A randomized, double-blind, placebo-controlled, double-dummy study to determine the safety/tolerability of a simultaneous subcutaneous treatment of BM41 and vitamin D3 in patients with moderate to severe allergic rhinitis/ rhinoconjunctivitis caused by birch pollen.

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Upper respiratory tract disorders (excl infections)
Study type	Interventional

Summary

ID

NL-OMON45256

Source
ToetsingOnline

Brief title
BM41ViD

Condition

- Upper respiratory tract disorders (excl infections)

Synonym
allergic rhinitis, birchpollen allergy

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: European Commission 7th Framework Programme for research technological Development and Demonstration

Intervention

Keyword: allergic rhinitis/ rhinoconjunctivitis, birch pollen, BM41, vitamin D 3

Outcome measures

Primary outcome

The primary endpoint is the number of treatment-related systemic reactions (classified in accordance with the WAO-grading system) in the BM41/VD3 treatment group compared to BM41/Placebo2, VD3/Placebo1 and Placebo1/Placebo2 throughout the pre-seasonal treatment course. This will be determined at every visit according to the reports of the patient.

Secondary outcome

1) Reduction of upper airway response to allergen compared to baseline evaluation (Visit 1) as assessed by a TNPT after the first maintenance shot, before start birch-pollen season at Visit 10 and at end of trial at Visit 12 (after grass/weed pollen seasons).

Patients will receive incremental dosages of intranasal birch pollen extract (100, 1,000 and 10,000 AU/ml, HAL Allergy B.V., Leiden, The Netherlands) at baseline to determine the upper airways response and the threshold dose to

birch pollen. The upper airways response to intranasal birch pollen extract will be quantified using the symptom score according to Lebel et al.. The mean total symptom score is calculated from the response to the allergen dosage which evoked a positive test. After the preseasonal treatment course before birch-pollen season at Visit 10 and at end of trial at Visit 12 the TNPT will be repeated with the same incremental allergen dosages as used at baseline. The mean total symptom score to the allergen dosage which evokes a positive test at Visit 10 (before birch-pollen season) and at end of trial at Visit 12 will be compared to the baseline values. For a description of the TNPT and the Lebel scores.

2) Improvement in nasal patency compared to baseline evaluation (Visit 1) as assessed by Peak Nasal Inspiratory Flow (PNIF) after TNPT after the first maintenance shot, before birch-pollen season at Visit 10 and at end of trial at Visit 12 (after grass/weed pollen seasons).

3) Furthermore, clinical efficacy will investigated by analyzing the reduction in a combined symptom and medication score (CSMS) as assessed during the birch pollen season. The BM41/VD3 (the combination treatment), the BM41/Placebo 2 (BM41 alone), and the VD3/Placebo1 (VD3 alone) treatment groups will be compared to each other and to Placebo1/Placebo2. This clinical endpoint refers to the recently published EAACI Position Paper on *Recommendations for the standardization of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis* highlighting the CSMS as harmonized standard in

future clinical AIT trials for allergic rhinoconjunctivitis. For this, patients will be asked to keep a daily e-diary to collect the CSMS during the birch pollen season.

The following definition will be used to calculate the CSMS:

CSMS = (daily) Symptom Score (dSS) + (daily) Medication Score (dMS)

The dSS comprises of six individual symptom scores: four nasal symptoms (Itchy Nose, Sneezing, Runny Nose, Blocked Nose) and two ocular symptoms (Itchy/red eyes, Watery eyes), all daily scored (by patients in e-diaries in the birch pollen season) on a scale from 0-3. The dSS will be calculated as mean of all non-missing daily SS during the birch pollen season (range 0-18) divided by the number of individual symptoms (6 symptoms). As such the dSS has a range from 0-3.

The dMS is based on the following scores: 0 = no (anti-allergic) rescue medication, 1 = antihistamines (oral and topical), 2 = nasal corticosteroids, 3 = oral corticosteroids . The dMS will be scored as the average of the daily MS during the birch pollen season. As such, the dMS has a range from 0-3.

Therefore, the corresponding CSMS (dSS + dMS) has a range from 0-6.

4) A self questionnaire for assessing the control of allergic rhinitis has been recently proposed and validated based on 5 standardized questions as being scored from 1 to 5 points (on a Likert-scale) reporting the severity of AR over the previous 2 week. This score showed a good correlation to the symptomatology and QoL-related impairment caused by the disease. Moreover, it revealed to be sensitive in demonstrating treatment effects of (anti-allergic)

pharmacotherapy. The standardized 5 questions will be assessed at baseline, during birch pollen-season 2018 at Visit 11 and at the end of the trial (Visit 12, EoT). Averages of this *control-score* will be compared between the treatment groups.

5) The *Mini-Rhinoconjunctivitis Quality of Life Questionnaire (mini-RQLQ)* will be assessed at baseline, during birch pollen-season 2018 and at the end of the trial. This self-administered questionnaire assesses (the disease specific) patients* quality of life (QoL) and has been standardized and validated. Moreover, validated translations are available in different languages which will be used in the four different participating European countries.
The m-RQLQ comprises five domains (activity limitation, practical problems, nose symptoms, eye symptoms and non-nose/eye symptoms) based on 14 standardized questions. The Quality of Life Total Score will be assessed based on subject's self-filled Mini-RQLQ at baseline, during birch pollen-season 2018 at Visit 11 and at the end of the trial (EoT) (Visit 12). Averages of the m-RQLQ will be compared between the treatment groups.

6) Based on the dSS and the dMS, the percentage of *well days* (=days with no intake of (anti-allergic) rescue mediation and a symptom score * 2) and *severe days* (a symptom score of 3 for any of the rhinoconjunctivitis symptoms, both reviewed in) will be compared between the treatment groups.

7) Changes of serum specific immunoglobulin levels (total IgE, rBet v 1- and

birch pollen-specific IgE, IgG, and IgG4) (all centers, see Appendix 8 in

manual and cellular immunology (two centers) at Visit 6, Visit 10, Visit 11 and

Visit 12 compared to baseline evaluation (Visit 1).

8) Average of Asthma Control Score, will be obtained during baseline and during

the birch pollen season (V 11) and at Visit 12 (eoT).

9) Nasal brushing and analysis of basal nasal cells and nasal microbiom (two

centers, at Visit 1, 6, 10 and Visit 12 will be compared between the treatment

groups.

Study description

Background summary

For decades, allergen immunotherapy (AIT) is used as a causal therapeutic option in the treatment of IgE-mediated allergic diseases such as allergic rhinitis (AR), allergic rhinoconjunctivitis (ARC) or allergic asthma (AA). Efficacy of this therapeutic principle is well documented for allergen extract-based products, but the required duration of the treatment of at least three years of monthly injections and the (controlled) risk of severe side-effects are experienced to be significant drawbacks. There is a need for a treatment with a lower risk of side-effects and a more rapid onset of longlasting efficacy, i.e. less injections. BM41 is a hypoallergenic (safer) but hyper-immunogenic (more effective) recombinant variant of Bet v 1, the major allergen of birch pollen, whereas vitamin D3 (VD3) is a promising adjuvant to more rapidly skew the allergic immune response towards a protective anti-inflammatory immune status.

Study objective

Secondary objectives:
The secondary objectives include demonstration of clinical efficacy of SCIT with BM41 alone, with BM41 plus VD3 and with VD3 alone, all three compared to placebo. Efficacy will be analysed for the upper airways by titrated nasal

provocation test (TNPT) including an objective read-out i.e. peak nasal inspiratory flow (PNIF). Moreover, the clinical efficacy of SCIT with BM41 alone, with BM41 and VD3 and with VD3 alone, is further evaluated by recording birch seasonal allergic symptoms and medication use, by control of rhinitis symptoms, and by Health-Related Quality of Life and *well-days/severe days*, compared to placebo. Further secondary objectives include the assessment of serological and cellular immunological changes induced by SCIT with BM41 alone, BM41 with VD3 and VD3 alone compared to placebo, the onset of clinical and immunological changes induced by SCIT with with BM41 alone compared to BM41 with VD3, the indentification of predictive and efficacy-associated biomarkers by transcriptomics on nasal brushing, the assessment of the hypoallergenicity of BM41 and possible de-novo sensitization to BM41 by titrated skin prick test (tSPT). In a subset of patients, asthma control will be evaluated during birch pollen season.

Study design

This trial is planned as a randomized, double-blind, placebo-controlled, parallel group, double-dummy, multicentre (four European centres with three additional satellite centres), Phase I/IIa study. A total of 160 patients will be randomized to four treatment groups in a 1:1:1:1 manner as follows: 40 patients receiving BM41/VD3, 40 patients receiving BM41/Placebo 2 (=placebo matching VD3), 40 patients receiving VD3/Placebo 1 (=placebo matching BM41) and 40 patients receiving Placebo1/Placebo2.

The whole pre-seasonal treatment course will comprise eight treatment visits and 16 injections in total. It will begin between 15 Oct and 15 Dec 2017. SCIT treatment will be administered as two separate subcutaneous injections within 1 cm of each other in a blinded double-dummy design. The treatment will be scheduled with an initial phase of five simultaneous injections (5xBM41/Placebo2 and 5x VD3/Placebo1) with increasing doses of BM41 in weekly intervals followed by three simultaneous injections in 3 weeks intervals (maintenance phase BM41). The whole treatment course will therefore be approximately 13 weeks. The VD3 dosage will not be up-dosed, but be administered at the maintenance dose level from the first treatment day already.

Intervention

SCIT treatment will be administered in a blinded double-dummy design as two separate subcutaneous injections (one BM41/Placebo 1, one VD3/Placebo 2) within 1 cm of each other to ensure that subcutaneous allergen presenting cells such as e.g., dendritic cells are exposed to BM41 in the context of VD3.
The treatment will be scheduled with an initial phase of five simultaneous injections (with increasing doses of BM41) in weekly intervals followed by three simultaneous injections with maintenance dose in 3 weeks intervals. The

whole treatment course will therefore be approximately 13 weeks. The VD3 dosage will not be up-dosed, but will be administered as a single dose level throughout the treatment.

Study burden and risks

BM41 is developed for the causal treatment of immediate type allergic disorders (IgE-mediated), such as allergic rhinitis, allergic conjunctivitis and allergic bronchial asthma, triggered by sensitisation to allergenic substances from birch pollen. This study will investigate if addition of VD3 enhances clinical efficacy of BM41. The risk assessment is low. The potential benefit for patients is that they will receive approximately 13 weeks of AIT treatment free of charge during the study. The results of this study will indicate if BM41 and/or a combination of BM41/VD3 is safe and induces a more rapid onset and enhancement of efficacy. In future, other patients with a birch pollen allergy may benefit from this combined therapy.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105AZ
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Signed informed consent
2. Age *18 * 65 years
3. Moderate to severe birch-pollen-induced AR/ARC of at least 2 years according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines (Appendix 1, see manual) with or without concomitant mild to moderate persistent asthma
4. FEV1>70% for patients with a history of asthma, FEV1>70% or PEF>80% for patients without a history of asthma
5. A positive SPT (mean wheal diameter * 3mm compared to negative control and negative control should be negative) for birch pollen assessed within 1 year before randomization
6. A positive TNPT for birch pollen at screening (Lebel score *6)

Exclusion criteria

1. Clinically relevant co-sensitization (others than hazel, alder and elm) expected during the birch-pollen season.
2. Chronic asthma with an FEV1<70 % of predicted value.
3. History of AIT (SCIT or SLIT) with any allergen within the past 5 years
4. Ongoing AIT (SCIT or SLIT) with any allergen(s) during the study period
5. Current Treatment with VD3 analogue.
6. Vaccination within one week before or during the treatment phase.
7. Immunosuppressive or biological medication (e.g. IL-5, anti-IgE therapy) within the last six months prior to inclusion and up to end of trial (EoT).
8. Severe immune disorders (including auto-immune diseases) and/or diseases requiring immunosuppressive drugs.
9. Uncontrolled asthma or other active respiratory diseases.
10. Active malignancies or any malignant disease during the previous 5 years.
11. Severe uncontrolled diseases that could increase the risk for patients participating in the study, including but not limited to: cardiovascular insufficiency, any severe or unstable lung diseases, endocrine diseases, clinically significant renal or hepatic diseases, or haematological disorders.
12. Active inflammation or infection of the target organs (nose, eyes or lower airways) at the start of the study.
13. Moderate to severe nasal obstructive diseases that preclude a TNPT (e.g., septal deviation, nasal polyps) or nasal/sinus surgery in the last 3 months.
14. Diseases with a contraindication for the use of adrenaline (e.g. hyperthyroidism, glaucoma).
15. Use of systemic steroids within 4 weeks before start of the study and during the study.
16. Treatment with systemic and local *-blockers.

17. Pregnancy, lactation or inadequate contraceptive measures for women of child-bearing age (adequate contraceptive measures will be the use of a contraceptive device or oral contraceptive pill).
18. Alcohol, drug or medication abuse within the past year.
19. Any clinically significant abnormal laboratory parameter at screening.
20. Lack of cooperation or compliance.
21. Any physical or mental condition that precludes administration of SCIT, compliance or participation in a clinical trial.
22. Patients who are students or employees of the institution or 1st grade relatives or partners of the investigators
23. Participation in a clinical trial within 3 months prior to the current trial.

Study design

Design

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	40
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	BM41
Product type:	Medicine
Brand name:	Zemplar
Generic name:	Paricalcitol
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	25-04-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-07-2017
Application type:	First submission
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	EUCTR2016-004827-22-NL
CCMO	NL60701.000.17