year to the lower dose (20µg of API) in the second treatment year and thus, skip the high dose arm. As a consequence the statistical part of the protocol had to be updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported