Statistical Analysis Plan
Study: 1847/MAY

TITLE: SAFETY AND DOSE FINDING STUDY OF BM32 IN SUBJECTS SUFFERING FROM GRASS POLLEN ALLERGY

Protocol-No.: CS-BM32-002 (HCR: 1847/BIO)

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1 List of abbreviations and acronyms

AE	Adverse event
BMI	Body mass index
CDISC	Clinical Data Interchange Standard Consortium
CDM	Clinical Data Manager
CDMS	Clinical Data Management System
CRF	Case report form
CS/ CNS	Clinical significant/ not clinical significant
FEV1	Forced expiratory volume in 1 second
FPI	First patient in (enrolled) in study
FVC	Forced Vital capacity
GCP	Good Clinical Practice
HCR	Harrison Clinical Research
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
MedDRA	Medical Dictionary for Regulatory Activities
ODM	Operational data model
OSS	Other symptom score
PT	Preferred term
QC	Quality Control
SA	Safety analysis
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
SOP	Standard Operating Procedure
SS	Safety set
SSL	secured socket-layer
TLG	Tables, listings, figures
TNSS	Total nasal symptom score
TNNSS	Total non-nasal symptom score
TOSS	Total ocular symptom score
VCC	Vienna Challenge Chamber
WHO DD	World Health Organization Drug Dictionary
XML	eXtensible Markup Language

2 Purpose

This statistical analysis plan specifies in more detail the planned statistical analyses described in the protocol. Furthermore, special considerations or deviations (that are not necessary to be included in a protocol amendment) are documented in this plan.

3 Methods

Raw data listings, summary tables, graphs and statistical tests will be generated by means of the program SAS Vers. 9.1. Special non-parametric tests will be done with Proc-StatXact 9® from ©Cytel Software, which is completely linked to SAS. Figures may be done with MS-Excel, if deemed necessary.

Data from the Marvin database will be exported and downloaded from the Marvin Web interface via a secured socket-layer (SSL) connection from the host server to the HCR file server. The raw data is in CDISC ODM XML Vers. 1.2 compliant format (see http://www.cdisc.org/models/odm/v1.2.1/index.html for details).
This ODM XML file will be imported into SAS via the SAS procedure 'proc CDISC'.

Appropriate SAS programs will be prepared and validated according to HCR SOPs.

4 Study documents

The following study documents are used for the preparation of the SAP:

- Study Protocol (Version 1.0, 5 September 2011)
- Data Management Plan (Version 1.0, 1 February 2012)
- Paper CRF (Version 3.0, 4 October 2011)
- Annotated CRF (Version 2.0, 29 February 2012)

5 Presentation of data

5.1 General

A fully integrated clinical study report according to the ICH guideline E3 will be prepared. As part of this, all raw data will be listed in section 16.2 of the clinical study report. Additional text entries in the CRF, which did not clearly belong to pre-defined CRF and database fields, will be reviewed for relevance. Entries deemed as not relevant will not be entered into the database and therefore not listed. Summary tables will be provided for all parameters of interest and presented in section 14 of the clinical study report. Special statistical considerations including this SAP and relevant statistical output will be presented in section 16.1.9 of the clinical study report. SAS Output for relevant statistical tests will be given there.

- All tables and data listings will be presented in Landscape Orientation, unless presented as part of the text in a CSR.
- Figures will be presented in Landscape Orientation, unless Portrait Orientation suggests that the information presented is easier to interpret.
- Legends will be used for all figures with more than one variable or item displayed.
- Figures will be in black and white (no colour) unless colours add value to the clarity and readability of a figure. Lines should be wide enough to see the line after being copied.
- Specialized text styles, such as bolding, italics, borders, shading, superscripted and subscripted text will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.

- Only standard keyboard characters should be used in tables and data listings.
- Special characters, such as non-printable control characters, printer specific, or font specific characters, will not be used on a table, figure, or data listing.
- Hexadecimal character representations are allowed (e.g., µ, a, ß).
- All titles will be left-aligned on a page. The ICH numbering convention is to be used for all TLGs.
- All footnotes will be left justified and at the bottom of a page. Footnotes should be used sparingly and must add value to the table, figure, or data listing.
- All date values will be presented as SAS date9. (e.g., 29AUG2001) format.
- All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds should only be reported if they were measured as part of the study.

Empty data fields in the CRF are generally treated as missing values.

5.2 Layout of tables, listings and figures

5.2.1 Notation of treatment groups

The following notation of treatment groups will be used throughout the report:

Full notation (as used in the study protocol)	**Notation as used throughout all tables, listings and figures**
• Concentration BM32 (total sum of all 4 APIs BM321, BM322, BM325, BM326) [mg/mL]: 0.1 mg/mL • Dose of individual BM32 API per 400µL injection: 10 µg	**BM32/S1**
• Concentration BM32 (total sum of all 4 APIs BM321, BM322, BM325, BM326) [mg/mL]: mL 0.2 mg/mL • Dose of individual BM32 API per 400µL injection: 20 µg	**BM32/S2**
• Concentration BM32 (total sum of all 4 APIs BM321, BM322, BM325, BM326) [mg/mL]: 0.4 mg/mL • Dose of individual BM32 API per 400µL injection: 40 µg	**BM32/S3**
• Concentration BM32 (total sum of all 4 APIs BM321, BM322, BM325, BM326) [mg/mL]: 0.0 mg/mL • Dose of individual BM32 API per 400µL injection: 0 µg	**Placebo**

5.3 Visit terminology

VISIT	NOTATION AS USED THROUGHOUT ALL TABLES, LISTINGS AND FIGURES	TREATMENT PERIOD
Visit 1 – Pre-Screening	**Visit 1**	**Screening**
Visit 2 – SPT &Immunology	**Visit 2**	**Baseline**
Visit 3 – VCC Baseline	**Visit 3**	
Visit 3: Pre-Challenge	**as shown in left column**	
Visit 3: 0:15		
Visit 3: 0:30		
Visit 3: 0:45		
Visit 3: 1:00		
Visit 3: 1:15		
Visit 3: 1:30		
Visit 3: 1:45		
Visit 3: 2:00		
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Visit 3: 4:45		
Visit 3: 5:00		
Visit 3: 5:15		
Visit 3: 5:30		
Visit 3: 5:45		
Visit 3: 6:00		
Visit 3: Post-Challenge		
Visit 4 – Injection 1	**Visit 4**	**Treatment period**
Visit 5 – Injection 2	**Visit 5**	
Visit 6 – Injection 3	**Visit 6**	
Visit 7 – SPT & Immunology	**Visit 7**	**Post-treatment-evaluation**
Visit 8 – VCC	**Visit 8**	
Visit 8: Pre-Challenge	**as shown in left column**	
Visit 8: 0:15		
Visit 8: 0:30		
Visit 8: 0:45		
Visit 8: 1:00		
Visit 8: 1:15		
Visit 8: 1:30		
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Visit 8: 5:00		
Visit 8: 5:15		
Visit 8: 5:30		
Visit 8: 5:45		
Visit 8: 6:00		
Visit 8: Post-Challenge		
Visit 9 – Follow-up	**Visit 9**	**Follow-up**

5.3.1 Descriptive statistical parameters

The following descriptive statistical parameters will be shown in summary tables

- Metrical variables: Mean, Median, SD (Standard deviation), Min, Max, n (Valid cases). For immunogenicity data geometric mean and SD thereof will be presented, too.
- Nominal/ categorical variables: Count and Percentage of category. Percentages for missing values are omitted and do not account for the percent calculation of other categories. Percentages are routinely based on the total category count excluding the missing category if not otherwise mentioned. Percentages showing a rate relative to the total number of subjects in this group are given in special tables (e.g. AE tables). Footnotes will specify the percent basis.

5.3.2 Presentation

5.3.2.1 Summary tables

5.3.2.1.1 Qualitative/ Quantitative variables

Rows: Categories/classes of a specific variable
Columns: Treatment group
Cells: Qualitative variables: Absolute and relative count within each treatment and class
Cells: Quantitative variables: Mean, Median, SD (standard deviation), Min, Max, n (valid cases)

Example: See section 10.1

5.3.2.1.2 Longitudinal data:

Rows: Treatment group
Columns: Time: Visit time points as described above.
Cells: Qualitative variables: Absolute and relative count within each treatment and class
Cells: Quantitative variables: Mean, Median, SD (standard deviation), Min, Max, n (valid cases)

Example: See section 10.2
If necessary, a vertical display as described in 10.3 will be used.

5.3.2.2 Raw data listings

All CRF data will be listed in raw data listings (section 16.2 of clinical report). If not otherwise specified, all data listings will be sorted by subject number and visit/ time point if necessary.
Only in the demographics listing, in addition to these primary keys, the screening number will be shown as 2nd column.

Example: See section 10.8

5.3.3 Questionnaires and Scores

5.3.3.1 Total Nasal Symptom Score (TNSS)

The TNSS consist of four areas - the nasal obstruction, rhinorrhoea, itchy nose and sneezing. Each of them will be scored before the challenge and then every 15 minutes up to 6 hours (Screening) or 6 hours (Visit 8) on a categorical scale from 0 to 3 at the times described in the section 5.3.

Area	**Scale of Symptoms**
Nasal obstruction	0 - 3
Rhinorrhea	0 - 3
Itchy nose	0 - 3
Sneezing	0 – 3
Total **TNSS**	Sum of all 4 symptom categories ranging from 0 to a maximum of 12

The categorical scale of symptoms will be defined as follows:

Code	Specification	Description
0	None	No symptoms of disease
1	Mild	Signs of disease/ symptoms present from time to time, easily being tolerated
2	Moderate	Signs of disease/ symptoms always present, disturbing, but can be tolerated
3	Severe	Signs of disease/ symptoms always present, can hardly be tolerated

The total TNSS Score is the sum of all 4 symptom categories ranging from 0 to a maximum of 12.

5.3.3.2 Total Non-Nasal Symptom Score TNNSS: Total Ocular Symptom Score (TOSS) and Other Symptoms Score (OSS)

Three areas will be evaluated for the Total Ocular Symptoms Score (TOSS):

Area	**Scale of Symptoms**
Watery eyes	0 – 3
Itchy eyes	0 – 3
Red eyes	0 – 3
Total **TOSS**	Sum of all 3 symptom categories ranging from 0 to a maximum of 9

Area	**Scale of Symptoms**
Cough	0 – 3
Itchy throat	0 – 3
Itchy ears	0 – 3
Total **OSS**	Sum of all 3 symptom categories ranging from 0 to a maximum of 9

Both will be scored before the challenge and then every 15 minutes up to 6 hours (screening) or 6 hours (Visit 8) on a categorical scale from 0 to 3.

The categorical scale of symptoms will be defined as follows:

Code	Specification	Description
0	None	No symptoms of disease
1	Mild	Signs of disease/ symptoms present from time to time, easily being tolerated
2	Moderate	Signs of disease/ symptoms always present, disturbing, but can be tolerated
3	Severe	Signs of disease/ symptoms always present, can hardly be tolerated

The **TNNSS** is calculated by the sum of the TOSS and OSS Score.

5.3.3.3 Global Symptom Score (TNSS and TNNSS)

The Global Symptom Score will be calculated from the sum of the Total Nasal Symptom Score (TNSS) and the Total Non-Nasal Symptom Score (TNNSS).

6 Planned Statistical analysis

6.1 Study objectives

6.1.1 Primary Efficacy Objective

To assess the minimum effective dose after three subcutaneous injections of different dose levels of BM32 as compared to placebo. The effects of different dose levels of BM32 compared to placebo are evaluated by the grass pollen-specific Total Nasal Symptom Score (TNSS – nasal obstruction, rhinorrhoea, itchy nose and sneezing) of grass pollen-induced allergic rhinitis provoked by spending 6h in the VCC at screening and 6h in the VCC after the last injection (Visit 8) of the treatment.

6.1.2 Secondary Efficacy Objective(s)

Secondary efficacy objectives are as follows:

1. To evaluate the effects of different dose levels of BM32 compared to placebo by studying the grass pollen-specific Total Non-Nasal Symptom Score (TNNSS), i.e. the Total Ocular Symptom Score (TOSS) (watery eyes, itchy eyes, red eyes) and the Other Symptom Score (OSS) (cough, itchy throat, itchy ears) of grass pollen-induced allergic rhinitis provoked by spending 6h in the VCC at screening and 6h in the VCC after the last injection (Visit 8) of the treatment.
2. To assess the effects of different dose levels of BM32 compared to placebo, by evaluating the Global Symptom Score (Total Nasal Symptom Score (TNSS) and Total Non-Nasal Symptom Score (TNNSS) combined) of grass pollen-induced allergic rhinitis provoked by spending 6h in the VCC at screening and 6h in the VCC after the last injection (Visit 8) of the treatment.
3. To determine the effects of vaccination with BM32 versus placebo on allergen-specific skin responses by titrated skin prick testing (SPT) via measuring wheal areas at screening and at visit 7 and to evaluate the change in the threshold concentration of grass pollen extract necessary to provoke a positive skin reaction (SPT).
4. To evaluate the effects of different dose levels of BM32 compared to placebo by the mean cross-sectional area (MCA) using anterior rhinomanometry (NAR) provoked by spending 6h in the VCC at screening and 6h in the VCC after the last injection of the treatment (Visit 8).
5. To evaluate the effects of different dose levels of BM32 compared to placebo by FEV1 (Forced Expiratory Volume in 1 second) and FEV1/FVC (Tiffeneau-Value) as measured during challenge sessions at visit 3 and at visit 8.

6.1.3 Primary Safety Objective

The primary safety objective is to evaluate the relative safety and tolerability of three different dose levels of BM32 compared to placebo.

6.1.4 Secondary Safety and Immunogenicity Objective(s)

Secondary safety and immunogenicity objectives are:

1. To determine the effects of vaccination with BM32 versus placebo on allergen-specific antibody responses.
2. To determine the effects of vaccination with BM32 versus placebo on allergy related immunological parameters. In particular, antibody subtypes, T-cell responses and cytokine responses to recombinant allergens, grass pollen extract, BM32 components, and the carrier (PreS), as well as the sensitivity to recombinant grass pollen allergens and timothy grass

pollen extract in allergen induced basophile activation and in the CD203c assay will be studied.

6.2 Power considerations and determination of sample size

Three verum dose groups (i=1,2,3) with different levels of timothy grass pollen allergens will be applied:

1) Dose D_1: Verum Group 1 - 0,01 mg of each BM32 component
2) Dose D_2:Verum group 2 - 0,02 mg of each BM32 component)
3) Dose D_3: Verum Group 3 - 0,04 mg of each BM32 component)

For comparison of the three verum doses to placebo the following primary efficacy endpoint will be used: Difference in the TNSS Score between Screening (pre-treatment) and Visit 8 (post treatment).

This endpoint is assumed to follow a normal distribution (for the normal distribution assumption refer to Horn, Vollandt (1998)[1])

Let $D_1 < D_2 < D_3$ denote the three doses of the drug. Each of the 3 independent dose groups shall have the size $n=n_1=n_2=n_3$. The untreated group has the size $n_0=r*n$ with letting r=1 (1:1:1:1 group allocation). The three dose groups will be each compared to Placebo. A monotone dose-relationship is assumed, which means that the effect by drug (i.e. the difference to the control), is increasing (or at least non-decreasing) with increasing doses.

The minimum effective dose will be the drug dose, with the lowest dose to be still effective. This is the lowest dose for which the response is significantly higher than that at the zero dose level.

Following Tamhane, Hochberg, Dunnett (1996)[2] there is the need to perform **three separate one-sided α-level tests** for the individual comparisons of the different dose groups against the control group (placebo) in a stepwise manner.

1) Step 1: Starting with the highest dose D_3, this dose is compared to Placebo. If its response is not significantly higher than that of Placebo, D_3 and all other doses are considered as non-effective. The procedure stops.
If we get significance, D_3 is considered as effective and it is proceeded to step 2.

2) Step 2: The group treated with D_2 will be compared to Placebo. If its response is not significantly higher than that of Placebo, D_2 and D_1 are considered as non-effective and D_3 is declared to be the MED. The procedure stops.
If we get significance, D_2 is considered as effective, too, and it is proceeded to step 3.

3) Step 3: The group treated with D_1 will be compared to Placebo. If its response is not significantly higher than that of Placebo, D_1 is considered as non-effective and D_2 is declared to be the MED. The procedure stops.
If we get significance, D_1 is considered as effective and declared as the MED.

All responses X_0, X_1, X_2, X_3 are assumed to have a normal distribution with the same (known) variance σ^2. The following three hypotheses are tested:

Null Hypothesis: H_{0i}: $\mu_i \leq \mu_0$ (i=1,2,3)
Alternative Hypothesis: H_{Ai}: $\mu_i > \mu_0$

Δ is the bound such that a difference $\mu_i - \mu_0 \geq \Delta$ is regarded as clinically important.

The multiple testing is done by a multiple t-testing and controls the comparison wise type I error rate.

[1] Horn, M., Vollandt, R. (1998): Sample sizes for comparisons of k treatments with a control based on different definitions on power. Biometrical Journal 40, 589-612.
[2] Tamhane, A.C., Hochberg, Y., Dunnett, C.W. (1996): Multiple test procedures for dose finding. Biometrics 52, 21-37.

The sample size can be estimated by the following assumptions:

Results of sample size estimation

Power	90%
Significance level	5%
Test assumption	one sided, superiority testing, normal distribution
Delta Δ: Difference between Placebo and the high dose group D_3 in the TNSS Score between Screening and Visit 8 (Placebo group TNSS reduces 15% and D_3 reduces 50%)	2,65
Standard Deviation	2
The sample size formula (n per group)	$n=\lambda^2\sigma^2/\Delta^2$ with $\lambda^2=(1+1/r)\ (u_{1-\alpha} + u_{k,1/(1+r),1-\beta})^2$ [3]
Estimated number of patients per group	13
Estimated number of patients incl. drop-out rate (15%)	15
Total patient number to be randomized	60

This leads to an estimated number of patients of **13** per group. Adding a drop-out rate of 15% leads to a total of patients to be randomized of **15 per group**.

Having four treatment groups with equal patient sizes leads to a total of **60** patients.

6.3 General considerations

Generally all statistical tests – if applied - will be performed on a two-sided basis. In case of two-sided testing a p-value of less than 5% will be considered as statistically significant if not stated otherwise.

6.4 Analysis Sets

For the statistical analysis the patients will only be grouped into several analysis populations. They are defined as follows:

Analysis set	Analysis set includes:
Safety analysis (SA)	All subjects who were randomized and received at least one dose of the trial medication (verum or placebo).
Full analysis (FA)	All subjects of the SA set with at least one measurement of the primary efficacy variable TNSS.
Per Protocol (PP)	All subjects of the FA set for whom no relevant protocol deviations were documented.

The decision whether a protocol deviation is relevant or not for the exclusion of subjects from the PP set will be made case by case in a data review meeting.

The primary population subset will be the FA set. All confirmatory testing is based on this subgroup. For further descriptive purposes, the same statistical procedures will be applied to the PP set.

Analysis of safety will be based on the SA dataset.

[3] Horn, M., Vollandt, R. (2000): A manual for determination of sample sizes for multiple comparisons. Institut für medizinische Statistik, Information und Dokumentation. Friedrich-Schiller Universität Jena, p.29

6.5 Planned Statistical Analyses

All data available in the CRF will be presented by listings.

6.5.1 Check on baseline/ demographic variables

For the main continuous baseline characteristics age and BMI a 2-factorial ANOVA with factors subgroup will be performed. If the normal distribution assumption does not hold, an appropriate non-parametric model will be applied (e.g. Kruskal-Wallis test).
For categorical or binomial baseline variables sex a Cochran-Mantel-Haenszel will be performed.

6.5.2 Subgroup analyses

No subgroup analysis is planned. However, should there be evidence that the study population would be inhomogeneous and this fact could possibly influence the statistical analysis, an appropriate analysis for the main efficacy parameter will be undertaken.

6.5.3 Patient disposition

Disposition of patients (number of subjects screened, number of patients not meeting in-/ exclusion criteria, drop-outs before 1st treatment, patients included and treated, completed whole study, number of premature terminations (whole and by discontinuation reasons), patients included in the FA, PP and SA dataset) will be presented.

6.5.4 Screening and baseline characteristics

A summary table for the safety population will be prepared with summary statistics for age, height, weight and BMI. Sex will be counted and tabulated including percentages.

Results of physical examinations and ECG (visit 1) will be tabulated by frequency tables. Vital signs (blood pressure, pulse rate, body temperature and breathing frequency) at baseline (visits 1 to 3) and results of urine dipstick test and pregnancy test will be tabulated as well.

Medical history as documented under 'General medical history' will be coded by MedDRA (Medical Dictionary for Regulatory Activities), latest available version, and will be listed and tabulated by frequency.

SPT and RAST at visit 1 (screening) will be evaluated by the following variables:

- Result of SPT to grass pollen extract (positive/negative)
- Results of RAST (positive (≥ class 2)/ negative, laboratory results for rPhl p 1 / rPhl p 5 RAST1 – RAST6 (visit 1)

SPT results at screening and laboratory results for RAST will be presented descriptively by frequency tabulations (counts/ percentages).

6.5.5 Infection serology (Hepatitis B, Anti-HBc, Hepatitis C, HIV 1/2)

Results of infection serology will be tabulated by counts and frequencies, for hepatitis surface AK descriptive measures will be presented.

6.5.6 Spirometry results at baseline

FEV1 (L) (readings 1–3, predicted, % pred. of highest reading), FVC (L) (readings 1- 3), ratio FEV1/FVC at baseline (visit 1) will be presented via descriptive measure tabulations.

6.5.7 Treatment regimen

Vaccination will be applied three times, application volume is the same for each subject (3x 400µL (400µL in each monthly injection)). Data on time of injection will be presented within listings. Number of injections applied per treatment arm will be presented by frequency tabulations.

6.5.8 Efficacy parameter(s)

The primary efficacy endpoint is the difference in the mean total Nasal Symptom Score (TNSS) (nasal obstruction, rhinorrhoea, itchy nose and sneezing) between spending 6h in the VCC at VCC baseline (visit 3) and spending 6h in the VCC 4 weeks after the last injection of the treatment (visit 8).

The secondary efficacy endpoints are:

a) Difference in the mean Total Non-Nasal Symptom Score TNNSS (TOSS and OSS) between the 6h spent in the VCC at screening and the 0-6h period spent in the VCC 4 weeks after the last injection of the treatment (Visit 8).
b) Difference in the mean Global Symptom Score (TNSS and TNNSS) between the 6h spent in the VCC at VCC baseline visit 3 and the 0-6h period spent in the VCC 4 weeks after the last injection of the treatment (Visit 8).
c) Difference in the nasal airflow resistance (NAR) (measured using active anterior rhinomanometry) between the 6h spent in the VCC at VCC baseline visit 3 and the 0-6h period spent in the VCC 4 weeks after the last injection of the treatment (Visit 8).
d) Change in skin reaction to grass pollen allergens (SPT) before (visit 2) and after the treatment (visit 7) by dose titration of the grass pollen extract measuring the difference in the sum of wheal areas between these two visits and evaluating the change in the threshold concentration of grass pollen extract necessary to provoke a positive skin reaction (SPT)
e) Difference in the FEV1 and FEV1/FVC between VCC baseline visit 3 and Visit 8

6.5.8.1 Primary Efficacy Endpoint: Difference in the total Nasal Symptom Score (TNSS) between VCC baseline and visit 8

The TNSS will be evaluated once before challenging and 24 times afterwards at visit 3 and as often at visit 8.

Only the values on and after 2hrs are considered for the calculation of an aggregated endpoint.

The mean TNSS score from t=2-6h will be used for the confirmatory primary analysis.

In addition, a secondary analysis of the AUC (area under curve) TNSS score from t=2-6h will be done as well.

The difference between the mean TNSS between VCC baseline (visit 3) and visit 8 will be evaluated using the Tamhane, Hochberg, Dunnett (1996)[4] procedure as proposed in the section 6.2, sample size estimation.

The three dose groups D1< D2< D3 will be each compared to Placebo. The minimum effective dose (MED) will be the drug dose, with the lowest dose to be still effective. This is the lowest dose for which the response is significantly higher than that at the zero dose level. Following Tamhane, Hochberg, Dunnett (1996) there is the need to perform three separate one-sided α-level tests (α=0.05) for the individual comparisons of the different dose groups against the control group (placebo) in a stepwise manner.

The multiple testing is done by a multiple t-testing procedure. As indicated section 6.2, sample size estimation, it can be assumed that asymptotically, the categorical outcomes are normally distributed. Nevertheless, this will be tested and if there are evident deviations from normal distribution, non-parametric methods will be applied (Wilcoxon-Mann-Whitney testing).

[4] Tamhane, A.C., Hochberg, Y., Dunnett, C.W. (1996): Multiple test procedures for dose finding. Biometrics 52, 21-37.

For evaluation of within group differences between visits paired t-tests or Wilcoxon signed rank tests will be applied depending on the distribution (5% significance level). No adjustment for multiple testing will be applied for within-group testing.

In addition ANCOVAs will be applied with factors treatment and strata (moderate and severe allergy) (cf. CRF section 'Stratification'). For each comparison of placebo to verum group a separate ANCOVA will be applied. No adjustment for multiple testing will be performed – each test will be evaluated at a significance level of 5%.

Beside descriptive measures of the AUC and mean TNSS figures will be generated showing descriptive measures for each treatment group pre- and post-injection period, differences will be also displayed graphically for each treatment group.
All figures will be presented for the AUC and mean total TNSS.

In addition to the baseline-adjusted analysis, the unadjusted AUC and mean total TNSS values at visit 3 and 8 are compared between treatment groups by means of t-tests or Wilcoxon-Mann-Whitney tests. No adjustment for multiplicity is done.

6.5.8.2 Secondary efficacy endpoints

All aggregated variables based on scores (AUC TNNSS and mean TNNSS and the AUC of global symptom score and mean global symptom score) will be presented with descriptive statistics presented for each visit.
Descriptive measures of the mean TNSS, mean TNNSS and the mean global symptom score will be graphically displayed with bar charts for each treatment group and visit.
No figures are presented for the AUC, but only for the mean scores.

6.5.8.2.1 Difference in the Total Non-Nasal Symptom Score TNNSS between VCC baseline visit 3 and visit 8

The difference between the TNNSS between VCC baseline visit 3 and visit 8 will be calculated and presented with descriptive statistics (using both the difference between mean TNNSS and the difference between AUCs). Comparisons between each verum group and the placebo will be performed using two-sided t-tests (or Wilcoxon two sample tests in case of non-normality, 5% significance level).

For evaluation of within group differences between visits paired two-sided t-tests or Wilcoxon signed rank tests will be applied depending on the distribution (5% significance level).

6.5.8.2.2 Difference in the Global Symptom Score between VCC baseline visit 3 and visit 8

The difference in the global symptom score will be evaluated in the same manner as the TNNSS. Both the mean global symptom score measured from 2 hours to 6 hours as well as the AUC measured form 2 hours to 6 hours will be evaluated.

6.5.8.2.3 Difference in the nasal airflow resistance (NAR) (active anterior rhinomanometry) between VCC baseline visit 3 and visit 8

Nasal airflow parameters will be evaluated at several time points at each visit 3 and 8: Nasal inspiratory airflow will be measured for right and left nostril each and total (sum of left and right value). Only the total value will be used for further analysis.

The mean total NAR value from t=2-6h will be used for the analysis. The percent change of the mean NAR value (2-6hrs) compared to the pre-challenge value will be calculated and compared between verum and placebo treatment group at visit 3 and visit 8 separately by applying two-sided t-tests (or Wilcoxon two sample tests in case of non-normality, 5% significance level).

6.5.8.2.4 Change in skin reaction to grass pollen allergens (SPT) before (visit 2) and after the treatment (visit 7) by dose titration of the grass pollen

Skin reactions will be evaluated by, counted and tabulated by frequency tables or descriptive measures:

- Histamine positive/ negative (visits 2 + 7)
- NaCl (0,9%) positive/ negative (visits 2 + 7)
- Timothy grass pollen extract undiluted, dilution 1:2, 1:4, 1:8, 1:16, 1:32, 1:64, 1:128 positive/ negative (visits 2 + 7)
- Wheal areas of individual wheals per dilution factor (visit 2 + 7)
- Highest dilution level to be evaluated as positive (visit 2 and 7) (Stratification: "Titrated SPT: Highest dilution resulting in a positive skin reaction)
- Sum of wheal areas (visits 2 and 7)

Histamine and NaCl results, titrated SPT and dilution factor results as well as highest dilution factor, which leads to a positive reaction, will be presented via frequency tabulations.

The highest dilution level is the highest level at which the patient is still showing a reaction (reaction='YES') and having no reactions afterwards (reaction='NO'). For example a patient is showing no reaction at dilution levels 1:128, 1:64; 1:32, but shows reactions at dilution levels 1:16, 1:8, 1:4 and 1:2. The highest dilution level is then 16.

The difference between the highest positive dilution level is calculated between pre- and post-injection period (visit 2 and visit 7). For example if a patient has the highest dilution level 1:64 at visit 2 and 1:8 at visit 7, the difference in dilution levels is calculated by 64:8=8 (that means the tolerance of grass pollen is 8 fold higher than before). For the difference between highest positive dilution level descriptive measures will be presented, comparisons between verum treatment groups and placebo will be done by Wilcoxon-two sample test for each visit. In between comparisons within each treatment group will be done with the Wilcoxon signed rank test.

Two wheal areas are measured per dilution factor. Per dilution factor the sum of both wheal areas is calculated to get a total wheal area per dilution factor. In a second step for all dilution factors (undiluted, dilution factors 1:2, 1:4, 1:8, 1:16, 1:32, 1:64, 1:128), all wheal areas are summed up to get a total sum of wheal area.

Wheal areas (sum of wheal areas per dilution factor and total sum of wheal areas) will be descriptively presented with tabulations by visit.

Change in skin reaction to grass pollen allergens will be evaluated by measuring the difference in the total sum of wheal areas between these visits 2 and 7, for which descriptive measures will be presented as well as results of Wilcoxon-two-sample tests.

If histamine result is negative or NaCl positive, SPT results are not valid and must be kept out of the analyses. A footnote under the respective table mentions the affected patients.

6.5.8.2.5 Spirometry: Difference in the FEV1 and FEV1/FVC between baseline visit 3 and visit 8

FEV1 (l/s) and FVC (l) will be measured once before challenging and 6 times after challenge at visits 3 and 8. For each timepoint the ratio FEV1/FVC will be calculated.

The maximum percent decrease compared to the pre-challenge value will be calculated at Visit 3 and Visit 8 and compared between treatment groups at visit 3 and 8 separately by using t-tests in case of normality. In case of non-normality non-parametric methods (Wilcoxon two sample test, significance level 5%) will be applied to evaluate differences between treatment groups.

In addition there will be measurements of FEV1 (L) (readings 1–3, mean of the three readings, predicted, % pred. of highest reading), and FVC (L) (readings 1-3, mean of the 3 readings), ratio FEV1/FVC at baseline for visits 1 and measurement of FEV1 (L) (readings 1–3, mean of the three readings, predicted, % pred. of highest reading) at visits 4 ,5, 6 and 9. These values will be presented via descriptive measure tabulations.

6.5.9 Safety and tolerability parameters

6.5.9.1 General

The following safety and tolerability parameters will be used:

- Vital signs and weight, height, BMI
- Physical examination and ECG
- Medical History
- Intake of rescue medication, previous and concomitant medication
- Laboratory values (haematology, biochemistry, and urinalysis, pregnancy test)
- Adverse Events (primary safety endpoint)
- SIT specific Adverse Events

All safety data obtained in this study will be tabulated with descriptive statistics. Comparisons to the screening visit will be based on descriptive statistics and tests where appropriate. This will be mentioned in the respective sections.

6.5.9.2 Vital signs, weight, height and BMI, physical examination, ECG

Vital signs (blood pressure, pulse rate, body temperature, breathing frequency, weight, height and BMI and physical examination (normal/ abnormal findings) will be descriptively tabulated in case of quantitative variables, counted in case of qualitative variables and summarized by study visit (including all pre- and post-injection measurements as well).

Changes to baseline (visit 1) will be calculated for vital signs for each visit and separately differences between pre- and post-injection vital signs will be evaluated.

Results of ECG will be presented for each visit (1, 4 (pre-/post), 5 (pre-/post), 6 (pre-/post), 8, 9) via frequency tabulations (recording normal yes/no, clinically significant yes/ no).

6.5.9.3 Medical History

Medical History will be tabulated by frequency tables using MedDRA codes with SOC and PT.

6.5.9.4 Previous and concomitant medication and intake of rescue medication

Both previous, concomitant medication and rescue medication will be coded using WHO-Drug Dictionary Version Q2/ 2011.

Concomitant medications will be tabulated by frequency tables using counts of events and patients and percentages. Anatomic group levels ATC 2 and ATC 4 will be presented as well as WHO Drug Dictionary preferred term (PT). Previous medications will be listed only.

Intake of rescue medication will be documented under the section concomitant medication. Intake of rescue medication like inhaled short-acting beta-agonists is permitted during the challenge period as rescue medication. Salbutamol use is to be avoided 8 hours before a challenge and for the duration of the challenge, nevertheless it is documented in case of.

Number and percentage of patients, who needed rescue medication, per visit will be tabulated. Comparisons between treatment groups will be performed for each visit using the Chi-Square test or exact Fisher's test in case of small cell frequencies.

6.5.9.5 Clinical laboratory test results: haematology, clinical chemistry, results of urine dipstick test and pregnancy test

Results of clinical haematology, clinical chemistry and urine dipstick test will be evaluated by descriptive statistics and counting the number of values within and outside the normal range for each

visit. The pregnancy test will be marked whether the result is positive or negative. The numbers in each category will be counted and percentages presented it.

6.5.9.6 Adverse Events

For specific regulations of documentation of adverse events, please refer to the study protocol.

Events related to study participation during the screening period (i.e. before administration of the investigational product) will be recorded as Serious Medical Events (SME). AEs and SAEs will be recorded between receipt of first dose and the further follow-up visits.

For presentation of AEs and SMEs, SMEs will be listed only; AEs will be presented in summary tables and listings. SMEs starting at day of vaccination (visit 4) will be accounted to adverse events AE.

AEs that are reported as “possibly” and “probable” related to the study medication will be considered treatment-related; missing classifications concerning study drug relationship will also be considered treatment-related. “Unrelated” classified AEs are considered not related to treatment.

6.5.9.6.1 General AEs

An overview frequency table of AEs will be prepared showing the number of subjects (percentage of subjects and events) with AEs, any treatment-related AEs, any serious AEs, any treatment-related serious AEs and any AEs leading to death as outcome, and AEs leading to discontinuation of the trial. In addition frequency tables will be prepared grouped by MedDRA terms (system organ class and preferred term, for reporting to European authorities and ethics committees lower level terms will be used), showing the following:

- All AEs
- All treatment-related AEs
- Serious AEs
- Treatment-related AEs by intensity
- AEs that lead to study discontinuation

6.5.9.6.2 SIT specific injection site reactions and systemic reactions

On the AE CRF pages, each AE can be classified, if it is SIT specific or not: For the subclass of SIT specific AEs the same tables as mentioned in section 6.5.9.6.1 will be generated.

SIT specific local reactions (injection site reactions) and systemic reactions will be classified by a grading scheme according to the Position Paper of the German Society for Allergology and Clinical Immunology[5]: The grading is done by classification of SIT specific adverse events in the following categories:

Grade	Symptoms
0	Local reactions like local swelling (< 15 cm and > 15 cm), redness at injection site
1	Light general reactions: e.g. mucous membrane reactions (e.g. conjunctivitis, rhinitis), general urticaria, itching, erythema, pruritus, general symptoms like cough, wheezing, headache, Agitation
2	Distinct general reactions: circulatory dysregulation (change in blood pressure and pulse), dyspnea, beginning bronchospasm, gastrointestinal reactions, anxiety
3	Strong general reactions: shock (e.g. severe hypotension, paleness), bronchospasm with severe dyspnea, loss of consciousness, fecal and urinary incontinence

[5] Kleine-Tebbe, J. , Fuchs, T. , Klimek, L., et al.: Die spezifische Immuntherapie (Hyposensibilisierung) mit Allergenen. Positionspapier der deutschen Gesellschaft für Allergologie und klinische Immunologie inhaltlich abgestimmt mit dem Ärzteverband Deutsche Allergologen. Pneumologie 2001; 55, pp. 438-44.

Grade	Symptoms
4	Overall organ failure, apnea, circulatory arrest

Tabulations will present number of events, number of patients and percentages of SIT specific reactions by grade and by SOC and PT. Comparisons will be done using a Chi-square-test (significance level 5%).

6.5.10 Immunogenicity parameters

6.5.10.1 General

The following immunogenicity endpoints will be analysed:

- Change in specific IgG levels after 3 s.c. injection with BM32, as measured at screening and visit 7
- Change in specific IgE levels after 3 s.c. injection with BM32, as measured at screening and visit 7
- Change in allergy related immunological parameters (T-cell responses and cytokine responses to recombinant allergens, grass pollen extract, BM32 components, and the carrier (PreS), as well as the sensitivity to recombinant grass pollen allergens and timothy grass pollen extract in allergen induced basophile activation and in the CD203c assay) levels after 3 s.c. injection with BM32, as measured in blood or serum samples collected at screening (Baseline) and after the last injection of the treatment (visit 7).

All immunogenicity data will be presented by listings, only selected parameters will be presented by descriptive measures for each visit/ time point available.

6.5.10.2 Change in specific IgG and IgE levels after 3 s.c. injection with BM32, as measured at visit 2 and visit 7

IgG and IgE levels will be determined using different analytical methods:
Allergen-specific antibody levels and antibodies specific for the carrier element PreS in serum will be measured by ELISA and ImmunoCAP (Phadia, SE), and sensitization profiles will be determined using the ImmunoCAP ISAC mulitplex assay (Phadia, SE).

In particular, the following parameters will be determined:

Analytical Method	Antibody class/ subclass	Specificity of antibodies
ImmunoCAP	IgE, IgG	Phl p 1, Phl p 2, Phl p 5, Phl p 6, grass pollen extract, total IgE
ELISA	IgE, IgG, IgG1, IgG2, IgG3, IgG4, IgA, IgM	Phl p 1, Phl p 2, Phl p 5, Phl p 6, BM321, BM322, BM325, BM326, PreS (all three dilution levels)
ImmunoCAP ISAC	IgE, IgG4	Cyn d 1, Phl p 1, Phl p 2, Phl p 4, Phl p 5, Phl p 6, Phl p 7, Phl p 11, Phl p 12, Bet v 1

All parameters will be listed.

Red marked parameters in the table above will be analyzed with further statistical methods:

- Descriptive statistics
- Changes (defined both as difference and ratio) between visit 2 and 7 will be calculated and descriptively presented.
- Comparisons between treatment groups will be done via non-parametric methods (Wilcoxon-two-sample test) by using the difference of immunogenicity data between visits; or the

Wilcoxon-signed rank test is performed if comparing between the visits within treatment groups.

- Besides presentation of descriptive measures of antibodies, graphical profiles showing the time-dependent development of the antibodies via barcharts/ line plots will be presented (showing each patient with pre- post values, descriptive measures grouped by treatment and visit).

6.5.10.3 Change in allergy related immunological parameters

In addition, the following allergy related immunological parameters will be evaluated at visit 2 (pre-treatment) and visit 7 (post-treatment):

- CD203c assay for assessment of the allergic sensitivity to grass pollen allergens: Basophils from heparinized blood samples are exposed to different concentrations of equimolar mixtures of recombinant grass pollen allergens Phl p1, Phl p2, Phl p5, and Phl p6, , and anti-IgE as positive control.

  For up-regulation the following parameters will be used for each pre and post vaccination visit: *CD203c DONE?, Stimulation index [SI] after stimulation with anti-IgE 0,1 pg/mL, anti-IgE 1 pg/mL, rMix 1 pg/mL, rMix 5 pg/mL, rMix 25 pg/mL, rMix 125 pg/mL*

- T-cell proliferation assay: Peripheral blood mononuclear cells (PBMC) are isolated from heparinised blood samples. Cells are stimulated with different concentrations of BM32 active components (equimolar mixture), equimolar concentrations of synthetic peptides, PreS, recombinant grass pollen allergens, and grass pollen extract. The cell proliferation is detected via incorporation of 3H-thymidine by liquid scintillation counting.

  The following parameters will be analyzed for each pre and post vaccination visit:, Simulation index after stimulation with BM32 Mix 0,25 µg/well, Peptide Mix 0,125 µg/well, rAllergen Mix 0,25 µg/well, Extract 25µg/well, PreS 0,15 µg/well.

- The cytokine expression of T-cells after activation with mixtures of recombinant grass pollen allergens, active components of BM32, or PreS will be determined. Expression of 17 human cytokines, chemokines, and growth factors will be assessed for each pre and post vaccination visit (*IL-1ß, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, G-CSF, GM-CSF, MCP1, MIP 1ß, IFN-g, and TNF-a*).

All allergy related immunological parameters will be listed only.

6.5.11 Missing Values

In case of drop-outs, for the main efficacy parameter, the latest available measurement will be written forward for subsequent (missing) measurements ("last-observation-carried-forward", LOCF). Empty data fields in the CRF will generally be treated as missing values.
Analysis of all other efficacy and safety variables will be done on a valid case basis, i.e. for missing observations no imputation technique like LOCF (last observation carried forward) will be applied.

7 Changes to endpoints or analysis compared to trial protocol

7.1 Changes to endpoints

Not applicable.

7.2 Changes to analyses

In the protocol total amount of rescue medication intake was planned to be calculated per patient and presented with descriptive statistics. As no standard rescue medication is given, only number of patients having taken rescue medication per visit will be analysed with statistical methods.

The primary endpoint was defined as the “Difference in the total Nasal Symptom Score (TNSS) (nasal obstruction, rhinorrhoea, itchy nose and sneezing) between spending 6h in the VCC at screening and spending 6h in the VCC 4 weeks after the last injection of the treatment (Visit 8).”
Actually, the VCC produces one result before challenging and 24 individual measurements every 15min afterwards. Only the results from t=2h onwards are producing meaningful results.
As such, the mean TNSS from 2-6h is used for the confirmatory analysis.
This is also applicable for the secondary variables TNNSS and global symptom score.

As an additional analysis, the AUC from 2-6h of the TNSS score will be used.

Signature page

Statistical Analysis Plan approved:

Signatures:

Date	Anette Knoll, Statistician – HCR
18.4.2012	
Date	Rainer Henning, CEO – Biomay AG
18.4.2012	
Date	Angela Neubauer, Head Product Development – Biomay AG

8 Appendix 1: Index of section 14 of the clinical report

The following proposal for section 14 and 16.2 is completely done according to the pre-defined ICH-format. Minor changes from this planned index do not need to be amended in the SAP.

Comments in Italics will not be printed in table headers or footers.
Formal organization of tabulations may be changed during programming if appropriate, e.g., tables for the different variables may be combined into a single table, or tables with more than one variable may be split into several tables.

	TITLE	TABLE TYPE	ANALYSIS SET	COMMENT
14.	TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT			
14.1	**Demographic and screening data**			
14.1.1	Patients included by investigational site and strata	DESC	All[6]	
14.1.2	Subject disposition	DESC	All	*For total and strata (severe/ moderate allergy)as well*
14.1.3	Fulfilment of inclusion/exclusion criteria	DESC	All	
14.1.4	Demographic data	DESC	SA	
14.1.5	General medical history	AE	SA	
14.1.6	Case history: Seasonal allergic rhinitis, severe atopic dermatitis, asthma	DESC	SA	
14.1.7	Vital signs at baseline visits	LONG1	SA	*Baseline visits are visits 1-3*
14.1.8	Physical examination at baseline	DESC	SA	*Baseline visit is visit 1*
14.1.9	Urine dipstick test and pregnancy test at baseline	DESC	SA	*Baseline visit is visit 1*
14.1.10	ECG at baseline	DESC	SA	*Baseline visit is visit 1*
14.2	**Allergy specific baseline data**		**SA**	
14.2.1	Skin prick test (SPT) at baseline	DESC		*Baseline visits is visit 1*
14.2.2	RAST at baseline	DESC		*Baseline visit is visits 1*

[6] All : all patients included=all patients screened

	TITLE	TABLE TYPE	ANALYSIS SET	COMMENT
14.2.3	Spirometry at baseline	DESC		*Baseline visit is visit 1*
14.3	**Compliance and Drug Intake**			
14.3.1	In- and Exclusion Criteria and Eligibility	DESC	All	
14.3.2	Time between visits and total study duration	DESC	SA	
14.3.3	Drug administration	DESC	SA	*If 'injection time' is not missing, then drug application at this visit is defined as 'done'.*
14.4	**EFFICACY DATA**		**FAS + PP**	
14.4.1	Main efficacy endpoint: TNSS score (LOCF, 2h-6h)			
14.4.1.1	*MEAN TNSS SCORE (LOCF, 2H-6H): DESCRIPTIVE MEASURES*	LONG2		*Raw values and change from baseline; Including p-values for within group testing*
14.4.1.2	*MEAN TNSS SCORE (LOCF, 2H-6H): INFERENTIAL STATISTICAL RESULTS*	LONG2/ TEST		*Including p-values of testing procedure according to Tamhane et al.* *Additionally ANCOVAs with factors treatment and strata (3 separate ANCOVAs for each dose against placebo*
14.4.1.3	*AUC OF THE TNSS SCORE (LOCF, 2H-6H): DESCRIPTIVE MEASURES RESULTS*	LONG2		*Raw values and change from baseline; Including p-values for within group testing*
14.4.1.4	*AUC OF THE TNSS SCORE (LOCF, 2H-6H): INFERENTIAL STATISTICAL RESULTS*	LONG2/ TEST		*Including p-values of testing procedure according to Tamhane et al.* *Additionally ANCOVAs with factors treatment and strata (3 separate ANCOVAs for each dose against placebo*
14.4.1.5	*FIGURES: MEAN TNSS SCORE (LOCF, 2H-6H)*	Figures		*Barchart showing mean scores by visit, and treatment group*
14.4.1.6	*FIGURES: AUC OF THE TNSS SCORE (LOCF, 2H-6H)*	Figures		*Barchart showing mean AUC by visit, and treatment group*
14.4.2	Secondary Efficacy Endpoints			
14.4.2.1	TNNSS (LOCF, 2h-6h)			
14.4.2.1.1	*MEAN TNNSS (LOCF,2H-6H): DESCRIPTIVE MEASURES*	LONG2		*Including p-values for within group testing.*
14.4.2.1.2	*MEAN TNNSS SCORE (LOCF, 2H-6H): INFERENTIAL STATISTICAL RESULTS*	LONG2/ TEST		*Including p-values for between-group testing*
14.4.2.1.3	*AUC OF THE TNNSS SCORE (LOCF,2H-6H): DESCRIPTIVE MEASURES*	LONG2		*Including p-values for within group testing.*
14.4. 2.1.4	*AUC OF THE TNNSS SCORE (LOCF, 2H-6H): INFERENTIAL STATISTICAL RESULTS*	LONG2/ TEST		

	TITLE	TABLE TYPE	ANALYSIS SET	COMMENT
14.4.2.1.5	*FIGURES: MEAN TNNSS SCORE (LOCF, 2H-6H)*	Figures		*Figures for TNNSS like for the TNSS: no subscales are presented*
14.4.2.2	Global symptom score (LOCF, 2h-6h)			
14.4.2.2.1	*GLOBAL SYMPTOM SCORE (LOCF, 2H-6H): DESCRIPTIVE MEASURES*	LONG2		*Including p-values for within group testing.*
14.4.2.2.2	*GLOBAL SYMPTOM SCORE (LOCF, 2H-6H): INFERENTIAL STATISTICAL RESULTS*	LONG2/ TEST		*Including p-values for between-group testing*
14.4.2.2.3	*AUC OF THE GLOBAL SYMPTOM SCORE (LOCF, 2H-6H): DESCRIPTIVE MEASURES*	LONG2		*Including p-values for within group testing.*
14.4. 2.2.4	*AUC OF THE GLOBAL SYMPTOM SCORE (LOCF, 2H-6H): INFERENTIAL STATISTICAL RESULTS*	LONG2/ TEST		
14.4.2.2.5	*FIGURES: MEAN GLOBAL SYMPTOM SCORE (LOCF, 2H-6H)*	Figures		*Figures for global symptom score like for the TNSS; no subscales are presented..*
14.4.2.3	Nasal airflow resistance (NAR)			
14.4.2.3.1	*NASAL AIRFLOW RESISTANCE (NAR) : DESCRIPTIVE MEASURES*	LONG2		
14.4.2.3.2	*NASAL AIRFLOW RESISTANCE (NAR) : INFERENTIAL STATISTICAL RESULTS*	LONG2/ TEST		
14.4.2.4	Skin prick test (SPT)			
14.4.2.4.1	*SKIN PRICK TEST (SPT): DESCRIPTIVE MEASURES*	LONG2		
14.4.2.4.2	*SKIN PRICK TEST (SPT): INFERENTIAL STATISTICAL RESULTS*	LONG2/ TEST		
14.4.2.4.3	*FIGURES: SKIN PRICK TEST (SPT) - SUM OF WHEAL AREAS*	Figures		*Sum of wheal areas pre and post injection period, presented by bar-charts for each treatment group*
14.4.2.5	Spirometry			
14.4.2.5.1	*SPIROMETRY (VCC CHALLENGE CHAMBER): DESCRIPTIVE MEASURES*	LONG2		
14.4.2.5.2	*SPIROMETRY (VCC CHALLENGE CHAMBER): INFERENTIAL STATISTICAL RESULTS*	LONG2/ TEST		.
14.4.2.5.3	*SPIROMETRY (CRF): DESCRIPTIVE MEASURES*	LONG2		*Spirometry values taken out of CRF (visits 1, 4, 5, 6, 9)*
14.5	**IMMUNOLOGY DATA**		**SA**	
14.5.1	Results of ELISA: Antibodies	LAB		

	TITLE	TABLE TYPE	ANALYSIS SET	COMMENT
14.5.1.1	*Results of ELISA -Antibodies: Descriptive measures*	LONG1		*Absolute values and changes to visit 7, p-values for within and between group testing*
14.5.1.2	*Results of ELISA: Figures*	Figures		*Per treatment group and ELISA parameter: plotting each patient's value with a connected line btw. pre- and post-injection period value.* *Plots for each verum group against placebo with descriptive statistics for pre- and post- injection period values.*
14.5.2	Results of ImmunoCAP: Antibodies	LAB		
14.5.1.1	*Results of ImmunoCAP- Antibodies: Descriptive measures*	LONG1		
14.5.1.2	*Results of ImmunoCAP: Figures*	Figures		*See ELISA*
14.5.3	Results of ISAC Chip: Antibodies	LAB		
14.5.1.1	*Results of ISAC Chip- Antibodies: Descriptive measures*	LONG1		
14.5.1.2	*Results of ISAC Chip: Figures*	Figures		*See ELISA*
14.6	**ADVERSE EVENT DATA**		**SA**	*All tables are split by general and SIT specific.*
14.6.1	General adverse events			
14.6.1.1	Adverse events: Overview	AESUM		
14.6.1.2	Adverse events: MedDRA coding by SOC and PT	AE		
14.6.1.3	Treatment-related adverse events: MedDRA coding by SOC and PT	AE		
14.6.1.4	Serious adverse events: MedDRA coding by SOC and PT	AE		
14.6.1.5	Treatment-emergent adverse events: MedDRA coding by intensity, SOC and PT	AE		
14.6.1.6	Adverse events that lead to study discontinuation: MedDRA coding by SOC, PT	AE		
14.6.2	SIT specific adverse events			
14.6.2.2	SIT specific adverse events: MedDRA coding by SOC and PT	AE		
14.6.2.3	Treatment-related SIT specific adverse events: MedDRA coding by SOC and PT	AE		
14.6.2.4	Serious SIT specific adverse events: MedDRA coding by SOC and PT	AE		
14.6.2.7	Treatment-emergent SIT specific adverse events: MedDRA	AE		

	TITLE	TABLE TYPE	ANALYSIS SET	COMMENT
	coding by intensity, SOC and PT			
14.6.2.8	SIT specific adverse events that lead to study discontinuation: MedDRA coding by SOC, PT	AE		
14.6.2.9	SIT specific adverse events by Klein-Tebbe grading: MedDRA coding by SOC, PT	AE		*Frequency tabulation including Chi-square test comparing frequency in grades between each verum group and placebo.*
14.7	**LABORATORY DATA**		**SA**	
14.7.1	Hepatitis B and C, HIV1/2	LAB		
14.7.2	Clinical haematology	LAB		
14.7.3	Clinical chemistry	LAB		
14.7.4	Urine dipstick test	LAB		
14.7.5	Pregnancy test	LONG1		*All visits*
14.8	**FURTHER SAFETY DATA**		**SA**	
14.8.1	Medications			
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14.8.1.2	Rescue medication	??		*Frequency tabulation: number of patients taking rescue medication at each visit. Comparisons between treatment groups by Fisher's exact test or Chi-square test.*
14.8.2	Vital Signs			
14.8.2.1	Vital Signs: Descriptive measures	LONG1		*Blood pressure, pulse rate, body temperature, breathing frequency, height, weight, BMI*
14.8.2.2	Vital Signs: Changes between to baseline, and changes between pre- and post-injection	DESC		
14.8.3	General physical examination	LONG1		*Descriptive measures*
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16.2.1.2	ALL DISCONTINUED PATIENTS	
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16.2.6.1	INCLUSION/EXCLUSION CRITERIA	IN-/ EXCLUSION CRITERIA AND ELIGIBILITY
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16.2.7.3	SKIN PRICK TEST (TITRATED)	
16.2.8	ADVERSE EVENTS	
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Section number	Title	Comment
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16.2.10.4	CLINICAL CHEMISTRY	
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16.2.11	FURTHER SAFETY DATA	
16.2.11.1	PREVIOUS AND CONCOMITANT MEDICATION	PREVIOUS MEDICATION: START AND END OF MEDICATION BEFORE FIRST APPLICATION OF STUDY MEDICATION (VISIT 3, VCC BASELINE), CONCOMITANT MEDICATION: STARTING BEFORE AND ONGOING AT VISIT 3, STARTING AT VISIT 3, MISSING END DATE
16.2.11.2	RESCUE MEDICATION	
16.2.11.3	VITAL SIGNS	BLOOD PRESSURE, PULSE RATE, BODY TEMPERATURE, BREATHING FREQUENCY, HEIGHT, WEIGHT, BMI
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16.2.11.5	ELECTROCARDIOGRAM (ECG)	
16.2.11.6	COMMENTS	

10 Appendix 3: Mock tables and listings

10.1 Qualitative/ Quantitative variables (Type : DESC)

Title, Dataset
Title2
Title3

	Descriptive statistics / n (%)			
	Treatment			
	Treatment xx (N=xxx)	Treatment xx (N=xxx)	Treatment xx (N=xxx)	Total (N=xxx)
Categorical Parameter 1				
category 1	x (xxx.x)	x (xxx.x)	x (xxx.x)	x (xxx.x)
category 2	x (xxx.x)	x (xxx.x)	x (xxx.x)	x (xxx.x)
Categorical Parameter 2				
category 1	x (xxx.x)	x (xxx.x)	x (xxx.x)	x (xxx.x)
category 2	x (xxx.x)	x (xxx.x)	x (xxx.x)	x (xxx.x)
category 3	x (xxx.x)	x (xxx.x)	x (xxx.x)	x (xxx.x)
category 4	x (xxx.x)	x (xxx.x)	x (xxx.x)	x (xxx.x)
Metric Parameter [unit]				
Mean	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx
StdDev	xx.xx	xx.xx	xx.xx	xx.xx
Min	xx	xx	xx	xx
Max	xx	xx	xx	xx
n	xx	xx	xx	xx

PROGRAM SOURCE: ...\xxxx_xxxxx.sas, EXTRACT DATE:ddmmmyy RUN DATE: ddmmmyy mm:xx

10.2 Longitudinal tabulation, horizontal display (Type : LONG1)

Title, Dataset
Title2
Title3

		Visit									
Treatment		V1 (N=xx)	V2 (N=xx)	V3 (N=xx)	V4 (N=xx)	V5 (N=xx)	V6 (N=xx)	V7 (N=xx)	V8 (N=xx)	Vx (N=xx)	Vy (N=xx)
xxxxxxxx	Mean	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	Median	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	SD	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
	Min	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
	Max	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
	n	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
xxxxxxxx	Mean	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	Median	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
	SD	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
	Min	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
	Max	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
	n	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx

PROGRAM SOURCE: ...\xxxx_xxxxx.sas, EXTRACT DATE:ddmmmyy RUN DATE: ddmmmyy mm:xx

10.3 Longitudinal tabulation, vertical display (Type : LONG2)

Title, Dataset
Title2
Title3

	Descriptive statistics					
	Treatment					
	Treatment xx (N=xxx)	Treatment xx (N=xxx)	Treatment xx (N=xxx)	Treatment xx (N=xxx)	Total (N=xxx)	p-value
Visit 1						
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xxxxxxxx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	
Min	xx	xx	xx	xx	xx	
Max	xx	xx	xx	xx	xx	
n	xx	xx	xx	xx	xx	
Visit 2						
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xxxxxxxx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	
Min	xx	xx	xx	xx	xx	
Max	xx	xx	xx	xx	xx	
n	xx	xx	xx	xx	xx	

PROGRAM SOURCE: ...\xxxx_xxxxx.sas, EXTRACT DATE:ddmmmyy RUN DATE: ddmmmyy mm:xx

10.4 TEST

Variable	Treatment Group 1	Treatment Group 2	Mean Difference	95% CI for mean difference*	p-value for treatment effect
Difference in XXX Score between baseline visit 3 and visit 8	Placebo	BM32/S3	xxx.x	(xxx.xx; xxx.xx)	0.xxxx

Variable	Treatment Group 1	Treatment Group 2	Mean Difference	95% CI for mean difference*	p-value for treatment effect
Difference in XXX Score between baseline visit 3 and visit 8	Placebo	BM32/S2	xxx.x	(xxx.xx; xxx.xx)	0.xxxx

Variable	Treatment Group 1	Treatment Group 2	Mean Difference	95% CI for mean difference*	p-value for treatment effect
Difference in XXX Score between baseline visit 3 and visit 8	Placebo	BM32/S1	xxx.x	(xxx.xx; xxx.xx)	0.xxxx

In case of ANCOVA

Variable	Treatment Group 1	Treatment Group 2	Mean Difference	95% CI for mean difference*	p-value for treatment effect	p-value for strata effect
Difference in XXX Score between baseline visit 3 and visit 8	Placebo	BM32/S3	xxx.x	(xxx.xx; xxx.xx)	0.xxxx	0.xxxx
	Placebo	BM32/S2	xxx.x	(xxx.xx; xxx.xx)	0.xxxx	0.xxxx
	Placebo	BM32/S1	xxx.x	(xxx.xx; xxx.xx)	0.xxxx	0.xxxx

10.5 Overview of adverse events (Type : AESUM)

	Number of Subjects (%) Event Count					
Preferred term	Treatment xxx (N=xx)	Treatment xxx (N=xx)	Treatment xxx (N=xx)	Treatment xxx (N=xx)	Treatment xxx (N=xx)	Total (N=xx)
Any AEs	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	x (xx.x) xx	xx (xx.x) xx
Treatment-related[1] AEs	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Serious AEs	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
AEs leading to withdrawal	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx

[1]: Treatment-related: possible, probable, and missing

PROGRAM SOURCE: ...\xxxx_xxxxx.sas, EXTRACT DATE:ddmmmyy RUN DATE: ddmmmyy mm:xx

10.6 AE summary table (Type : AE)

Dataset

SOC Preferred term	Number of Patients (%) Event Count Treatment xx (N=xx)	 Treatment xx (N=xx)	 Treatment xx (N=xx)	 Total (N=xx)
SOC class 1				
Any PT	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT term 1	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT Term 2	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT Term 3	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT Term xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
SOC class 2				
PT term 1	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT Term 2	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT Term 3	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT Term xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
SOC class xx				
Any PT	1 (4.2) 1	1 (4.2) 1	2 (8.3) 2	3 (12.0) 4
PT term 1	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT Term 2	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT Term 3	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT Term xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
...				

A subject with more than one event in a specific category was only counted once
Percentages based on total no. of subjects in each treatment group
Table is sorted by descending subject count on the PT level

Laboratory summary table (Type : LAB)

Laboratory panel name=xxxx

Laboratory test name xxx [xx/xx]

	N	Mean	Median	SD	Min	Max	below reference range		within reference range		above reference range	
							N	%	N	%	N	%
Visit 1	xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx	xx.x	xx	xx.x	xx.x
Visit 2	xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx	xx.x	xx	xx.x	xx.x
Visit x	xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx	xx.x	xx	xx.x	xx.x

10.7 Laboratory shift table (Type: LABSHIFT)

Screening	Visit x						Total	
	below reference range		within reference range		above reference range			
	n	%	n	%	n	%	n	%
LAB VALUE XX								
below reference range	x	x.x	x	x.x	x	x.x	x	x.x
within reference range	x	x.x	x	x.x	x	x.x	x	x.x
above reference range	x	x.x	x	x.x	x	x.x	x	x.x

10.8 Raw data listing (Type : LIST)

Example
Demographic data

Treatment	Subj	Date of birth	Date of informed consent	Age [years]	Sex	Height [cm]	Weight [kg]	Body mass index [kg/m²]
xxxxxxxxxxxxxxxxxx	xxx	ddmmmyyyy	ddmmmyyyy	xx	xxxx	xxx	xx.x	xx
xxxxxxxxxxxxxxxxxx	xxx	ddmmmyyyy	ddmmmyyyy	xx	xxxx	xxx	xx.x	xx
xxxxxxxxxxxxxxxxxx	xxx	ddmmmyyyy	ddmmmyyyy	xx	xxxx	xxx	xx.x	xx

PROGRAM SOURCE: ...\xxxx_xxxxx.sas, EXTRACT DATE:ddmmmyy RUN DATE: ddmmmyy mm:xx