Study CS-BM32-004

Sponsor

Biomay

Protocol title

Study to evaluate the effect of different pre-seasonal BM32 dosing schedules on the induction of a protective allergen-specific IgG Immune response

Clinical trial phase
Phase IIb

Study Start/End Dates

Dec. 14, 2015 to Oct. 4, 2016

Study Design

This was a prospective, double-blind, placebo-controlled, mono-centric study comprising three treatment arms and one placebo arm.
Test product (BM32, three different dosing schedules) and comparator (placebo) were applied five times from January to May 2016.
Treatment and evaluation were performed in the following way:

Screening and Baseline Assessments (Dec 2015/Jan 2016):
- Informed consent.
- Assessment of in-/exclusion criteria
- Blood collection for immunological assessments
- Pollen chamber session 1

Based on the initial session in the pollen chamber, and their grass pollen allergen-specific IgE levels subjects were stratified into 2 groups (medium or high level of symptoms) and randomized into 4 study arms (3 different dosing schedules of BM32, and placebo).

Treatment Period (Jan/Feb/Mar/Apr/May/2016):
- 5 Injections of BM32 or Placebo from January to May according to respective treatment schedule (Table 9-2) Blood collection for immunological assessments before each injection, and 4 weeks after the last injection
- in April: distribution of Patient´s Diary paper version.
- in April: patients were instructed to use their standard symptomatic medication throughout the study with the exception of certain disallowed drugs.
- Subjects filled in a Patient´s Diary (symptoms and medication) from 1. May – 15. July 2016

Post-Seasonal Assessments / Provocation (Jul / Sep 2016)
- pollen chamber sessions within 14 days (Jul/Aug 2016)
- 1 pollen chamber session 4-6 weeks later (Sep 2016)
- Collection of completed Diary
- Blood collection for immunological assessments prior to each pollen chamber session.

Safety Follow-Up (Oct 2016)

Assessments:
- Allergen-specific IgG1 and IgG4 antibodies
- Sensitivity to grass pollen as measured in the pollen chamber (TNSS)

- Mean daily combined SMS, SS, and MS during the peak of the grass pollen season (treated vs. placebo).
- Mean level of “well-being” of patients measured by VAS during the peak of the grass pollen season (treated vs. placebo)
- Development of allergen-specific IgG and IgG1, and IgG4 antibodies (treated vs. placebo, and differences between treatment groups)
- Frequency, intensity and relatedness of AEs
- Frequency and grading of SIT-specific AEs
- Spirometry (FEV1) and ECGs

Centers

Austria (1)

Objectives

Primary efficacy objective:

The primary criterion was to assess the development of a specific IgG immune response against the major grass pollen allergens Phl 1 and Phl p 5.

Major secondary efficacy objectives:

Secondary criteria were to assess the effect of treatment with BM32 on the level of allergy symptoms, the amount of stand-by-medication needed and the "well-being" of subjects during the peak of the grass pollen season and the whole grass pollen season. For the determination of the effect of treatment the following scores were applied: rhinoconjunctivitis symptom score (SS), stand-by medication score (MS) and a combined score from allergy symptoms and use of stand-by medication (SMS). Well-being was measured by using the visual analog scale method (VAS).
Another criterion was to assess the development of immunological parameters during the study by measuring grass pollen allergen-specific IgG, IgG1, IgG4 in serum samples collected from subjects at different time.

Primary safety objective:

Safety and tolerability of the different BM32 dosing regimen and schedules of the different study arms were assessed. Separately, the occurrence of immunotherapy-specific adverse events (local and systemic) were evaluated.

Test Product, Dose and Mode of Adminstration

BM32 consisting of 4 active ingredients (APIs) - BM321, BM322, BM325, and BM326
20 µg of each individual API administered via subcutaneous injection; volume per injection: 400µL
Test product was applied 3, 4, or 5 times subcutaneously. Depending on the treatment group, 2 or 1 times placebo was applied in addition to active treatment.

Placebo: same mode of administration and dosing schedule as test product.

Statistical Methods

Analysis of the efficacy endpoints:

Primary and secondary endpoints were analysed by descriptive methods. Comparisons between the groups (in a descriptive sense) were done by median test.
Based on the observed variance heterogeneity between the placebo and verum groups the non-parametric median test was used to compare the medians of placebo against any of the three verum groups for the analysis of the primary endpoint.

Study Population. Key Inclusion/Exclusion Criteria

Main Inclusion criteria:

The subjects are grass pollen allergic but otherwise healthy. Healthy subjects are defined as individuals who are free from clinically significant illness or disease as determined by their medical history (including family), physical examination, laboratory studies, and other tests.

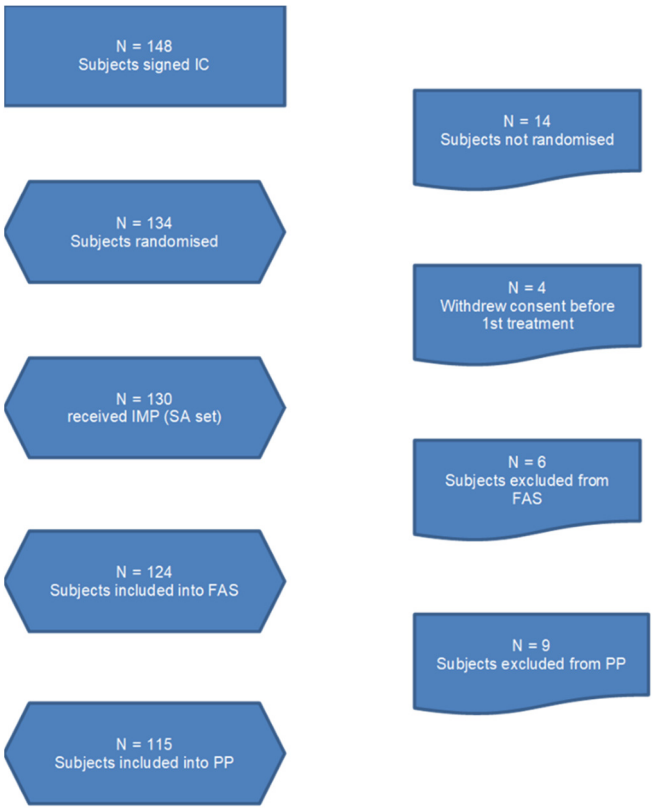
- Age: 18 to 60 years inclusive.
- History of seasonal allergic rhinitis (SAR) to grass pollen.
- Normal electrocardiogram without clinically significant abnormalities.
- Exhibition of a moderate to severe response to approximately 1500 grass pollen grains/m3 within the first 2 hours in the Vienna Challenge Chamber, which is defined as a nasal symptom score (TNSS) of at least 6. (Nasal symptom score is the sum of nasal obstruction, rhinorrhea, itchy nose and sneezing, each of which have been scored on a scale from 0 to 3.
- Positive skin prick test with a wheal diameter of at least4mm for grass pollen extract at the screening visit.

- Positive serum IgE test for timothy grass pollen and to rPhl p 1+rPhl p 5 at the screening visit or within the previous six months
    - o timothy grass (g6): ImmunoCAP IgE level ≥ 3.5 kUA/l
    - o rPhl p 1/rPhl p 5 (g213): ImmunoCAP IgE level ≥ 2.0 kUA/l

Main Exclusion criteria:

- Pregnant, lactating or sexually active women with childbearing potential who are not using a medically accepted birth control method (pregnancy to be controlled by a pregnancy dipstick test).
- On examination the subject is found to have any structural nasal abnormalities or nasal polyposis, a history of frequent nosebleeds, recent nasal surgery or ongoing upper respiratory tract infection which in the Responsible Physician's opinion renders the subject unsuitable for participation in the study.
- Any respiratory disease other than mild stable asthma that is controlled with occasional use of as-needed short-acting beta-agonists or low-dose inhaled corticosteroid and associated with normal lung function: baseline FEV1 <70% (maximum recorded value) of the predicted value as specified in the GINA guidelines.
- They have a positive serum IgE test for rPhl p 7 at the screening visit or during the last six months (ImmunoCAP IgE level ≥0.35 kUA/l)
- They have a positive skin prick test to Alternaria and this is confirmed by their ISAC sensitization profile
- The subject is concurrently participating or has participated in any clinical study in the previous month. However, participation solely in the form of blood donation and/or without other interventions will be acceptable
- Participation in a SIT trial for grass pollen allergy in the three years prior to this study.
- Past or present disease, which as judged by the investigator, may affect the outcome of this study. These diseases include, but are not limited to, cardiovascular disease, malignancy, hepatic disease, renal disease, haematological disease, neurological disease, endocrine disease or pulmonary disease (including but not confined to chronic bronchitis, emphysema, bronchiectasis or pulmonary fibrosis).
- Documented autoimmune diseases, immune defects including immuno-suppression, immune-complex-induced immunopathies as judged by the Investigator
- Suspected hypersensitivity to any ingredients of the study medication
- Use of prohibited medication:
    - Depot corticosteroids – 12 weeks prior to Visit 1
    - Oral corticosteroids – 8 weeks prior to Visit 1
    - long-acting inhaled corticosteroids – 4 weeks prior to Visit 1
    - depot corticosteroids or long-acting inhaled corticosteroids throughout the study
    - anti-histamines (histamine H1 blockers) three days prior to pollen chamber sessions
- Allergic symptoms at the time of screening which may interfere with the results of the screening assessments deemed by the Investigator.

Subject Disposition



Subject Characteristics

	BM32 3x	BM32 4x	BM32 5x	Placebo
No. of Subjects	*33*	*32*	*31*	*34*
Age				
Mean	*33*	*33*	*28*	*33*
Median	*31*	*29*	*28*	*31*
Range	*18-56*	*18-58*	*19-57*	*18-56*
Height				
Mean	*170*	*172*	*172*	*173*
Median	*173*	*172*	*169*	*175*
Range	*150-193*	*149-191*	*160-190*	*156-190*
Weight				
Mean	*68.5*	*67.3*	*67.1*	*72.1*
Median	*68.0*	*67.0*	*66.0*	*71.0*
Range	*45-100*	*48-91*	*51-100*	*50-105*
Male Gender (%)	*16 (48.5)*	*12 (37.5)*	*9 (29)*	*17 (50)*
Subjects with history of asthma (%)	*6 (18.2)*	*4 (12.5)*	*3 (9.7)*	*3 (8.8)*

Primary Outcome Results

Change in Phl p 1- and Phl p 5-specific IgG1 betwe en V3 and V8, EP1 (FAS population, descriptive statistics)

		Treatment Group			
		BM32 3x	BM32 4x	BM32 5x	Placebo
Change in IgG1 leves [µg/mL]	N	32	30	30	32
	Mean	63.07	41.96	90.87	0.80
	Median	40.15	29.09	46.61	0.00
	95.0% Lower CL for Median	19.23	19.60	21.76	0.00
	95.0% Upper CL for Median	59.79	45.66	86.72	1.70
	Standard Deviation	89.38	38.49	143.89	6.87
	Minimum	5.43	6.40	4.27	-9.09
	Maximum	465.81	185.87	732.73	37.07
Nominal p< median test BM32 vs placebo		0.0001	0.0001	0.0001	

Change in Phl p 1- and Phl p 5-specific IgG4 betwe en V3 and V8, EP1 (FAS population, descriptive statistics)

		Treatment Group			
		BM32 3x	BM32 4x	BM32 5x	Placebo
Change in IgG4 levels [µg/mL]	n	32	30	30	32
	Mean	129.09	38.03	267.50	-2.99
	Median	7.92	11.54	71.23	0.00
	95.0% Lower CL for Median	5.36	6.07	20.71	0.00
	95.0% Upper CL for Median	29.74	16.71	193.10	2.50
	Standard Deviation	240.75	96.79	438.29	15.20
	Minimum	-0.76	-78.74	0.00	-67.00
	Maximum	989.02	468.48	1689.36	10.68
	Nominal p< median test BM32 vs placebo	0.0001	0.0001	0.0001	

Major Secondary Outcome Results

Mean daily SMS, SS, MS and VAS during the pollen peak in treatment year 2, FAS population

		Treatment group			
		BM32 3x	BM32 4x	BM32 5x	Placebo
SMS	n	32	30	30	32
	Mean	0.89	1.00	0.77	1.01
	95.0% Lower CL for Mean	0.65	0.74	0.55	0.71
	95.0% Upper CL for Mean	1.13	1.27	0.99	1.30
	Median	0.72	0.72	0.64	0.79
	Minimum	0.07	0.00	0.01	0.00
	Maximum	3.07	2.89	2.48	3.04
SS	n	32	30	30	32
	Mean	0.80	0.68	0.63	0.78
	95.0% Lower CL for Mean	0.60	0.53	0.48	0.59
	95.0% Upper CL for Mean	1.00	0.83	0.79	0.97
	Median	0.66	0.63	0.54	0.76
	Minimum	0.07	0.00	0.01	0.00
	Maximum	2.13	1.70	1.54	2.04
MS	n	32	30	30	32
	Mean	0.08	0.32	0.14	0.23
	95.0% Lower CL for Mean	0.02	0.14	0.04	0.09
	95.0% Upper CL for Mean	0.15	0.50	0.23	0.36
	Median	0.00	0.13	0.00	0.00
	Minimum	0.00	0.00	0.00	0.00
	Maximum	0.93	2.00	0.93	1.00
Well-Being VAS	n	32	30	30	32
	Mean	23.28	20.73	22.19	25.28
	95.0% Lower CL for Mean	16.30	15.06	15.79	18.02
	95.0% Upper CL for Mean	30.27	26.41	28.58	32.55
	Median	16.30	16.53	18.10	23.17
	Minimum	0.40	0.27	1.87	0.87
	Maximum	83.27	59.53	63.73	75.40

Safety Results

Number of patients with at least one AE

Treatment group	Patients with at least one AE	
	n	%
BM32 3x (n= 33)	25	75,8
BM32 4x (n=32)	29	90,6
BM32 5x (n=31)	24	77,4
Placebo (n=34)	32	94,1

Number of SIT specific adverse reactions

	Treatment group									
	BM32 3x		BM32 4x		BM32 5x		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
missing	0	0,00%	1	0,20%	0	0,00%	1	0,20%	2	0,30%
No	57	8,80%	74	11,40%	49	7,50%	63	9,70%	243	37,40%
Yes	111	17,10%	127	19,50%	120	18,50%	47	7,20%	405	62,30%
Total	168	25,80%	202	31,10%	169	26,00%	111	17,10%	650	100,00%

Number and grading of SIT specific systemic reactions (per EAACI grading scheme)

	Treatment group									
	BM32 3x (N=33)		BM32 4x (N=32)		BM32 5x (N=31)		Placebo (N=34)		Total (N=130)	
	n	(%)[1)]	n	(%)	n	(%)	n	(%)	n	(%)
SIT-specific systemic reactions	2	3,0%	1	3,1%	2	3,2%	0	0,0%	5	2,2%
No. reactions grade 1	0	0,0%	1[2)]	3,1%	2[3)]	3,2%	0	0,0%	3	1,5%
No. reactions grade 2	2[4)]	3,0%	0	0,0%	0	0,0%	0	0,0%	2	0,8%
No. reactions grade 3, 4, or 5	0	0,0%	0	0,0%	0	0,0%	0	0,0%	0	0,0%

Other relevant findings

None

Study summary

Vaccination with BM32 induced a robust IgG response to all 4 major grass pollen allergens. Levels above baseline were maintained throughout the study and at all times, specific IgG levels were significantly higher than those measured in the placebo group. More specifically, the difference of allergen specific IgG1 and IgG4 levels against Phl p 1 and Phl p 5 compared to baseline were highly significantly different to placebo after the completion of treatment regimens. Antibody levels remained above baseline until the end of the study. Moreover, Phl p 1 and Phl p 5-specific IgG4 levels in the group having received 5 injections of BM32 were significantly higher compared to all other treatments following the completion of dosing.

Subjects who received 5 injections clearly benefited most from BM32 treatment. BM32 5x-treated subjects showed a markedly reduced mean daily SMS, SS and MS during the pollen peak and the whole pollen season. The difference to placebo in this group was statistically significant when the area under the curve (AUC) of daily mean SMS was analyzed. This was also reflected in the improvement of well-being measured by VAS, which was also significantly better in the BM32 5x group as compared to placebo.

BM32 injections were well tolerated. By far the most common AEs were injection site reactions, in particular swelling, erythema and pruritus. The symptoms were mostly mild to moderate. Systemic reactions, all of which were late-phase reactions, were observed in a total of 3 patients and did not exceed WAO grade 2, which is a very low frequency and intensity.

Based on the results of safety and efficacy obtained in this study, the dose of 20µg per API component of BM32 injected 5x over a course of 4 months preceding the grass pollen season has been identified as the best dose regimen for BM32 in adults and will be used in future phase III trials. This dose regimen provides protection from grass pollen induced allergic inflammation already in the first treatment year comparable in an extent comparable to standard extract based immunotherapy, albeit with much fewer injections, and an improved safety profile.

Date of Clinical Trial Report

June 13, 2017

Publication reference

Manuscript in preparation