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

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ObjectivesPrimary Efficacy Objective• To assess the sustained clinical effect of BM32 during 2 consecutive treatment years compared to placebo. The clinical effect of BM32 is evaluated by a combined Symptom-Medication-Score (SMS) which is recorded…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Allergic conditions
Study type	Interventional

Summary

ID

NL-OMON39223

Source
ToetsingOnline

Brief title
CS-BM32-003

Condition

- Allergic conditions

Synonym
grass pollen allergy

Research involving
Human

Sponsors and support

Primary sponsor: Biomay AG

Source(s) of monetary or material Support: Biomay AG

Intervention

Keyword: allergy, BM32, grass pollen

Outcome measures

Primary outcome

Primary endpoints will be:

• The mean daily combined Symptom-Medication-Score (SMS)

during the grass pollen peak of treatment year 1. The mean

daily combined SMS will be compared between the treatment group and placebo.

• The mean daily combined Symptom-Medication-Score (SMS)

during the grass pollen peak of treatment year 2. The mean

daily combined SMS will be compared between the treatment groups and placebo.

Co-primary Safety Endpoints

• Frequency of AEs concerning occurrence, seriousness,

intensity and relationship to study drug.

• Frequency and grading of local and systemic reactions.

• Vital functions and findings of physical examination

• Safety Laboratory (Hematology, blood biochemistry, and urine

analysis)

Secondary outcome

Secondary efficacy endpoints will include

• Mean daily combined SMS during the whole grass pollen

season (treated vs. placebo)

• Mean daily Symptom-Score (SS), and Medication-Score (MS)

during peak of the pollen season and during whole pollen season (treated vs. placebo).

• Mean of each individual symptom of the SS

o BM32-treated patients compared to placebo

o during pollen peak and the whole pollen season

• Mean level of *well-being* of patients measured by VAS during the grass pollen season (treated vs. placebo)

• Number of *bad days* during the whole grass pollen season and during the grass pollen peak (treated vs. placebo).

• Number of symptom-free days during the whole grass pollen season and during grass pollen peak (treated vs. placebo).

• Change in skin reactivity determined by titrated SPT (treated vs. placebo)

o comparing treatment year 1 and 2 each to baseline

o comparing skin reactivity as measured at different time points during the study (Visits 2,3,5,8,9,12,15, and 16)

• Mean RQLQ in each treatment year (treated vs. placebo)

• Mean asthma score (grouped by whole grass pollen season and grass pollen peak period) (treated vs. placebo)

Secondary immunogenicity endpoints are as follows:

• Mean allergen-specific and PreS-specific antibodies (IgG and IgE) as measured at different time points during the study (Visits 2,3,5,8,9,10,11,12,15,16, and 17) compared between

verum treated and placebo treated patients

Study description

Background summary

Specific immunotherapy (SIT) is the only allergen-specific and disease-modifying therapeutic modality for IgE-mediated allergies. However, the current clinical use of extracts from allergy causing agents (pollen, mites, animal dander) is limited by many problems caused by the poor quality of natural allergen extracts, including poor characterization, lack of important allergens and contaminations of the API. Because this results in inconvenient dosing schemes and occurrence of side effects, in the worst case severe and life-threatening anaphylactic side effects, the use of SIT is limited. It is therefore highly desirable to develop products for SIT, which overcome these problems and provide a safe and convenient treatment so that a larger number of patients can benefit from it. This promise is approaching reality with improved understanding of the molecular nature of the disease-causing allergens and the disease process itself. Pure allergens can now be obtained by recombinant expression and molecular modifications of the allergens allow development of vaccines with reduced side effects and enhanced efficacy.
The recombinant proteins constituting the grass pollen vaccine BM32 are the first members of a new generation of allergy vaccines, which have been designed to minimize side effects and to allow establishment of a convenient immunotherapy schedule for all major seasonal and perennial allergies. They have been engineered to reduce IgE reactivity and T cell reactivity but to retain the ability to induce protective IgG antibody responses against the natural allergens upon vaccination. Their safety has been studied in grass pollen allergic patients by skin testing showing almost complete lack of allergenic activity. Currently, a study (CS-BM32-002) is investigating safety and dose dependent effects of 3 subcutaneous injections of BM32 on immunological and clinical responses to grass pollen allergens in patients suffering from grass pollen-induced rhinoconjunctivitis. In this study, antibody responses to grass pollen allergens are studied in patients treated with 3 different doses of BM32 or placebo. Clinical effects are evaluated by respiratory exposure to grass pollen allergens in an environmental exposure chamber and by titrated skin prick testing. The aim is to determine a safe dose of BM32 which affects grass pollen-specific allergic reactions in the skin and upon exposure in the pollen chamber and induces immunological changes expected to be associated with clinically effective SIT. The study has started in October 2011 and will be carried out until the end of February 2012; data will be available in the second quarter of 2012.
The present study CS-BM32-003 is designed to evaluate the safety and efficacy of a treatment with BM32 during 2 grass pollen seasons under natural pollen

exposure. 180 grass pollen allergic individuals will be randomized into 3 study arms (2 dose levels BM32 + placebo). After patient assessment during the first grass pollen season for screening purposes, subjects will be randomized to receive 3 monthly injections before each of the next 2 grass pollen seasons and a boost injection between the seasons to maintain the desired allergen-specific IgG response. The dose levels of BM32 will be 20 mcg and 40 mcg per protein component, unless safety and efficacy assessment of study CS-BM32-002 suggest a different dose selection.
In December 2013, after reviewing unblinded safety and efficacy data, the DMC recommended to continue with the study with the lower dose of BM32 only and switch patients, who have received high dose in the first treatment year to the lower dose in the second treatment year.

Study objective

Objectives
Primary Efficacy Objective
• To assess the sustained clinical effect of BM32 during 2 consecutive treatment years compared to placebo. The clinical effect 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.

Secondary Efficacy Objective(s)
• To assess the sustained clinical effect of BM32 during 2 consecutive treatment years
compared to placebo. The clinical effect of BM32 is
evaluated by a combined Symptom-Medication-Score (SMS) which is 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 stand-by-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 are 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 vs. placebo on the severity of grass
pollen allergy by evaluation of the
- Number of *bad days* and
- Number of *symptom-free* days

during the pollen season.
• To assess the effect of treatment with BM32 vs. treatment with placebo on the skin
reactivity to a commercially available grass pollen extract. The change from baseline
in skin reactivity of each individual subject is measured by titrated SPT.
• 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 BM32
compared to placebo.
Secondary Safety and Immunogenicity Objective(s)
• 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 intra-group comparison of treatment years with baseline.
• To assess effects of subcutaneous administration of BM32 on parameters of vital
signs and safety laboratory parameters.

Study design

The study will be performed over 3 years (baseline year + 2 treatment years) as a
randomized, double-blind, and placebo-controlled multi-center study. 250-270 individuals
with sensitivity to grass pollen will be screened and 180 will be randomized into 2 study arms
(BM32 and placebo). The study will consist of 17 visits.

Intervention

7 subcutaneous injections: 3 in the first treatment year and 3 in the second treatment year with a distance of 4 weeks before the grass pollen season and in between 1 boost injection.

Study burden and risks

No information is yet available about potential side effects of BM32 hyposensitization therapy. BM32 hyposensitization therapy is currently investigated in another study, but the study is still ongoing and results are

not yet available. Safety results are available from a first study with 60 subjects with grass pollen allergy where BM32 or components of BM32 were applied on the skin, but not injected under the skin as it is being done in this study. Only one adverse event (skin rash and itching on the neck) was observed in this study, which was considered as possibly related to the application of BM32. The rash resolved within the same day.

Because allergies can never be definitely foreseen in individual cases, there is always the possibility that the patient may experience local allergic reactions such as redness of the skin, itching or wheals at the injection site that usually resolve within a few days. There is also a risk of more severe allergic reactions such as skin rash, blistering, swelling of the mucous membrane, difficulty in breathing, inflammation, fever or very seldom an anaphylactic shock (allergic circulatory collapse) that may become life-threatening. In addition to an immediate allergic reaction, allergy symptoms may present after several hours or days (delayed allergic reaction). In case of extreme allergic reactions, medical equipment for an emergency and study personnel trained in emergency measures are available at the study site.

Subcutaneous injection
A subcutaneous injection can lead to transient redness of the skin and swelling at the injection site.

Blood sampling
Blood sampling could lead to bleeding/bruising or irritation at the puncture site and in rare cases to inflammation or closure of the relevant vein, faintness/collapse or damage to a nerve.

Skin allergy test (Skin Prick Test)
The skin allergy test may cause allergy symptoms as described above

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

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 screening period (exact definition of this criterion is specified in the study reference manual (SRM))
* Age between 18 and 60 years (m/f)
* Subjects must have a standard health care insurance
* Subject must appear capable to understand and comply with all relevant aspects of the study protocol
* Subject must be available during the study period to complete all treatments and assessments

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 are not using a medically accepted birth control method
* autoimmune diseases, immune defects including immunosuppression, immune-complex-induced immunopathies
* contra-indication for adrenaline

* severe general maladies, malignant diseases
* patients under long-term treatment with systemic corticosteroids,
* contra-indications for skin prick testing such as: skin inflammation
in the test area, urticaria facticia.
* bronchial asthma not controlled by low dose inhaled corticosteroids This means that
Patients with a history of concomitant asthma should have a FEV1 > 70% at inclusion.
Patients without a history of asthma should have FEV1 >70% or a 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 will be
acceptable
* patients who participated in a pollen SIT trial or received marketed pollen SIT in 2 years
prior to study
* patients who had a previous grass pollen SIT or have participated in a clinical trial of grass
pollen SIT
* risk of non-compliance with the study procedure and restrictions (e.g. with alcohol, drug or
medication abuse within the past year)
* Use of prohibited medication prior to Screening (Visit 1) and
throughout the study:
- Depot corticosteroids - 12 weeks prior to Visit 1
- Oral corticosteroids - 8 weeks prior to V1
- High -dose inhaled corticosteroids - 4 weeks prior to V1
* Use of anti-histamines three days prior to V1 or V2
* Patients with nasal polyposis
* Patients sensitized to Phl p 7
(specific IgE to Phl p 7 and/or Bet v 4 > 0,35 kUA/L)

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-07-2012
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BM32

Ethics review

Approved WMO Date:	15-05-2012
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-09-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-09-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-01-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-08-2013
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-08-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-01-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-02-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-000442-35-NL
CCMO	NL39805.000.12