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 Klinik für Dermatologie, Venerologie und Allergologie, jan.simon@medizin.uni-leipzig.de
Scientific contact	Regina Treudler, Prof., MD, University Leipzig Klinik für Dermatologie, Venerologie und Allergologie, 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 Units: Subjects			
positive	55		
negative	1		
total IgE at BL Units: kU/L median inter-quartile range (Q1-Q3)	--		
specific IgF ab Bet v 1 Units: kU/L at BL median inter-quartile range (Q1-Q3)	--		
specific IgE ab Gly m 4 Units: kU/L at BL median inter-quartile range (Q1-Q3)	--		
BMI Units: kg/m²			
arithmetic mean 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: 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: experimental arm	
Reporting group title	placebo injections
Reporting group description: 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: - eligibility criteria - Decision rules for patients' inclusion to interventional SCIT - 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 Changes in defintion of adverse events Further trial sites will be involved in order to increase the recruitment rate of patients. 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