Study CS-BM32-003

Sponsor

Biomay

Protocol title

Phase IIb study on the safety and efficacy of BM32, a recombinant hypoallergenic vaccine for immunotherapy of grass pollen allergy

Clinical trial phase
Phase IIb

Study Start/End Dates

May 2, 2012 to Oct. 14, 2014

Study Design

This was a randomized, double-blind, and placebo-controlled multi-center study. The study was performed over three years including a "baseline year" for screening and two treatment years and required a total of 17 visits to the study site. Following screening at Visit 1, the severity of grass pollen allergy was assessed in eligible subjects before and approx. two weeks after the end of the grass pollen season (Visit 2 and 3, respectively), and via an electronic diary during the grass pollen season. At the end of the baseline year, subjects were randomized to 20µg or 40µg per active pharmaceutical ingredient (API) component of BM32 or placebo (three study arms).
Seven visits were scheduled in treatment year 1 (Visits 5-11) and six visits in treatment year 2 (Visit 12-17). In each treatment year, subcutaneous injections of BM32 or placebo were administered three times at monthly intervals before the grass pollen season (Visits 5, 6, 7 in Year 1 and Visits 12, 13, and 14 in Year 2). Additionally, one booster injection was administered after the grass pollen season (Visit 10) in treatment year 1.

Centers

Austria (2), Germany (5), Belgium (1), Netherlands (1), Denmark (1), Slovenia (1)

Objectives

Primary efficacy objective:

- 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 in the first treatment year and 1 dose level of BM32 in the second treatment year was to be evaluated by a combined Symptom-Medication-Score (SMS) which was recorded during the peak of the grass pollen season of each treatment year. The original objective was to assess also 2 dose levels in the second treatment year, but due to the results of an interim analysis it was decided to only use the lower dose level of BM32 in the second treatment year.

Major secondary efficacy objectives:

- 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 in the first treatment year and 1 dose level of BM32 in the second treatment year was to be evaluated by a combined SMS which was recorded during the whole grass pollen season of each treatment year.

- To assess separately, the effect of BM32 on the level of allergy symptoms and the amount of standby-medication needed during the peak of the pollen season as well as during the whole grass pollen season of each treatment year. The recorded Symptom-Scores (SS) and Medication-Scores (MS) of subjects treated with BM32 were to be compared to those of subjects having received placebo.

- To assess the effect of BM32 on individual allergy symptoms by comparing scores of BM32-treated subjects and subjects having received placebo for each individual symptom.

- To assess the effect of treatment with BM32 on the “Well-being” of subjects during the grass pollen season as measured via a visual analogue score (VAS).

- To assess the effect of treatment with BM32 on the quality of life of grass pollen allergic individuals via a Rhinoconjunctivitis-Quality-of-Life-Questionnaire (RQLQ).

- To explore a potential effect of treatment with BM32 on asthma symptoms.

Primary safety objective:

- To evaluate the relative safety and tolerability of two different dose levels of BM32 compared to placebo.

Major secondary safety and immunogenicity objective:

- To assess the development of immunological parameters during treatment by measuring grass pollen allergen-specific IgG and IgE, de-novo IgE, carrier specific antibodies in serum samples collected from subjects at different time points. Comparison of BM32-treated vs. placebo and intragroup comparison of treatment years with baseline.

- To assess effects of subcutaneous administration of BM32 on parameters of vital signs and safety laboratory parameters.

Test Product, Dose and Mode of Adminstration

BM32 consisting of 4 active ingredients (APIs) - BM321, BM322, BM325, and BM326
Treatment year 1: 20 µg or 40 µg of each individual API administered via subcutaneous injection; volume per injection: 400µL
Treatment year 2: Due to the results of an interim analysis, only the lower dose level of BM32 (20 µg) was used. Patients on the higher dose level (40µg) in treatment year 1 were switched to 20µg (lower dose level) in treatment year 2.
Seven injections total; 3 monthly, pre-seasonal injections and one booster injection after the grass

pollen season in the first treatment year and again 3 monthly, pre-seasonal injections in the second treatment year.

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

Statistical Methods

Analysis of the primary efficacy endpoint:

Two primary efficacy endpoints (mean daily combined SMS during the grass pollen peak of treatment year 1 and mean daily combined SMS during the grass pollen peak of treatment year 2) were tested simultaneously using a closed/hierarchical testing procedure and a Bonferroni adjustment for multiplicity. At each step, analyses of variance (ANOVAs) with factors treatment, allergy severity (moderate/severe) and center were performed.

Analysis of the secondary efficacy endpoints:

Secondary endpoints were analyzed as the primary endpoints except that no adjustment for multiplicity was applied.
The total RQLQ score and sub-scores and mean asthma score were analyzed with descriptive statistics. Comparisons between BM32 and placebo treated patients were performed using the two sample Wilcoxon test.
Selected immunological parameters were analyzed descriptively including changes from baseline, which were compared between treatment groups using the Wilcoxon-two-sample test. The Wilcoxon-signed rank test was used for comparisons between visits within treatment groups.
Safety data were analyzed descriptively (tabulation with descriptive statistics or number and percentage of subjects depending on the variable).

Study Population. Key Inclusion/Exclusion Criteria

Main Inclusion criteria:

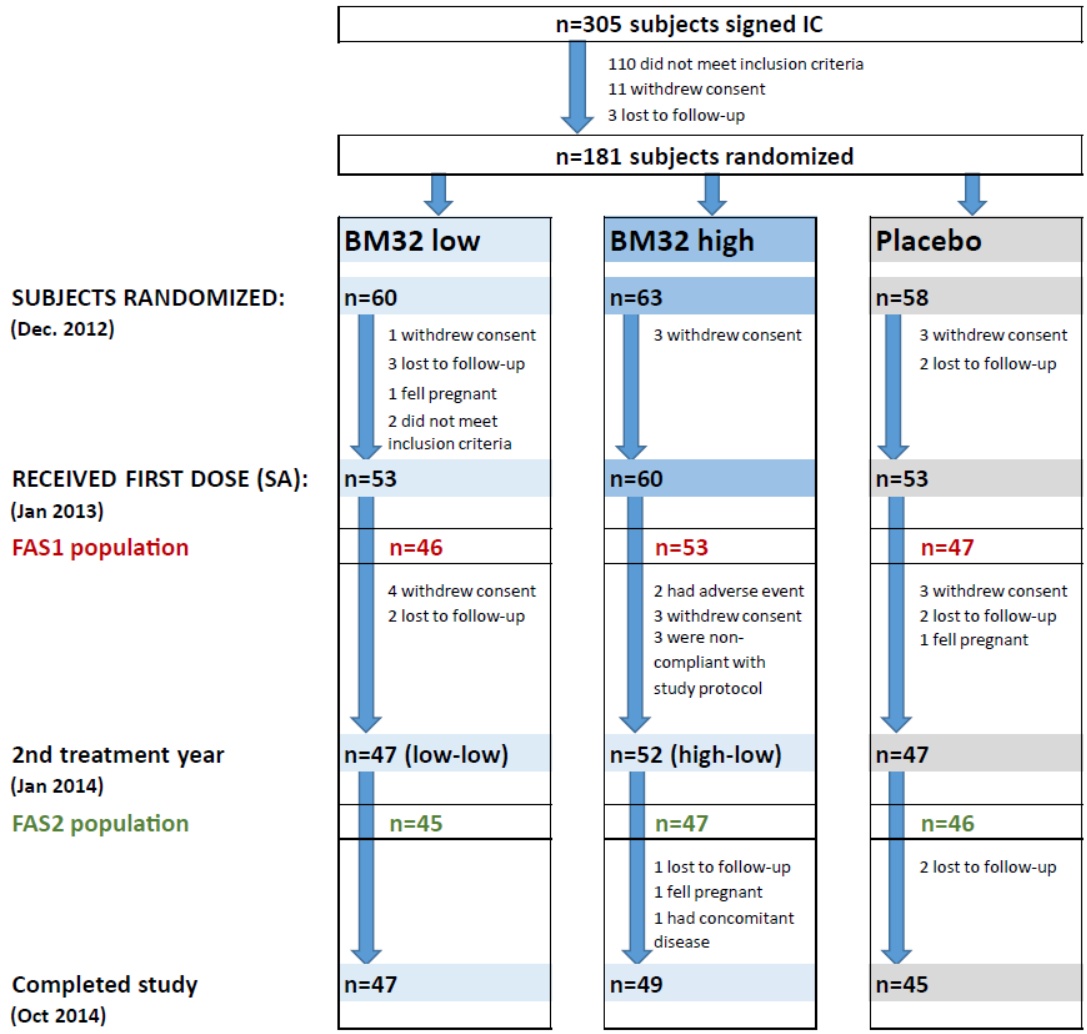
- Positive history of grass pollen allergy, positive skin prick test reaction to grass pollen extract, grass pollen allergen-specific IgE and rPhl p 1/rPhl p 5-specific IgE (at least 3.5 kUA/L) at the screening visit or within 12 months prior to the screening visit.
- Moderate to severe symptoms of grass pollen allergy during pollen peak in the baseline period
- Age between 18 and 60 years (m/f)

Main Exclusion criteria:

- Symptomatic perennial allergies or symptomatic seasonal co-allergies during the grass pollen season
- Atopic dermatitis
- Pregnancy or breast feeding
- Women with childbearing potential who were not using a medically accepted birth control method
- Autoimmune diseases, immune defects including immuno- suppression, immune-complex-induced immunopathies
- Contra-indication for adrenaline
- Severe general maladies, malignant diseases
- Patients under long-term treatment with systemic corticosteroids, immunosuppressive drugs, tranquilizers or psychoactive drugs
- Contra-indications for skin prick testing such as: skin inflammation in the test area, urticaria facticia.
- Asthma not controlled by low dose inhaled corticosteroids. This meant that patients with a history of concomitant asthma had to have a forced expiratory volume ($FEV_{1)}$ > 70% at inclusion. Patients without a history of asthma had to have a FEV_1 >70% or a peak expiratory flow (PEF) > 80% at inclusion.
- Chronic use of beta-blockers
- Participation in another clinical trial within one month prior to the study; however, participation during the previous month solely in the form of blood donation and/or without other interventions was acceptable

- Patients who participated in a pollen specific immunotherapy (SIT) trial, or received marketed pollen SIT in 2 years prior to study
- Patients who had a previous grass pollen SIT or participated in a clinical trial of grass pollen SIT
- Use of prohibited medication prior to Screening (Visit 1) and throughout the study:
    - Depot corticosteroids – 12 weeks prior to V1
    - Oral corticosteroids – 8 weeks prior to V1
    - High –dose inhaled corticosteroids – 4 weeks prior to V1
- Use of anti-histamines (histamine H1 blockers) three days prior to V1 or V2

Subject Disposition



Subject Characteristics

	BM32 low	BM32 high	Placebo	Total
No. of subjects	53	60	53	166
Age (V1)				
Mean	28.7	29.8	29.1	29.2
Median	26	28	25	26
Range	18-53	18-52	18-58	18-58
Sex (V1)				
Male (%)	34 (64.2)	36 (60.0)	31 (58.5)	101 (60.8)
Ethnic group (V1)				
White (%)	53 (100.0)	59 (98.3)	52 (98.1)	164 (98.8)
Asian (%)	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.6)
African (%)	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.6)
Severity of grass pollen allergy (V1)				
Moderate (%)	34 (64.1)	39 (65.0)	37 (69.8)	110 (66.3)
Severe (%)	19 (35.9)	21 (35.0)	16 (30.2)	56 (33.7)
Subjects with a history of grass pollen–associated asthma (V1)				
No. (%)	20 (38.5)	12 (20.0)	14 (26.4)	46 (27.7)
Total IgE (kU/L) (V5)				
Mean	273	179	194	214
Median	118	117	129	119
Range	20.6-1235	10.4-2217	8.8-1121	8.8-2217
sIgE, Timothy grass (kU_A/L [V1])				
Mean	35.0	29.0	33.3	32.3
Median	21.0	21.6	19.9	21.0
Range	3.45-100	3.48-100	2.63-100	2.63-100
sIgE, Timothy grass (kU_A/L [V5])				
Mean	29.9	21.9	26.0	25.8
Median	17.0	17.3	17.4	17.3
Range	2.07-100	2.95-76.3	2.20-100	2.07-100
sIgE, Phl p 1 (kU_A/L [V5])				
Mean	17.5	12.4	15.9	15.2
Median	8.56	9.82	8.46	8.67
Range	1.13-95.4	0.10-41.8	0.66-81.4	0.10-95.4
sIgE Phl p 2 (kU_A/L [V5])				
Mean	4.04	2.47	5.11	3.82
Median	1.92	1.67	2.27	1.76
Range	0.10-20.8	0.10-18.0	0.10-32.7	0.10-32.7
sIgE, Phl p 5 (kU_A/L [V5])				
Mean	20.0	14.1	14.5	16.1
Median	11.0	9.12	6.12	9.34
Range	0.10-100	0.10-100	0.10-100	0.10-100
sIgE, Phl p 6 (kU_A/L [V5])				
Mean	7.96	6.31	5.11	6.45
Median	3.71	2.66	2.05	2.99
Range	0.10-67.3	0.10-67.9	0.10-50.2	0.10-67.9
SPT, grass pollen (mm^2 [V5])				
Mean	67.7	77.3	77.0	74.2
Median	51.3	76.2	68.0	65.2
Range	8.17-241	7.72-190	0.75-443	0.75-443

V1 and V5 denote visits 1 and 5 before treatment, respectively.

Primary Outcome Results

Mean daily SMS during the pollen peak in treatment year 1, FAS1 and PPS1 population

	BM32 low		BM32 high		Placebo	
	FAS1	**PPS1**	**FAS1**	**PPS1**	**FAS1**	**PPS1**
	N=46	**N=43**	**N=53**	**N=49**	**N=47**	**N=43**
n	46	43	52	49	47	43
Mean	6.480	6.577	6.930	6.980	7.782	7.895
Median	6.349	6.556	6.577	6.583	7.091	7.091
SD	3.8086	3.8555	3.9623	4.0290	5.2377	5.3182
Min	0.30	0.30	0.43	0.43	0.00	0.00
Max	18.22	18.22	16.63	16.63	25.23	25.23

Mean daily SMS during the pollen peak in treatment year 2, pooled treatment, FAS2 and PPS2 population

	BM32 pooled		Placebo	
	N=92	**N=79**	**N=46**	**N=42**
	FAS2	**PPS2**	**FAS2**	**PPS2**
n	88	79	45	42
Mean	6.601	6.831	7.812	7.914
Median	6.683	6.800	7.091	7.112
SD	3.7238	3.7185	4.6010	4.6667
Min	0.36	0.36	0.00	0.00
Max	20.58	20.58	19.64	19.64

Mean daily SMS during the pollen peak in treatment year 2, un-pooled treatment,FAS2 and PPS2 population

	BM32 low-low		BM32 high-low		Placebo	
	FAS2	**PPS2**	**FAS2**	**PPS2**	**FAS2**	**PPS2**
	N=45	**N=40**	**N=47**	**N=39**	**N=46**	**N=42**
n	45	40	43	39	45	42
Mean	6.410	6.948	6.801	6.711	7.812	7.914
Median	6.429	6.823	7.167	6.667	7.091	7.112
SD	3.9082	3.8059	3.5555	3.6725	4.6010	4.6667
Min	0.75	0.86	0.36	0.36	0.00	0.00
Max	20.58	20.58	16.63	16.63	19.64	19.64

Major Secondary Outcome Results

Mean level of well-being (VAS) during the pollen peak in treatment year 1, FAS1 population

[VAS scale][1]	BM32 low N=46	BM32 high N=53	Placebo N=47
n	46	53	47
Mean	23.4	25.2	31.3
Median	21.4	22.9	28.6
SD	17.96	18.31	22.03
Min	0	0	1
Max	100	76	99

[1] 0: not affected by allergy symptoms; 100: strongly affected by allergy symptoms during the whole day

Mean level of well-being (VAS) during the pollen peak in treatment year 2, FAS2 population

[VAS scale][1]	BM32 pooled N=92	Placebo N=46
n	92	46
Mean	22.0	30.8
Median	16.8	25.0
SD	17.39	22.41
Min	0	0
Max	74	91

[1] 0: not affected by allergy symptoms; 100: strongly affected by allergy symptoms during the whole day

Mean RQLQ scores during treatment year 2, FAS2 population

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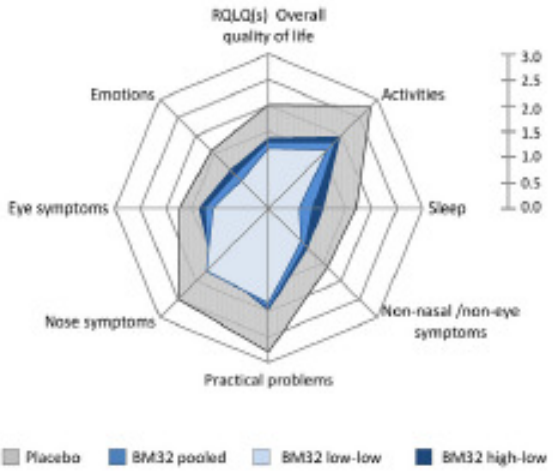
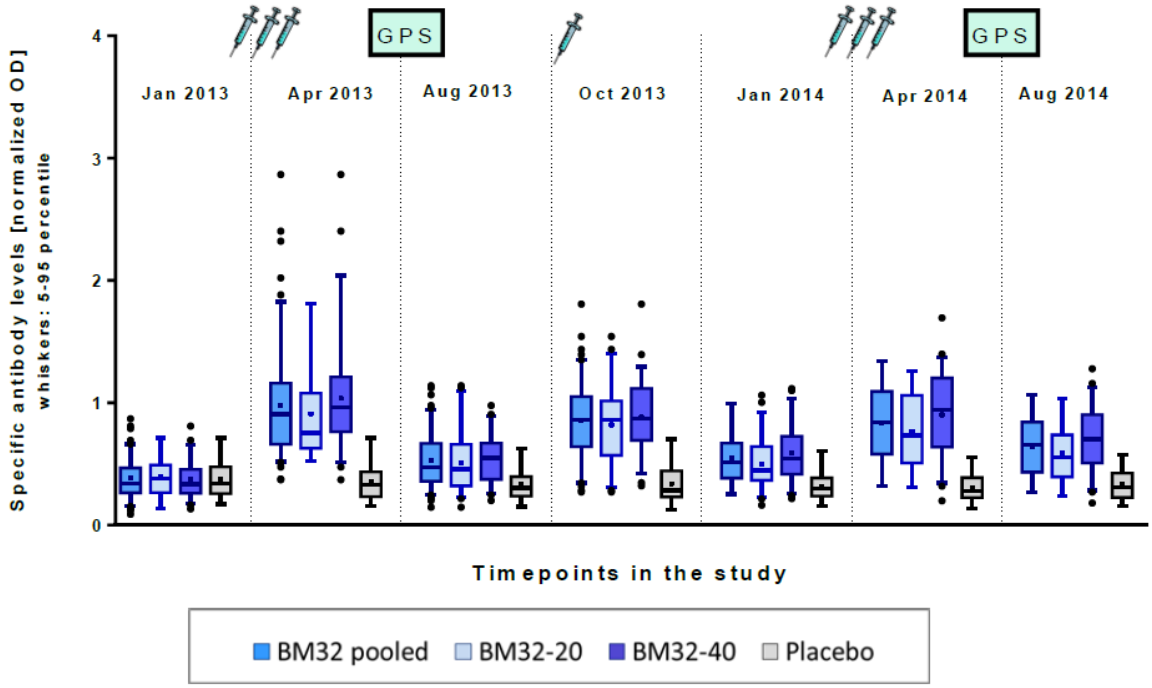
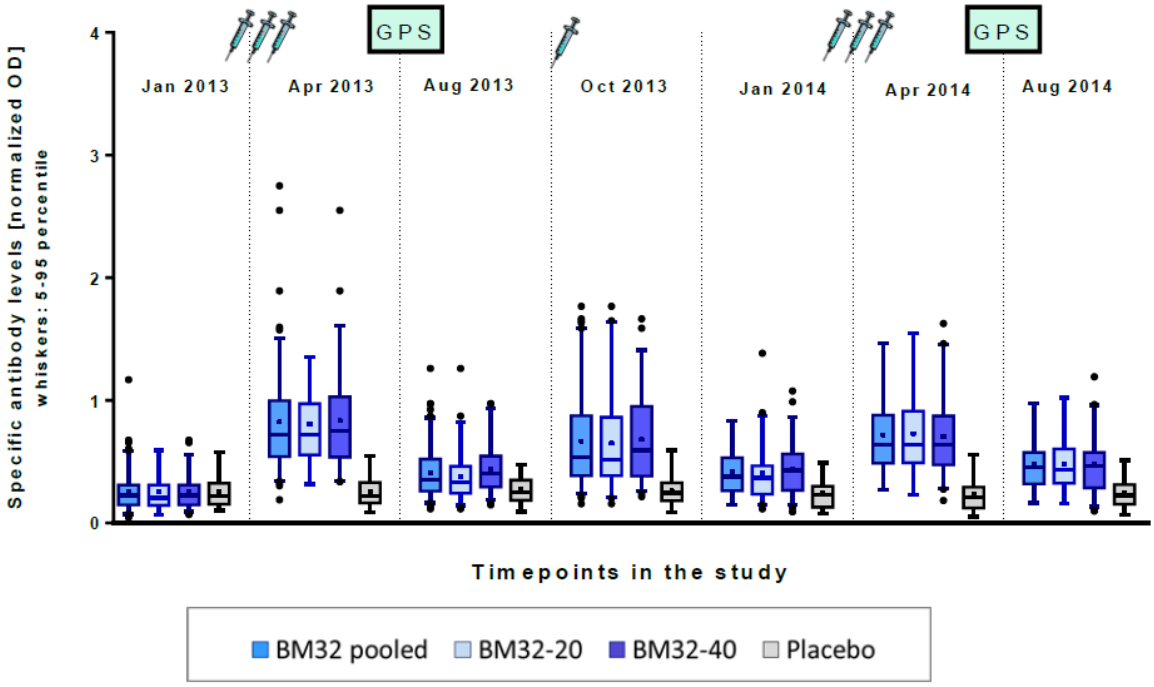


	RQLQ(s) Overall quality of life	Activities	Sleep	Non-nasal /non-eye symptoms	Practical problems	Nose symptoms	Eye symptoms	Emotions
p-value BM32 low-low vs. Placebo	0.004	<0.001	0.001	0.057	0.057	0.024	0.187	0.006
p-value BM32 high-low vs. Placebo	0.032	0.022	0.062	0.153	0.093	0.002	0.438	0.069
p-value BM32 pooled vs. Placebo	0.004	0.001	0.003	0.054	0.038	0.002	0.227	0.009

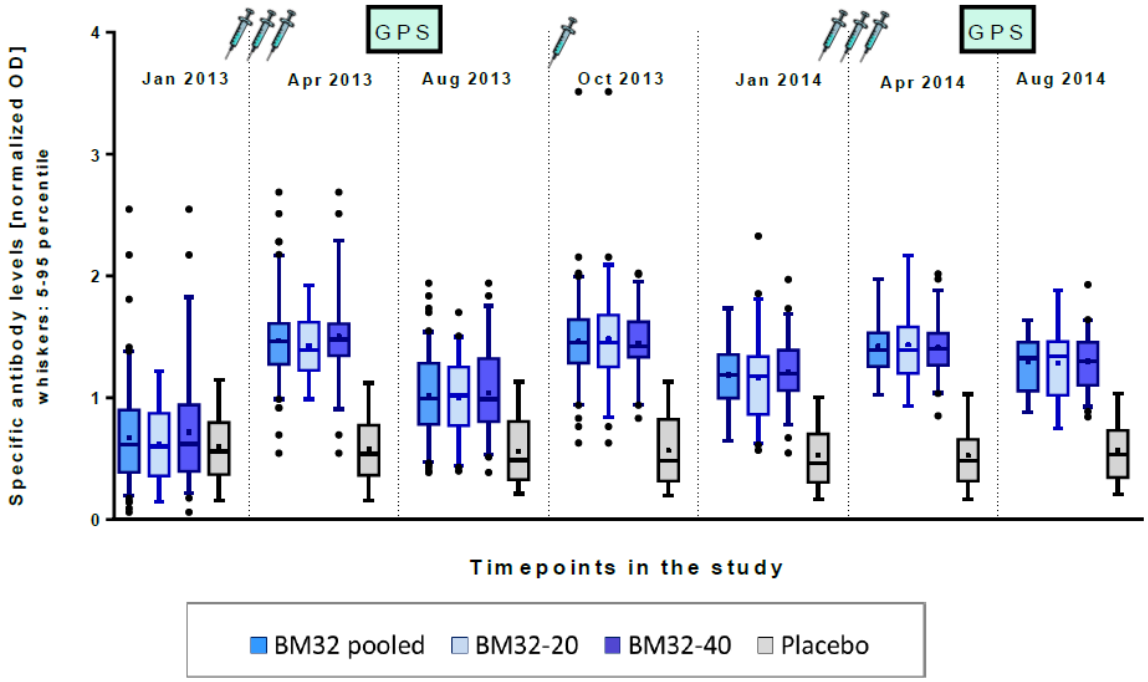
Phl p 1 specific IgG, safety population



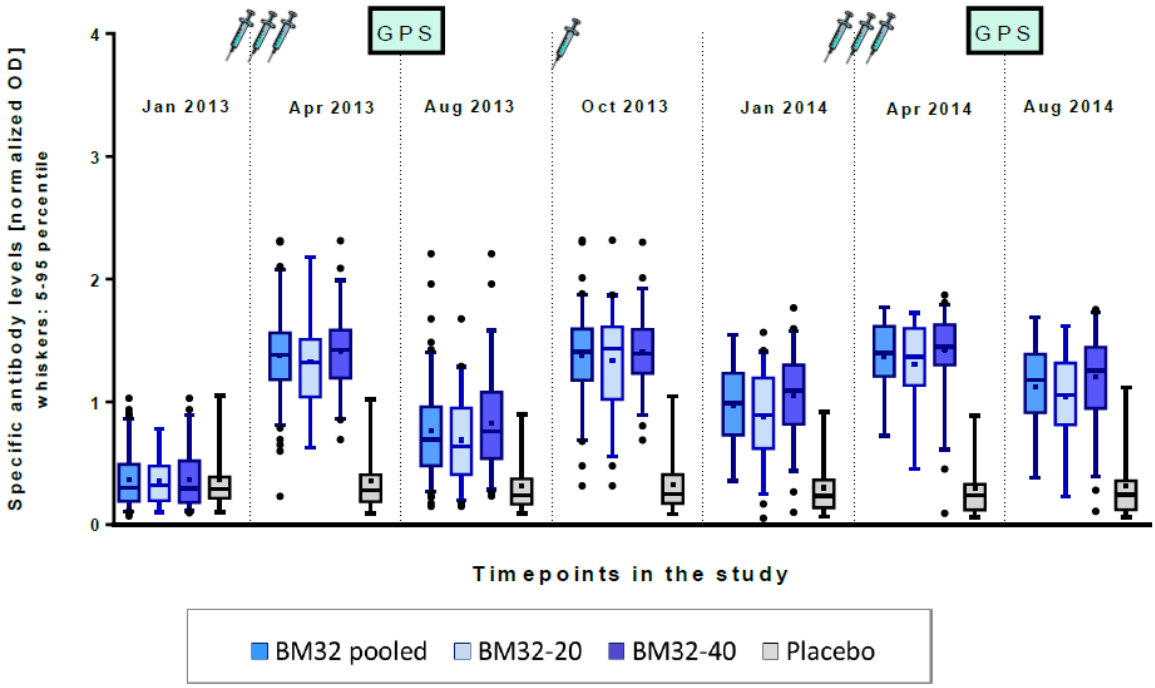
Phl p 2 specific IgG, safety population



Phl p 5 specific IgG, safety population



Phl p 6 specific IgG, safety population



Safety Results

Overview of the number of local and systemic reactions during treatment with BM32

	2013 (year 1)			2014 (year 2)	
	BM32 low (n = 53)	BM32 high (n = 60)	Placebo (n = 53)	BM32 pooled (n = 113)	Placebo (n = 53)
No. of injections	194	220	197	309	147
No. of severe AEs (%)	0	2 (3.3%)	0	1 (1.0%)	0
No. of systemic reactions	23 (28.3%)	18 (21.7%)	6 (9.4%)	6 (4.4%)	3 (5.6%)
No. of local reactions	313 (88.7%)	417 (86.7%)	197 (73.6%)	393 (55.8%)	124 (52.8%)

Numbers in parentheses indicate the percentage of subjects within the respective group in whom an event occurred.

Grading of systemic reactions according to the EAACI grading system

	2013 (year 1)			2014 (year 2)	
	BM32 low (n = 53)	BM32 high (n = 60)	Placebo (n = 53)	BM32 pooled (n = 113)	Placebo (n = 53)
Grade 0	7 (5.7%)	2 (3.3%)	3 (5.7%)	1 (0.9%)	2 (3.8%)
Grade 1	13 (17.0%)	11 (13.3%)	2 (1.9%)	4 (3.5%)	1 (1.9%)
Grade 2	3 (5.7%)	5 (5.0%)	1 (1.9%)	0	0
Grade 3	0	0	0	1 (0.9%)	0
Grade 4	0	0	0	0	0

Numbers in parentheses indicate the percentage of subjects within the respective group in whom an event occurred. Not graded refers to reactions that are not typical for allergic

Other relevant findings

None

Study summary

- Treatment of grass pollen allergic patients with BM32 was found to be safe and well tolerated.
    - The appearance and severity of local reactions, but not of systemic reactions appeared to be dose dependent in Year 1.
    - In year 2, the adverse event profile of BM32 was not different from placebo.
    - Overall the adverse event profile compares favorably to standard SCIT. The frequency of the most common systemic AEs in SCIT reported in the literature – i.e. fatigue, urticaria and thoracic AEs – was found to be lower after treatment with BM32 compared to SCIT based on allergen extracts (e.g. Alutard by ALK Abello)
- The treatment with BM32 was found to be clearly efficacious in improving the allergic condition of grass pollen allergic patients. Results from almost all efficacy endpoints were found to be in favor of BM32. Allergy symptom scores in the peak season of Year 2, and patients' well being as determined by VAS and RQLQ in treatment year 2 both for the peak season and the whole pollen season were found to be significantly improved in subjects treated with BM32 vs. placebo.
- The study together with the results from study CS-BM32-002 provides evidence of a bell-shaped
- dose response curve, with 20 µg per API being the optimal dose.
- The results from this study justify the evaluation of BM32 in larger phase III studies.

Date of Clinical Trial Report

July 2, 2015

Publication reference

Niederberger, V., Neubauer, A., Gevaert, P., Zidarn, M., Worm, M., Aberer, W., Malling HJ., Pfaar, O., Klimek, L., Pfützner, W., Ring, J., Darsow, U., Novak, N., Gerth van Wijk, R., Eckl-Dorna, J., Focke-Tejkl, M., Weber, M., Müller, H-H., Klinger, J., Stolz, F., Breit, N., Henning, R., Valenta, R.,(2018) **Safety and efficacy of immunotherapy with the recombinant B-cell epitope-based grass pollen vaccine BM32,** J. Allergy Clin. Immunol. (in press, doi.org./10.1016/jaci.2017.09.052)