# Clinical trial results:
# A multi centre randomised placebo-controlled double-blind clinical trial for the evaluation of efficacy of specific immunotherapy with an aluminium hydroxide-adsorbed recombinant hypoallergenic derivative of the major birch pollen allergen r Bet v1-FV on Bet v 1 associated soy allergy

## Summary

| | |
|---|---|
| EudraCT number | 2009-011737-27 |
| Trial protocol | DE |
| Global end of trial date | 18 July 2014 |
| **Results information** | |
| Result version number | v1 (current) |
| This version publication date | 18 July 2020 |
| First version publication date | 18 July 2020 |
| Summary attachment (see zip file) | 2015-07-13_BASALIT_Ergebnisbericht_in_Arzneimittelpruefungen_final1.0 (2015-07-13_BASALIT_Ergebnisbericht_in_Arzneimittelpruefungen_final1.0.pdf) |

## Trial information

| | |
|---|---|
| **Trial identification** | |
| Sponsor protocol code | BASALIT |
| **Additional study identifiers** | |
| ISRCTN number | ISRCTN67316358 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

| | |
|---|---|
| **Sponsors** | |
| Sponsor organisation name | University Leipzig |
| Sponsor organisation address | Ritterstr. 26, Leipzig, Germany, 04109 |
| Public contact | Jan Christoph Simon, Prof., MD, University Leipzig<br>Klinik für Dermatologie, Venerologie und Allergologie,<br>jan.simon@medizin.uni-leipzig.de |
| Scientific contact | Regina Treudler, Prof., MD, University Leipzig<br>Klinik für Dermatologie, Venerologie und Allergologie,<br>regina.treudler@medizin.uni-leipzig.de |

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 | 19 January 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 18 July 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 July 2014 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To determine the efficacy of specific subcutaneous immunotherapy (SCIT) against birch allergen Bet v 1 on birch pollen associated soy allergy.

Protection of trial subjects:

For the analyses of the clinical endpoints, patients will undergo several allergological tests, all of which will be perfomed in a standardized matter according to current position papers. . This will include questionnaires, skin prick tests, blood draws for in vitro tests and oral provocation tests with soy-containing or placebo meals.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 03 February 2010 |
| 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 | Germany: 56 |
| Worldwide total number of subjects | 56 |
| EEA total number of subjects | 56 |

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) | 56 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

All patients are undergoing initial screening and baseline examinations (up to 9 months) before intervention phase - including double blind placebo controlled food challenge (DBPCFC).

### Pre-assignment

Screening details:

The aim was to include a total number of 84 patients with evaluable data with regard to the primary and secondary endpoints after intervention with rBet v1 or placebo.
To obtain reliable information, about 385 patients were planned to be recruited and screened for eligibility.

### Pre-assignment period milestones

| | |
|---|---|
| Number of subjects started | 195[1] |
| Number of subjects completed | 56 |

### Pre-assignment subject non-completion reasons

| | |
|---|---|
| Reason: Number of subjects | Screening failure: 139 |

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 139 of these patients are Screening failures.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Verum |

Arm description: -

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | rBet v1-FV |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Duration of intervention per patient will be divided into three phases: up-dosing; prolongation; maintenance
Up-dosing will start with initial injections of 0.15 ml (strength A), continues with increasing dosages of strength A (5 µg/ml) and then of strength B (100 mg/ml). Injections will be administered at weekly intervals (+7 days) according to the dosage schedule, with a maximum dose of 0.8 ml of strength B. During prolongation, there will be gradually increased injection intervals: 7 (+7 days) 14 (+/-7days), 28 (+/-7 days). Thereafter, injections will be applied every 28 (+ 14 days) resulting in the maintenance phase, which is scheduled for nine injections during 38 weeks.

| | |
|---|---|
| **Arm title** | Placebo |

Arm description: -

| | |
|---|---|
| Arm type | Placebo |

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

Dosage and administration details:

Duration of intervention per patient will be divided into three phases: up-dosing; prolongation; maintenance
The same time schedule and injection regimes as in verum arm. During prolongation, there will be gradually increased injection intervals: 7 (+7 days) 14 (+/-7days), 28 (+/-7 days). Thereafter, injections will be applied every 28 (+ 14 days) resulting in the maintenance phase, which is scheduled for nine injections during 38 weeks.

| **Arm title** | Dropout before intervention |
|---|---|

Arm description:

these patients (one per arm) were excluded from analysis acc. to statistical analysis plan

| Arm type | No intervention |
|---|---|

No investigational medicinal product assigned in this arm

| **Number of subjects in period 1** | Verum | Placebo | Dropout before intervention |
|---|---|---|---|
| Started | 37 | 17 | 2 |
| Completed | 37 | 17 | 2 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Verum |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |
| Reporting group title | Dropout before intervention |
| Reporting group description: | |
| these patients (one per arm) were excluded from analysis acc. to statistical analysis plan | |

| Reporting group values | Verum | Placebo | Dropout before intervention |
|---|---|---|---|
| Number of subjects | 37 | 17 | 2 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 37 | 17 | 2 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Age at Screening | | | |
| Units: years | | | |
| arithmetic mean | 37.8 | 37.4 | 39 |
| standard deviation | ± 14.6 | ± 13.8 | ± 25.5 |
| Gender categorical | | | |
| Gender | | | |
| Units: Subjects | | | |
| Female | 25 | 12 | 2 |
| Male | 12 | 5 | 0 |
| hyposensitization in history | | | |
| Units: Subjects | | | |
| yes | 25 | 10 | 1 |
| no | 12 | 7 | 1 |
| Food allergies | | | |
| Units: Subjects | | | |
| against <=4 foods | 3 | 4 | 0 |
| 5 to <=10 | 17 | 7 | 2 |
| >10 | 17 | 6 | 0 |
| Skin prick test soy | | | |
| standardized commercially available soy drink used | | | |
| Units: Subjects | | | |
| positive | 36 | 16 | 2 |

| | | | |
|---|---|---|---|
| negative | 1 | 1 | 0 |
| skin prick test birch | | | |
| Units: Subjects | | | |
| positive | 36 | 17 | 2 |
| negative | 1 | 0 | 0 |
| total IgE at BL | | | |
| Units: kU/L | | | |
| median | 163 | 147 | 124 |
| inter-quartile range (Q1-Q3) | 74 to 375 | 67 to 242 | |
| specific IgF ab Bet v 1 | | | |
| Units: kU/L at BL | | | |
| median | 34 | 28 | 22 |
| inter-quartile range (Q1-Q3) | 17 to 66 | 16 to 64 | |
| specific IgE ab Gly m 4 | | | |
| Units: kU/L at BL | | | |
| median | 9 | 6 | 3.1 |
| inter-quartile range (Q1-Q3) | 4 to 16 | 4 to 11 | |
| BMI | | | |
| Units: kg/m² | | | |
| arithmetic mean | 24.5 | 23.8 | 22.8 |
| standard deviation | ± 3.7 | ± 3.6 | ± 0.13 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 56 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 56 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Age continuous | | | |
| Age at Screening | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical | | | |
| Gender | | | |
| Units: Subjects | | | |
| Female | 39 | | |
| Male | 17 | | |
| hyposensitization in history | | | |
| Units: Subjects | | | |
| yes | 36 | | |
| no | 20 | | |
| Food allergies | | | |

| | | | |
|---|---|---|---|
| Units: Subjects | | | |
| against <=4 foods | 7 | | |
| 5 to <=10 | 26 | | |
| >10 | 23 | | |
| Skin prick test soy | | | |
| standardized commercially available soy drink used | | | |
| Units: Subjects | | | |
| positive | 54 | | |
| negative | 2 | | |
| skin prick test birch<br>Units: Subjects | | | |
| positive | 55 | | |
| negative | 1 | | |
| total IgE at BL<br>Units: kU/L<br>median<br>inter-quartile range (Q1-Q3) | -- | | |
| specific IgF ab Bet v 1<br>Units: kU/L at BL<br>median<br>inter-quartile range (Q1-Q3) | -- | | |
| specific IgE ab Gly m 4<br>Units: kU/L at BL<br>median<br>inter-quartile range (Q1-Q3) | -- | | |
| BMI<br>Units: kg/m² | | | |
| arithmetic mean<br>standard deviation | -- | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Verum |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |
| Reporting group title | Dropout before intervention |
| Reporting group description: | |
| these patients (one per arm) were excluded from analysis acc. to statistical analysis plan | |

### Primary: LOAEL obj

| | |
|---|---|
| End point title | LOAEL obj[1][2] |

End point description:

Performance of a double-blind placebo-controlled food challenge:
9 standardized meals within a food challenge were applied to the patient in predefined schedule within various hours of a day; the order of active (with increasing contents of soy) or placebo (withouth any soy but the same size, texture and colour of meals) food challenge was randomized and both challenges took place on 2 different days near in time;
both the appearance of objective and/ or subjective symptoms were assessed by the investigators and/or reported by the patients after any meal incorporated and the lowest level identified in which signs/ symptoms occurred;
the "Lowest observe adverse effect levels (LOAEL)" inducing objective signs/ subjective symptoms were regarded as two primary endpoints without hierarchy

| | |
|---|---|
| End point type | Primary |

End point timeframe:

after the end of the intervention period

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: see attached Chart/document for statistics from the main publication

[2] - 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: both dropouts before intervention started; no data available

| End point values | Verum | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 | 15 | | |
| Units: gram(s) of soy | | | | |
| median (inter-quartile range (Q1-Q3)) | 24.7 (24.7 to 24.7) | 24.7 (2.2 to 24.7) | | |

| | |
|---|---|
| **Attachments (see zip file)** | Basalit_statistics_main-results.pdf/Basalit_statistics_main- |

### Statistical analyses

No statistical analyses for this end point

## Primary: LOAEL subj

| End point title | LOAEL subj[3][4] |
|---|---|

End point description:

2nd primary end point; analysis with Bonferroni-Holm correction for multiplicity

| End point type | Primary |
|---|---|

End point timeframe:

after the end of intervention

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: see attached Chart/document for statistics from the main publication

[4] - 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: both dropouts before intervention started; no data available

| End point values | Verum | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33[5] | 15[6] | | |
| Units: gram(s) of soy | | | | |
| median (inter-quartile range (Q1-Q3)) | 4.7 (0.7 to 24.7) | 2.2 (2.2 to 24.7) | | |

Notes:

[5] - in 4 patients refused to perform the DBPCFC after their ent of intervention

[6] - 2 patients refused to perform the DBPCFC after therin end of intervention

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events:<br>Adverse events are recorded during intervention period. | |
| Assessment type | Systematic |
| **Dictionary used** | |
| Dictionary name | MedDRA |
| Dictionary version | 16.1 |
| **Reporting groups** | |
| Reporting group title | rBet v 1 |
| Reporting group description:<br>experimental arm | |
| Reporting group title | placebo injections |
| Reporting group description:<br>control arm | |

| Serious adverse events | rBet v 1 | placebo injections | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 37 (16.22%) | 2 / 17 (11.76%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Investigations | | | |
| Arthroscopy | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Brain contusion | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaw fracture | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 17 (5.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolism arterial | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Papilloma excision | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Migraine | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion | | | |
| subjects affected / exposed | 0 / 37 (0.00%) | 1 / 17 (5.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Vascular stent thrombosis | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 3 %

| **Non-serious adverse events** | rBet v 1 | placebo injections | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 30 / 37 (81.08%) | 15 / 17 (88.24%) | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 11 / 37 (29.73%) | 6 / 17 (35.29%) | |
| occurrences (all) | 25 | 17 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 4 / 37 (10.81%) | 1 / 17 (5.88%) | |
| occurrences (all) | 4 | 4 | |
| Influenza like illness | | | |
| subjects affected / exposed | 4 / 37 (10.81%) | 2 / 17 (11.76%) | |
| occurrences (all) | 5 | 2 | |
| Injection site erythema | | | |
| subjects affected / exposed | 3 / 37 (8.11%) | 1 / 17 (5.88%) | |
| occurrences (all) | 3 | 4 | |
| Injection site pain | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | 3 / 17 (17.65%) | |
| occurrences (all) | 4 | 3 | |
| Injection site pruritus | | | |
| subjects affected / exposed | 5 / 37 (13.51%) | 1 / 17 (5.88%) | |
| occurrences (all) | 15 | 4 | |
| Injection site swelling | | | |
| subjects affected / exposed | 5 / 37 (13.51%) | 1 / 17 (5.88%) | |
| occurrences (all) | 10 | 2 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 8 / 37 (21.62%) | 2 / 17 (11.76%) | |
| occurrences (all) | 11 | 2 | |
| Nausea | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | 1 / 17 (5.88%) | |
| occurrences (all) | 3 | 2 | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|---|---|---|
| Cough | | | |
| subjects affected / exposed | 7 / 37 (18.92%) | 2 / 17 (11.76%) | |
| occurrences (all) | 8 | 3 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 4 / 37 (10.81%) | 2 / 17 (11.76%) | |
| occurrences (all) | 4 | 2 | |
| Skin and subcutaneous tissue disorders | | | |
| Urticaria | | | |
| subjects affected / exposed | 6 / 37 (16.22%) | 0 / 17 (0.00%) | |
| occurrences (all) | 8 | 0 | |
| Pruritus | | | |
| subjects affected / exposed | 6 / 37 (16.22%) | 0 / 17 (0.00%) | |
| occurrences (all) | 7 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 5 / 37 (13.51%) | 3 / 17 (17.65%) | |
| occurrences (all) | 5 | 3 | |
| Infections and infestations | | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 7 / 37 (18.92%) | 1 / 17 (5.88%) | |
| occurrences (all) | 9 | 1 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 24 / 37 (64.86%) | 10 / 17 (58.82%) | |
| occurrences (all) | 62 | 21 | |
| Sinusitis | | | |
| subjects affected / exposed | 5 / 37 (13.51%) | 1 / 17 (5.88%) | |
| occurrences (all) | 5 | 3 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 25 June 2010 | changes in:<br>- eligibility criteria<br>- Decision rules for patients' inclusion to interventional SCIT<br>- Modification in covariates used during statistical analyses |
| 11 March 2011 | addition of new trial site |
| 14 March 2012 | Because of weak recruitment of patients a cost-neutral prolongation of study was performed in agreement with BMBF - Projekträger im DLR<br><br>Changes in defintion of adverse events<br><br>Further trial sites will be involved in order to increase the recruitment rate of patients.<br><br>Addition of one exclusion criterion: according to Leitlinien der Deutschen Gesellschaft Allergologie und klinische Immunologie (DGAKI) |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

In 2013 the manufacturer (Allergopharma Joachim Ganzer KG) announced that rBet v1-FV was no longer available to continue with the trial intervention. For that reason, the recruitment of patients was stopped prematurely.

Notes:

## Online references

http://www.ncbi.nlm.nih.gov/pubmed/27998002

http://www.ncbi.nlm.nih.gov/pubmed/27748994

http://www.ncbi.nlm.nih.gov/pubmed/22527380