Trial Synopsis

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 rBet v1-FV on Bet v 1 associated soy allergy

Birch Associated Soy Allergy and Immuno-Therapy
(BASALIT)

Protocol: Final 2.0/2009-12-10 incl. amendments

Name of Active Substance:
rBetv1-FV
(recombinant Betv1-Folding Variant)

Indication / Diagnosis:
Birch Associated Soy Allergy

Phase of Development:
Phase 2b

EudraCT-Number: 2009-011737-27

Registry-Number - CCT: ISRCTN67316358

Date of version: 2015-07-13
Version of report: final 1.0

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Biometry/ Project Management
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Date of first enrolment: 2010-02-03
Date of last completed: 2014-07-18

Signatures

With their signatures, the signing authors agree with the contents of presented report. The presented clinical trial was performed according to the principles of the Declaration of Helsinki, Good Clinical Practice and according the applicable legal requirements.

Coordinating investigator	Regina Treudler, Prof. Dr.	13.7.2015 Date
Legal representative of the sponsor and coordinating investigator	Jan C. Simon, Prof. Dr.	13.7.2015 Date
Biometry	Annegret Franke, Dr.	13.7.2015 Date
Project Management	Anett Schmiedeknecht, Dr.	14.07.2015 Date

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1 Name of the sponsor

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Authorised representative of the sponsor:
Prof. Dr. Jan C. Simon

2 Name of active substance

Recombinant Bet v1-Folding Variant (rBetv1-FV) - not approved

3 Individual trial table

not applicable

4 Title of Study

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 rBet v1-FV on Bet v1 associated soy allergy (Birch Associated Soy Allergy and Immuno-Therapy, BASALIT)

Protocol: Final 2.0/2009-12-10 incl. amendments

There have been three amendments to the clinical trial:

No.	Favourable opinion by ethics committee	Authorisation by competent authority	Contents
01 2010-06-25	2010-07-23	2010-07-21	• Change of investigators • Changes in decision rules for patients' inclusion to interventional SCIT • Specification of eligibility criteria • Procedural changes regarding DBPCFC
02 2011-03-11	2011-04-05	n.a.	• Addition of trial site
03 2012-03-06	2012-05-08	2012-04-16	• Addition of trial site • Change in duration of trial (prolongation) • Change of AE definition

Table 1: dates of approval and contents of amendment during trial implementation

5 Investigators	6 Study centre(s)

The list of investigators and study centres is given in the appendix (chapter 20.1)

7 Publications

Treudler R, Franke A, Kramer S, Simon JC.
How to standardize DBPC food challenge (FC): Experiences from the initiation of a multi-centre trial on the determination of threshold levels in soy allergy (BASALIT-study) Abstractband der Tagung der European Academy for Allergy and Clinical Immunology, London 2010

Treudler R, Kramer S, Kleine-Tebbe J, Simon JC.
Steigende Popularität von Sojaprodukten: Wie werden Birkenpollenallergiker richtig beraten? Allergo Journal 2011;19:243-250

Treudler R.
Pollenassoziierte Nahrungsmittelallergie: Hilft eine spezifische Immuntherapie?
MedReport 2012;36 (5):6

Treudler R, Simon JC.
Schwere Sojaallergie bei Erwachsenen: Hilft eine spezifische Immuntherapie? Hautarzt 2012;63(4):307-314

Treudler R, Franke A, Schmiedeknecht A, Holzhauser T, Vieths St , Worm M, Biedermann T, Werfel T, Jappe U, Ballmer-Weber B, Brehler R, Kleinheinz A, Bauer A, Schmitt J, Brüning H, Kleine-Tebbe J, Rueff F, Ring J, Saloga J, Schäkel K, Merk H, Simon JC
Double blind placebo controlled food challenge (DBPCFC) with soy in a multicentre setting: First data of the BASALIT trial Abstractband der Tagung der European Academy for Allergy and Clinical Immunology, Kopenhagen 2014

Felix Husslik, Kay-Martin Hanschmann, Ariane Krämer, Christian Seutter von Loetzen, Kristian Schweimer, Iris Bellinghausen, Regina Treudler, Jan C. Simon, Lothar Vogel, Elke Völker, Stefanie Randow, Andreas Reuter, Paul Rösch, Stefan Vieths, Thomas Holzhauser, Dirk Schiller
Folded or not? Tracking Bet v 1 conformation in recombinant allergen preparations PLOS ONE in press

Treudler R, Franke A, Schmiedeknecht A, Ballmer-Weber B.K., Worm M, Werfel T, Biedermann T, Jappe U, Schmitt J, Brehler R, Kleinheinz A, Brüning H, Kleine-Tebbe J, Rueff F, Ring J, Saloga J, Schäkel K, Merk H, Holzhauser T, Vieths St and Simon JC
Standardization of double blind placebo controlled food challenge with soy within a multicentre trial. Allergy, in final preparation

8 Studied period (years)

Date of first enrolment: 2010-02-03 (FPFV)
Date of last completed: 2014-07-18 (LPLV)

9 Phase of development

The BASALIT trial is a phase 2b trial.

10 Objectives

The BASALIT trial investigated primarily the effect of the study intervention (rBetv1-FV versus placebo) on the lowest observed adverse effect level (LOAEL) of objective and/or subjective symptoms of patients in a double blind placebo controlled food challenge (DBPCFC).
In addition, the impact of the intervention on

- sensitizations to birch and soy,
- sensitizations to other birch associated food allergens (apple, carrot, celeriac, cherry, hazel),
- food allergy-related quality of life (Flokstra de Blok et al. 2009),

were analysed.

11 Methodology

The BASALIT trial, a double blind, placebo-controlled, randomised multi-centre, two-armed therapy trial of phase 2b, was designed to evaluate the therapeutic benefit of a therapy with rBet v1-FV.
Patients were randomised in a 2:1 ratio in favour of the verum arm (rBetv1-FV). For the analyses of the clinical endpoints, patients underwent several allergological tests, all of them perfomed in a standardized manner according to current position papers. The tests included questionnaires, skin prick tests, blood draws for *in vitro* tests and oral provocation tests with soy-containing or placebo meals.
Confidential safety analyses and reports to the independent DMC were provided once a year regarding safety endpoints only.

12 Number of patients (planned and analysed)

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. Based on previous clinical experiences (Ballmer-Weber et al. 2007) only a small proportion of patients was expected to comply with criteria of inclusion for the intervention. It was planned to analyse data of 84 patients (56 verum-treated, 28 placebo-treated). Because of potential dropouts, 97 patients should be included for the intervention.

During the course of this clinical trial 196 patients were recruited in 16 trial centres. The first patient was recruited at 2010-02-03, the end of the study for the last patient was at 2014-07-18.
At the end of April 2013 the manufacturer of the investigational product rBet v1-FV (Allergopharma Joachim Ganzer KG) announced to the sponsor that rBet v1-FV will not be available for the last potential intervention period. For that reason, the recruitment of patients was stopped prematurely.

For further information regarding the number of patients analysed see also the CONSORT flow chart in appendix 20.4.

13 Diagnosis and main criteria for inclusion

Patients qualifying for experimental intervention must meet ALL of the following criteria:

1. Male or female adult patients aged 18 – 65 years inclusive, legally competent
2. Written informed consent
3. Suspected birch pollinosis
4. Sensitization to birch pollen as demonstrated by positive SPT to birch (wheal ≥ 3 mm)

5. Specific IgE for Bet v 1 (≥ ImmunoCAP class 3) and Gly m4 (≥ ImmunoCAP class 2) both to be determined in the laboratory at trial site
6. Clinical relevance of Gly m 4 sensitization as demonstrated by positive DBPCFC to soy proteins

14 Test product, dose and mode of administration, batch number

Investigational Product, Active drug: rBet v1-FV
Vials with the following concentrations were applied in this clinical trial:
Strength A (5 µg/ml)
Strength B (100 µg/ml)
Comparative compound, Placebo: sterile Aluminium-hydroxide suspension.

The trial medication as well as the comparative compound were manufactured by Allergopharma Joachim Ganzer KG according to the revised GMP Guidelines of the WHO. The production and purification process of the investigational preparation used in this clinical trial is described in the Investigational Medical Product Monograph rBet v1-FV to guarantee pharmaceutical quality.

Subcutaneous injections should be and were given in the upper arm.

Administration of study drug - see chapter 15 and 5.4 in trial protocol for more details.

15 Duration of treatment

All patients were treated with either placebo or the recombinant birch pollen allergen extract for 1 year. The **double-blind, placebo-controlled treatment (intervention) phase** was divided into three phases:

- up-dosing
- prolongation
- maintenance.

Dosing regimen:

a) Up-dosing:
1x/ week during 7 weeks, dosage 0.75 µg – 80 µg

b) Prolongation:
intervals: 1, 2 and 4 weeks during 7 weeks, dosage 80 µg

c) Maintenance:
every 4 weeks during 38 weeks, dosage 80 µg

See chapter 3.4 in trial protocol for more details.

16 Reference therapy, dose and mode of administration, batch number

See chapter 14 – Comparative compound, Placebo

17 Criteria of evaluation

17.1 Efficacy

According to protocol the study focused on two primary endpoints without hierarchy. Both endpoints resulted from the DBPCFC procedure and present the cumulative soy level thresholds, which induced either clinically objective ($LOAEL_{obj}$) or subjective symptoms

($LOAEL_{subj}$) in patients during the DBPCFC procedure. For both LOAELs, post-treatment measures after the ingestion of soy-containing meals prior to SCIT were considered for confirmatory analysis.

Secondary endpoints were:

- Overall rates for the occurrence of any objective symptom pre / post SCIT per group,
- (Dose level-adjusted) cumulative VAS sums (from all 8 subjective symptoms regularly assessed) at the lowest dose level with subjective symptoms,
- Reduction in skin prick test reaction to soy post intervention,
- specific IgE-levels for Bet v1, Gly m4 and relevant cross allergens (apple-Mal d1, carrot-Dau c1, cherry-Pru av1, celeriac-Api g1, hazel-Cor a1;as measured in kU/l),
- specific IgG_4-levels for Bet v1, Gly m4 and relevant cross allergens,
- FAQLQ-AD questionnaire.

17.2 Safety

Safety issues were analysed by

- (Serious) adverse events
- Abnormal lab values and
- Tolerability of treatment.

The cumulative doses of study medication (verum resp. placebo) applied during the course of the trial were [mean (standard deviation)]: 939.19 (336.46) µg in the verum arm and 956.57 (163.60) µg in the placebo arm, applied in 20.6 (4.9) resp. 21.1 (3.8) visits per patient. These results indicate successful randomisation and blinding procedures and well comparable treatment groups.

18 Statistical methods/ procedures of analysis

The confirmatory analysis was done within the Full Analysis Set (n=54 patients with at least a single injection of study medication (acc. to statistical analysis plan - SAP). Additional secondary analyses were performed within the Per Protocol Set (n=45 patients w/o pre-defined major protocol violations acc. SAP).

According to protocol, both primary endpoints were analysed separately using nonparametric analysis of covariance. SAS macros developed within the DFG-sponsored project "Ordinal data") and provided by the University of Göttingen were applied to compare the treatments (with resp. w/o verum SCIT) based on the LOAELs post SCIT (as ordinal response variable) with the respective pre-treatment LOAEL but no further covariates. Like justified within the SAP (and based on detailed analyses of the laboratory data - comprised in a laboratory analysis report which was acknowledged and signed by the coordinating investigators of the trial) the theoretically identified further covariates stated within the study protocol needed no further consideration due to stable gly m4 measures over the time and between the different batches of soy flour applied in the trial.

The global significance level of the clinical trial was limited to α=5%. Because of the two primary endpoints the test-wise α-levels was adjusted for multiplicity according to the Bonferroni-Holm method (Holm 1979). The smaller observed p-values $p_{(1)}$ (corresponding with either $LOAEL_{obj}$ or $LOAEL_{subj}$) had to be lower than/ equal to $\alpha_{(1)}=\alpha_{global}/2$ (i.e. $p_{(1)} \leq 0.025$) to identify a significant treatment effect in at least one LOAEL. For the larger 2nd p value $p_{(2)} \leq \alpha_{(2)}=0.05$ had to be found to establish significance in both endpoints.

For secondary endpoints exact Fisher test or Chi^2-Test for rates, Mann-Whitney U test/ Wilcoxon's matched pairs test test for independent/ paired ordinal (or skew symmetric) data, and repeated-measures ANCOVA for specific IgE and IgG_4 values were used to compare between-groups differences were applied.

19 Summary/ Conclusions

19.1 Results regarding efficacy

Mean age of the study population was 38 (SD 13) years; 64% were female. More than a third had experiences with former hyposensitization. Satisfying baseline comparability between groups was observed in all population characteristics and endpoints (see also appendix 0ff where some additional population characteristics are given).
The control-FC after SCIT could only be completed for n=48 patients of the respective N=54. Therefore, a missing value (MV) imputation assuming unchanged LOAEL compared to baseline was done for confirmatory analysis. Both LOAELs with and without MV-imputations were given in table 2.

		Group allocation	
		Verum: rBet V1	Placebo
LOAEL obj: soy protein [g] consumed at lowest dose with obj. S., TE soy meal (**with MV-imputation**)	N	37	17
	Mean (SD)	18.55 (9.75)	14.94 (10.97)
	Median [IQR]	24.70 [9.70; 24.70]	24.70 [2.20; 24.70]
LOAEL obj: soy protein [g] consumed at lowest dose with obj. S., EoT soy meal	valid N	**33**	**15**
	Mean (SD)	20.43 (8.54)	15.14 (10.91)
	Median [IQR]	24.70 [24.70; 24.70]	24.70 [2.20; 24.70]
LOAEL subj: soy protein [g] consumed at lowest sS dose (max or sum crit.), TE soy meal, (**with MV-imputation**)	N	37	17
	mean	10.50 (11.39)	11.13 (11.72)
	Median [IQR]	4.7048 [0.70; 24.70]	2.20 [2.20; 24.70]
LOAEL subj: soy protein [g] consumed at lowest sS dose (max or sum crit.), EoT soy meal	valid N	33	15
	Mean (SD)	11.54 (11.63)	12.32 (12.01)
	Median [IQR]	4.7048 [0.70; 24.70]	2.20 [2.20; 24.70]

Table 2: descriptive characteristics of the primary endpoints in both treatment arms

The nonparametric analyses within the FAS regarding the simple between-groups factor for $LOAEL_{obj}$ resulted in a p value=0.237 and for $LOAEL_{subj}$ in p=0.611.
No significant beneficial effect of the study intervention on soy tolerability could be shown with the BASALIT trial, at least with reduced number of patients (about 55% of the sample size planned) who could be recruited until the trial had to be stopped prematurely since no medications could be further provided by the manufacturer.
Within the PPS (n=45) non-significant p values of p=0.081 for $LOAEL_{obj}$ and p=0.785 for $LOAEL_{subj}$ were found.

Secondary endpoints:

- With proportions of 8/33 (verum intervention) and 7/15 Fisher's exact test resulted in p=0.180 for in overall occurrence rates objective symptom after SCIT (pre treatment rates 81% vs. 77%).
- The Mann-Whitney U test for (dose level-adjusted) cumulative VAS sums after SCIT revealed no significant group difference with p=0.657.
- Reduction in skin prick test reaction to soy was observed in 16/27 after verum and 5/16 patients after placebo injections (Fisher's exact test: p=0.116). For the remaining patients comparability from baseline to end of treatment results could not be assumed since the originally planned solution of a predefined standardised soy drink was not available during the total course of the trial.
- repeated-measures ANCOVA for specific IgE:

  - For Bet v 1: non-significant results for main factor "treatment" and course x group interaction (p=0.643 resp. p=0.147)
  - For Gly m 4: non-significant results for main factor "treatment" and course x group interaction (p=0.487 resp. p=0.357)
- repeated-measures ANCOVA for specific IgG_4
  - For Bet v 1: (borderline-)significant results for main factor "treatment" and course x group interaction (p=0.054 resp. p=0.045)
  - For Gly m 4: non-significant results for main factor "treatment" and course x group interaction (p=0.037 resp p=0.044)
- Change of FAQLQ-AD questionnaire from pre to post treatment measures: non-significant group difference with p=0.968

19.2 Results regarding safety

During the course of trial 531 AE in 69 patients were observed, of whom 391 events (in 61 participants) were unrelated to any study procedure.
In summary, 140 AE (26.4%) were assessed to be possibly related to any study procedure (including all 141 patients screened for possible randomisation but not fulfilling the criteria for inclusion resp. not started with the intervention). Six AE were possibly related to the skin prick test and 19 AE to the food challenge procedure while for 119 AE a possible causal relationship to the injections were assessed (with multiple causalities given in 3 AEs). Median [IQR] numbers of AE per patient were 6 [1;9] resp. 4 [3;7] within the verum resp. placebo arm.

Table 3 gives an overview regarding the potential relationship of AE to the study procedures. Three events were not clearly assessed to be associated with one study procedure (marked in *italics*) in spite of queries.

	frequency	per cent
unrelated to all 3 IMPs	391	73,6
to Inj.	117	22,0
to FC	16	3,0
to FC and Inj.	*1*	*,2*
to SPT	4	,8
to SPT and FC	*1*	*,2*
to all 3 IMPs	*1*	*,2*
Total	531	100,0

Table 3: AE and their relationship to the study procedures

In total, 14 serious AE (2.6%) were documented, of whom 2 (0.4%) were assessed to be possibly causally related to the DBPCFC procedure (with preferred term of MedDRA "*Hypersensitivity*"). Criterion for seriousness in those events was short-term hospitalisation (rather for further observation than for treatment). No deaths occurred during the course of the trial. In comparison to the last Annual Safety Report (cutoff date 2014-0-07) no further serious SAE were documented.
In a single patient of the verum and 3 of the placebo arm abnormal lab values post treatment were found.
The portions [mean(SD)] of well tolerated study interventions were 82 (19) % of verum and 78 (16) % of placebo injections.

19.3 Conclusions

In summary, in our investigational group, we were not able to demonstrate clinical efficacy of one year specific immunotherapy with the folded variant of recombinant Bet v 1 extract on birch associated soy allergy.

One major problem we had to face was that the trial had to be stopped prematurely due to logistic reasons since no medications could be further provided by the manufacturer. Only 56 participants of 97 planned could be randomized (and only n=54 treated), i.e. about 55% of the originally intended sample size.
With regard to the per protocol analyses of primary endpoints (based on n=45 patients without major protocol violations) at least a tendency toward group differences with p=0.08 for $LOAEL_{obj}$ were found (but clearly non-significant differences for $LOAEL_{subj}$). This result seems to be more promising regarding the study outcomes if the planned number of patients could have been recruited and treated.
The power for the $LOAEL_{obj}$ between-groups difference observed in the FAS (assuming the pooled heterogeneity and the originally planned sample size of 97 patients with a randomisation ratio 2:1 in favour of the verum arm) can be estimated to be $1-\beta \approx 65\%$ for $\alpha=0.05$ (resp. 54% with $\alpha=0.025$ if adjusted for 2 primary endpoints). Using the between-groups difference and pooled standard deviation within the PPS $1-\beta \approx 75\%$ for $\alpha=0.05$ (resp. 66%) were found. With the best/ worst-case groups-related observations (regarding between-groups difference, heterogeneity and $LOAEL_{obj}$ as exclusive primary endpoint) used, sample sizes of N=54+27=81/ N=107+55=162 patients would have been necessary to provide significant test results given that the future patients would have been similar to those recruited.
In vitro investigations showed a clear response of subjects with regard to main birch allergen Bet v1, where IgG_4 increase was rather strong. In contrast, only a minor IgG_4 response was seen on the major soy allergen Gly m 4. This might - beside the reduced sample size – be another possible explanation of the rather small clinical effect within the full analysis population.
Nevertheless in some subjects, the therapeutic intervention showed a beneficial effect on birch associated soy allergy – like also indicated by the more promising results within the per-protocol population. It might be assumed that a subgroup of patients may exist who could benefit from this therapy. Further detailed investigations will focus on this aspect.

The series of rBet v 1 injections applied in the trial can be regarded as safe intervention. The data evaluation of the BASALIT trial does not reveal any additional relevant risks or risk aspects compared to the product information or medical publications and literature and seemed without anynegative influence on the participant's safety.

Another most relevant aspect of the BASALIT trial was that a standardized performance and evaluation of double blind placebo controlled food challenges was mandantory but neither harmonized procedures and evaluation criteria nor other empirical data of relevant sample sizes exist to date. The procedures and criteria that had been developed by our study group will be published and discussed within the scientific community to support the development of a consensus position regarding the performance and evaluation of outcomes in food allergy related hyposensitizations.

20 Appendix

20.1 Table of investigators and study centres

1	Prof. Dr. med. Jan C. Simon (LKP acc. to german drug law), Prof. Dr. med. Regina Treudler (PI) Klinik für Dermatologie, Venerologie und Allergologie Universität Leipzig Philipp-Rosenthal-Str. 23 04103 Leipzig (03 41) 97 - 1 86 00
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9	Prof. Dr. med. Joachim Saloga Universitäts-Hautklinik Mainz Johannes-Gutenberg Universität Langenbeckstr. 1 55131 Mainz Tel.: 06131-17-3751
10	Prof. Dr. med. Margitta Worm Allergie- Centrum- Charité Klinik für Dermatologie, Venerologie und Allergologie Charité - Universitätsmedizin Berlin Luisenstraße 2-5 10117 Berlin Tel. +49 30 450 518 105
11	Prof. Dr. med. Hans F. Merk Klinik für Dermatologie und Allergologie Technische Hochschule Rheinisch-Westfälische Aachen Pauwelsstraße 30 52074 Aachen Tel.: +49 241 80 88331
12	Prof. Dr. med. Uta Jappe Forschungszentrum Borstel Leibniz-Zentrum für Medizin und Biowissenschaften Parkallee 1-40 23845 Borstel Tel: 04537 - 188 – 300
13	Prof. Dr. med. Knut Schäkel Hautklinik der Ruprecht-Karls-Universität Heidelberg Voßstr.2 69115 Heidelberg Tel. : +49 6221 56-8447/ 8445
14	Prof. Dr. med Tilo Biedermann Forschungsgruppe Allergie und Immunologie der Hautklinik Eberhard-Karls-Universität Tübingen Liebermeisterstr. 25 72076 Tübingen Tel.: 07071-2980836
15	Dr. med. Harald Brüning Tagesklinik für Allergie und Hautkrankheiten Schönberger Str. 72-74 24148 Kiel Tel.: 0431-726065
16	Dr. med. Andreas Kleinheinz Elbe Klinikum Buxtehude Dermatologisches Zentrum Am Krankenhaus 1 21614 Buxtehude Tel.: 04161-7036202

Table 4: investigators and study centres of the BASALIT-trial

20.2 Additional Information on baseline characteristics/ covariates

In the following section population's characteristics within the FAS are shown including both non-randomized and randomized patients.
Within the column "total" the BL characteristics of the screening population are to be found. Furthermore, a comparison of randomized groups is possible using the resp. columns referring to the treatment arms.

		Group allocation			total
		screened but not randomized	Verum: rBet V1	Placebo	
Age at 1st contact (screening) / years	N total/ N valid	N=139 / 136	N=38 / 38	N=18 / 18	N=195 / 192
	MW (SD)	38,2 (12,2)	37,8 (14.6)	37,4 (13.8)	38,1 (12.8)

Table 5: Patients' characteristics I

		Group allocation						total	
		screened but not randomized		Verum: rBet V1		Placebo			
		%	N	%	N	%	N	%	N
sex[1]	female	62,6%	87	65,8%	25	66,7%	12	63,6%	124
hyposensitization performed earlier[1]	yes	33,8%	47	34,2%	13	44,4%	8	34,9%	68

Table 6: Patients' characteristics II

		Group allocation						total	
		screened but not randomized		Verum: rBet V1		Placebo			
		%	N	%	N	%	N	%	N
Allergic diseases[1]	as many as one	38,1%	53	34,2%	13	38,9%	7	37,4%	73
	more than one (from max.3)	59,7%	83	65,8%	25	61,1%	11	61,0%	119
further allergies[1]	as many as 2	44,6%	62	34,2%	13	55,6%	10	43,6%	85
	3-6	53,2%	74	65,8%	25	44,4%	8	54,9%	107
Food allergies[1]	none	2,9%	4					2,1%	4
	against 1-4 foods	19,4%	27	7,9%	3	22,2%	4	17,4%	34
	against 5-10 foods	55,4%	77	47,4%	18	44,4%	8	52,8%	103
	against >10 foods	20,1%	28	44,7%	17	33,3%	6	26,2%	51

Table 7: Patients' characteristics III: anamnesis

[1] Three non-randomized patients without data

		Group allocation						total	
		screened but not randomized		Verum: rBet V1		Placebo			
		%	N	%	N	%	N	%	N
SPT results, negative control[2]	negative	94,2%	131	100,0%	38	100,0%	18	95,9%	187
SPT results, positive control[2]	positive	95,0%	132	94,7%	36	100,0%	18	95,4%	186
evaluation SPT results, birch[2]	positive	94,2%	131	97,4%	37	100,0%	18	95,4%	186
evaluation SPT results, drinks containing soy[2]	positive	79,1%	110	94,7%	36	88,9%	16	83,1%	162

Table 8: Rates of SPT reactions at baseline for selective allergens

		Group allocation						total	
		screened but not randomized		Verum: rBet V1		Placebo			
		%	N	%	N	%	N	%	N
CAP-Class specific IgE for Bet v1[3]	CAP 0	2,2%	3					1,5%	3
	CAP 1	0,7%	1					0,5%	1
	CAP 2	3,6%	5					2,6%	5
	CAP 3	25,2%	35	31,6%	12	27,8%	5	26,7%	52
	CAP 4	32,4%	45	34,2%	13	44,4%	8	33,8%	66
	CAP 5	23,0%	32	21,1%	8	16,7%	3	22,1%	43
	CAP 6	8,6%	12	13,2%	5	11,1%	2	9,7%	19
CAP-Class specific IgE for Gly m4[3]	CAP 0	5,0%	7					3,6%	7
	CAP 1	5,8%	8					4,1%	8
	CAP 2	25,2%	35	21,1%	8	16,7%	3	23,6%	46
	CAP 3	41,7%	58	52,6%	20	66,7%	12	46,2%	90
	CAP 4	14,4%	20	23,7%	9	11,1%	2	15,9%	31
	CAP 5	2,9%	4	2,6%	1	5,6%	1	3,1%	6
	CAP 6	0,7%	1					0,5%	1

Table 9: CAP classes regarding specific IgE for Bet v 1/ Gly m 4 at baseline

		Group allocation			
		screened but not randomized	Verum: rBet V1	Placebo	total
LOAEL obj: soy protein [g] consumed at lowest dose with obj. S., BL soy meal	N	82	38	18	138
	Mean (SD)	20.68 (8.96)	9.44 (9.78)	7.47 (9.77)	15.86 (10.94)
	Median [IQR]	24.70 [24.70; 24.70]	4.70 [0.70; 24.70]	2.20 [0.20; 9.70]	24.70 [2.20; 24.70]

[2] Four non-randomized patients without data
[3] Six non-randomized patients without data

LOAEL subj: soy protein [g] consumed at lowest sS dose (max or sum crit.), BL soy meal	N	82	38	18	138
	Mean (SD)	16.28 (11.30)	3.31 (5.64)	4.80 (9.19)	11.21 (11.52)
	25%	,7048	,7048	,2048	,7048
	Median [IQR]	24.70 [0.70; 24.70]	2.20 [0.70; 4.70]	0.70 [0.20; 2.20]	4.70 (0.70; 24.70)

Table 10: Baseline values of LOAELobj and LOAELsubj after soy meals (covariates in confirmatory analysis)

20.3 Concomitant diseases and medications

60 of 195 patients reported no concomitant disease[4]. The number of concomitant diseases/ medical history (MH) per patient varied between 0 und 11. Most common preferred terms reported were asthma (38x), dermatitis atopic (28x), hyperternsion (27x), conjunctivitis allergic (17x), hyperthyriodism (14x) and osteoarthritis (11x).

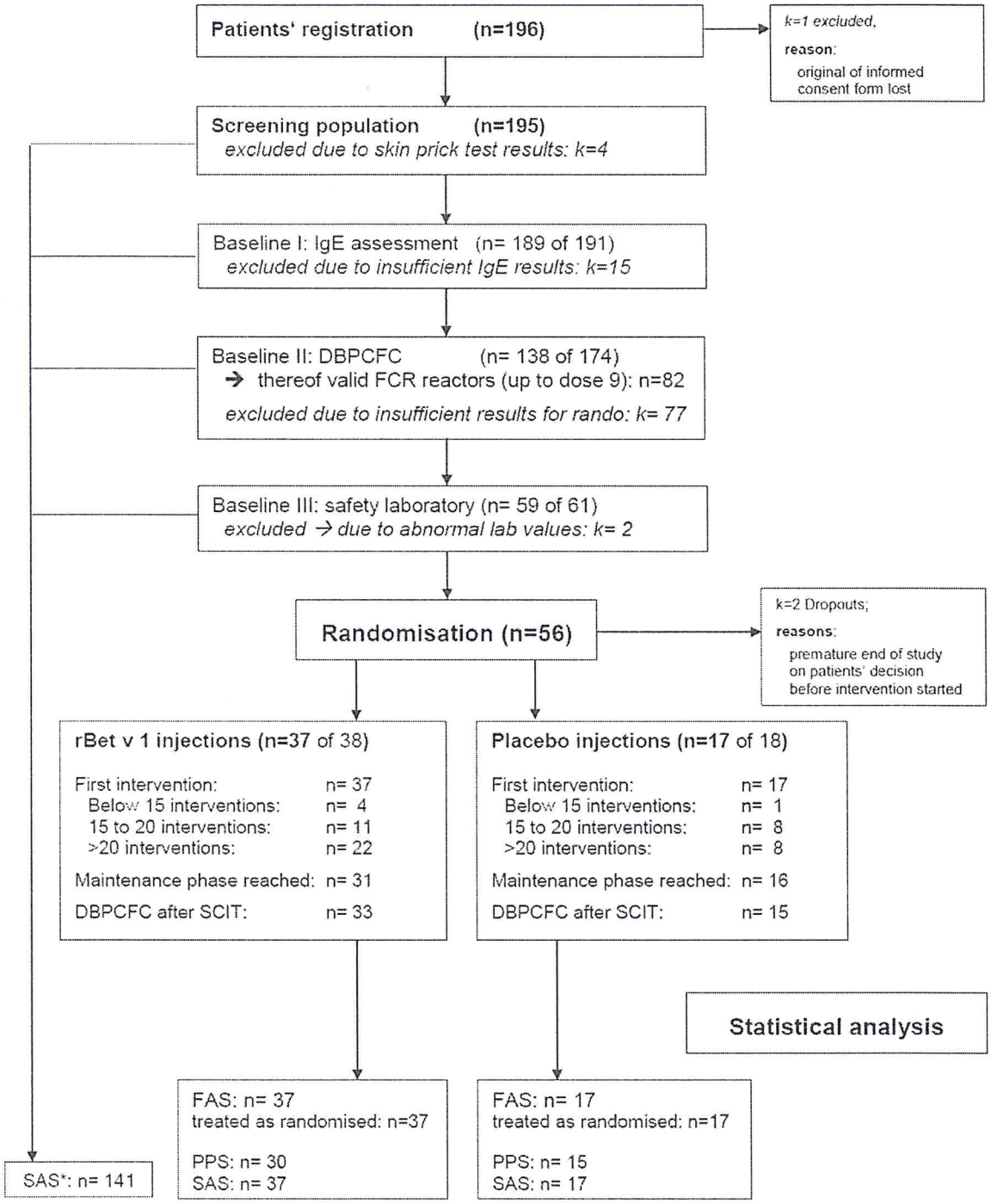
135 patients reported on concomitant medications (CM) because of their medical history with a range from none to 14 per patient.

		Group allocation						total	
		screened but not randomized		Verum: rBet V1		Placebo			
		%	N	%	N	%	N	%	N
number of concomitant diseases	1	38,7%	36	21,4%	6	57,1%	8	37,0%	50
	2	25,8%	24	21,4%	6	21,4%	3	24,4%	33
	3	16,1%	15	28,6%	8	14,3%	2	18,5%	25
	4	8,6%	8	10,7%	3	7,1%	1	8,9%	12
	5	4,3%	4	10,7%	3			5,2%	7
	6	4,3%	4					3,0%	4
	7	2,2%	2					1,5%	2
	8			3,6%	1			0,7%	1
	11			3,6%	1			0,7%	1
Number of medications due to MH, cumulative p.pt.	1	40,0%	36	12,9%	4	28,6%	4	32,6%	44
	2	26,7%	24	9,7%	3			20,0%	27
	3	14,4%	13	9,7%	3	21,4%	3	14,1%	19
	4	5,6%	5	3,2%	1	21,4%	3	6,7%	9
	5	6,7%	6	16,1%	5	14,3%	2	9,6%	13
	6	2,2%	2	19,4%	6	7,1%	1	6,7%	9
	7	3,3%	3	3,2%	1			3,0%	4
	8			3,2%	1	7,1%	1	1,5%	2
	9 to 14	*1,1%*	*1*	*22.6%*	*7*			*5.8%*	*8*

Table 11: Concomitant diseases and -medications

[4] Nevertheless, P14015 reported food allergy and P16010 atopic exzema (documented elsewhere within the CRF, too, and P16009 elevated liver encymes.

20.4 CONSORT Flow Chart



20.5 References

See trial protocol