Statistical Analysis Plan

A double-blinded, randomized, placebo-controlled, parallel-group study evaluating the effect of the probiotic *Lactobacillus reuteri* on recurrent urinary tract infection (UTI) in adult women recently treated for UTI.

Sponsors study code: CSUB0144

NCT 03366077

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CONFIDENTIAL

Statistical Analysis Plan (SAP)

Sponsor:	**BioGaia AB**
Study code:	**BioGaia CSUB 0144**
Study title:	**A double-blinded, randomized, placebo-controlled, parallel-group study evaluating the effect of the probiotic *Lactobacillus reuteri* on recurrent urinary tract infection (UTI) in adult women recently treated for UTI.**
Date:	**27MAR2019 – Draft 1** **08AUG2019 – Final 1.0** **03SEP2019 – Final 2.0**

1 VERSION HISTORY

This Statistical Analysis Plan (SAP) for study BioGaia CSUB 0144 is based on the protocol dated 24OCT2017.

Table 1 SAP Version History Summary

SAP version	Approval Date	Changes	Rationale
1	08AUG2019	NA	Original version
2	xxAUG2019		

2 INTRODUCTION

This Statistical Analysis Plan (SAP) gives details regarding the statistical analyses and data presentation outlined in the final Clinical study protocol (CSP) for the study BioGaia CSUB 0144 . Any changes from the final CSP are given in Section 0.

3 CLINICAL STUDY DETAILS

3.1 Clinical Study Objectives and Endpoints

Objects	Estimands/Endpoints
Primary	
• The primary objective is to evaluate the effect of oral supplementation with *Lactobacillus reuteri* on the frequency of confirmed UTI during six months from start of intervention in adult women with recurrent UTI.	• Mean number of confirmed UTIs during six months from start to intervention, as compared to placebo.
Secondary	
• To evaluate the effect of oral supplementation with *Lactobacillus reuteri* on the frequency of confirmed UTI during the three months´ intervention period and during the three months' follow-up period, respectively. • To evaluate the effect of oral supplementation with *Lactobacillus reuteri* on time to first relapse of UTI. • To evaluate the effect of oral supplementation with *Lactobacillus reuteri* on relapse rate at three and six months after start of intervention. • To assess the tolerability of oral supplementation with *Lactobacillus reuteri* in adult women with recurrent UTI.	• Mean number of confirmed UTIs during the three months' intervention period, as compared to placebo. • Mean number of confirmed UTIs during the three months' follow-up period, as compared to placebo. • Mean time from start of intervention to first relapse of UTI, as compared to placebo. • Proportion of subjects (%) who experienced at least one confirmed UTI during three months from start of interventions, as compared to placebo. • Proportion of subjects (%) who experience at least one confirmed UTI during six months from start of intervention, as compared to placebo. • Occurrence and frequency of Adverse Events (AEs)
Tertiary/Exploratory	
• Not applicable	• Not applicable

Objective Clinical Category	***Statistical Category***	***Estimand[1]*** ***Variable/ Endpoint***	***Population***	***IES[1]***	***PLS[1] (Analysis)***
Primary Objective: *To compare the efficacy superiority of the probiotic Lactobacillus reuteri to placebo/active control in participants of adult women with the frequency of confirmed UTI.*					
New episode of UTI	*Primary/MCP*	*Change from baseline in number of confirmed UTI at three and six months.*	*FAS*	*Initiation of rescue medication: "had rescue medication not been initiated" (hypothetical).* *Discontinuation of treatment due to adverse event (AE): "regardless of treatment discontinuation due to AE" (treatment policy)*	*Mean difference between interventions (LSMD from CFB ANCOVA with MI from participants from same randomized arm off-treatment at three to six months)*
	Sensitivity				*(LSMD from CFB ANCOVA with reference-based MI)*
	Supplementary	*Number of confirmed UTI responder (criterion) and rescue medication not initiated at three and six months and remained adherent to intervention*	*FAS*	*Captured in variable definition (composite)*	*Odds ratio between interventions (Logistic regression)*
	Secondary/MCP		*FAS*		
Number of confirmed UTI	*Secondary*				
Time from start of intervention to relapse of UTI	*Tertiary*				
	Exploratory				
Secondary Objective*: 1. To evcluate the effect of oral supplementation with Lactobacillus reuteri on the frequency of confirmed UTI during the three months´ intervention period and during the three months' follow-up period, respectively.*					

Objective Clinical Category	***Statistical Category***	***Estimand[1]***			
		Variable/ Endpoint	***Population***	***IES[1]***	***PLS[1] (Analysis)***
2. To evaluate the effect of oral supplementation with Lactobacillus reuteri on time to first relapse of UTI. *3. To evaluate the effect of oral supplementation with Lactobacillus reuteri on relapse rate at three and six months after start of intervention.* *4. To assess the tolerability of oral supplementation with Lactobacillus reuteri in adult women with recurrent UTI.*					
AEs		*Presence of TEAEs*	*Safety*		*Record from start of IP intervention.*
			Safety		*Medical events occurring between screening and start of IP intervention.*
SAEs			*Safety*		*Record from start of IP intervention.*
			Safety		*Medical events occurring between screening and start of IP intervention.*

IES = Intercurrent event(s) strategy; PLS = Population-level summary.

CFB = Change From Baseline

LSMD = Least Squares Mean Difference

FAS = Full Analysis Set

TEAE = Treatment Emergent Adverse Event

MCP = Multiple comparisons procedure: FWER controlled for hypothesis testing of selected endpoints as specified in Section <cross-reference>.

[1] All estimand attributes explicitly identified for primary/secondary and selected key estimands only.

3.2 Clinical Study Design

A double-blinded, randomized, placebo-controlled, parallel-group study.
The study will be performed in female subjects aged 18-50 since this is the population expected to benefit from the intervention studied.
The study structure based on assessments using video -and phone-calls to ensure access to a broad population in a wide area although only one study site will be involved.
No clinical safety assessments are considered necessary considering the general good safety profile of probiotics.

3.3 Statistical Hypotheses

Hypothesis:
H_0: Mean number of UTIs in Probiotic group = Mean number of UTIs in the placebo group.
H_1: Mean number of UTIs in Probiotic group ≠ Mean number of UTIs in the placebo group.

3.4 Number of Subjects

The number of subjects needed to verity that the mean number of UTIs during six months for the probiotic will be 0.75 and for placebo 1.35 with a common standard deviation of 1.15, will be 118 (1:1 randomization) using a significance level of 5% and a power of 80%.
Assuming a drop-out rate of 15% a total of 140 subjects will be included, 70 in each intervention arm.

3.5 Methods of Assigning Subject to IMP

The study will consist of a combined screening and randomization assessment, an IP first dose confirmation call and monthly follow up assessments for six months. The screening and randomization assessment will be performed as a phone call or a video-call using an e-health digital platform. Informed consent will be signed via Bank ID. The monthly follow-up assessments will be performed either as a video-call or by phone. However, physical visits to the clinic at CTC AB might be performed for subjects in Uppsala.
Subjects will be recruited from advertising (*e.g* in social media, at pharmacies etc.). The subjects will contact the study site by phone or e-mail. Brief oral information about the study will be given and pre-defined pre-screening questions will be asked. Written information will be sent to the subjects qualified for screening together with instructions regarding the e-health platform and Bank ID signing procedures.
During the screening and randomization assessment, full information about the study will be given and informed consent. Information regarding demographics, weight, height, medical history, UTI history, medication history, use of restricted products, and pregnancy will be collected and diet restrictions. Subjects will be screened for eligibility as per the pre-defined eligibility criteria.
Eligible and consenting subjects will be randomized to intervention with either *Lactobacillus reuteri* or placebo. The subject will be provided with Investigational Product (IP) for three months (90 days) and niture/Leu urine test kits. Instructions to start intake of IP as soon as the IP has been picked-up will be given. The subject will be contacted by study staff 1-3 days after randomization to confirm that first IP dose has been taken.
At the monthly assessments (video-call/phone-call or visit), the subject will be asked to answer predefined questions regarding symptoms (frequency, urgency and dysuria). If two out of three symptoms are present a UTI is confirmed. If only one symptom is present the subject will perform a niture/Leu urine test at home, preferably on urine retained in the bladder for approximately 3 hrs. If the test is positive (one of two analyses), a UTI is confirmed and the subject is recommended to contact the health care system for consultation regarding antibiotic treatment. Information on AEs, concomitant medications, use of restricted products, pregnancy, and compliance with instructions for IP intake will be collected.

An electronic diary will be used by the subject during the study period for recording of occurrence of UTI symptoms and sexual activity (frequency of intercourse, new partner, use of condom with spermicide).
The monthly follow-up assessment after six months will be the final study assessment. Number of empty sachets and any unused IP will be reported to CTC AB by the subject and documented by site staff on the IP accountability list.

3.6 Blinding

This is a double-blinded study. All study staff, including the Principal Investigator and the persons performing the subject assessments using the video link or phone calls, will be blinded during the study. Sealed individual treatment code envelopes will be kept at the clinic to be able to break the code if any emergency occurs, as judged by the Investigator.

4 STATISTICAL AND ANALYTICAL PLANS

4.1 Sample Size Determination

A total of 140 subjects completed will be required, 70 in each intervention arm.

4.2 Definition of Analysis Sets

4.2.1 Full Analysis Set

The Full Analysis Set (FAS) will consist of all subjects who have been randomized and received at least one dose of Intervention.

4.2.2 Per Protocol Analysis Set

The Per Protocol Set (PPS) will consist of all subjects who have been randomized, completed the three months of intervention period and without any major protocol deviations. All deviations will be presented and discussed at the clean file meeting. If the compliance with the IP regimen should be below 80% the subject will not be included in the PPS population. The definition of compliance by calculating the number of days in the study (90 days) in relation to number of unused IP as reported by the subject.

$$\frac{90\ days - number\ of\ doses\ unused}{study\ length\ with\ a\ maximum\ of\ 90\ days} \geq 0.80$$

Calculations for compliance will be used on visit 4 (3 month).
Subjects who have been used prohibited medications, long term antibiotics or Hipex during the study will be excluded from PPS.
Subjects not participated at visit 4 and 7 (3 month and 6 month) will not be included in the PPS population.

4.2.3 Use of analysis set

The FAS population will be used for both of efficacy (primary objectives and secondary objectives) and safety evaluation and the PPS will only be used for the efficacy (i.e. secondary objectives) evaluations.

4.3 Definition of Baseline

Baseline measurement is defined as the latest measurement prior to first dose of IMP.

4.4 Summary Statistics

In general, all data collected will be presented with summary statistics and given in patient data listings. Summary statistics will include at least number of patients, mean, standard deviation, median, minimum and maximum for continuous data and frequency and percentage for categorical data. Table with summary statistics will be divided by treatment group and dose group, and visit where applicable. Patient data listings will be sorted by treatment, subject and timing of assessments.

4.5 Significance Level

The estimated intervention difference will be presented by LSMeans and a 95% confidence interval.

4.6 Multiple Comparisons/Multiplicity

All statistical significant findings need to be interpreted from a medical perspective and judged as clinical relevant or not and therefore no adjustment for multiplicity will be performed.

4.7 Handling of Drop-outs, Missing Data and Outliers

Outliers will be included in summary tables and listings, and will not be handled separately in any analyses. No imputation of data will be performed.

4.8 Adjustment for Covariates

History of UTIs and age will be used as covariates in the analysis of mean number of UTIs. Sexual activity will only be used as a covariate in the analysis if it is possible.

4.9 Multicentre Studies

No adjustment for centre will be applied, since this will not be considered as a multi-centre study.

4.10 Examination of Subgroups

Will be discussed with the client.

4.11 Blind Review

Not applicable.

4.12 Deriving of confirmed and unique UTI

Definitions of confirmed UTI – If a subject have at least one of three statements:

- A total number of symptoms ≥ 2
- A positive urine test registered at site
- A positive test, self-reported

Definitions of unique UTI – If a subject have no confirmed UTIs within 14 days prior to the current confirmed UTI and have at least one of two statements:

- Confirmed UTI registered at site
- Confirmed UTI, self-reported and no confirmed self-reported UTIs within 14 days prior to the UTI (only applied to self-reported UTIs, since UTIs registered at site are assigned the date of telephone contact and not the date of the actual UTI)

Assigning dates to confirmed UTIs reported by site personnel: Date of previous telephone contact used if date is ≤ 14 days prior to registering in the UTI log. In case of later reporting of UTIs, the closest unmatched event date with indication of UTI prior to registration is used as date.

5 SUBJECTS

5.1 Subject Disposition

The number of subjects that entered the study, withdrawn subjects, completed subjects and the number of subjects at each visit will be summarized by treatment.

5.2 Baseline Characteristics and Demographics

The following baseline characteristics will be given by treatment:

- Age
- Ethnicity
- Weight, height and BMI
- Medical/Surgical history
- UTI history

6 TREATMENT INFORMATION AND EXTENT OF EXPOSURE

6.1 Active Treatment

The number of subjects on each IP will be tabulated with start time, stop time and duration of application will be tabulated using listings and summary statistics.

6.2 Prior and Concomitant Medications

Prior and concomitant medication data will be listed and tabulated by ATC code. Prior and concomitant medications will be coded according to the World Health Organization (WHO) Anatomic Therapeutic Chemical (ATC) classification system.

7 STATISTICAL METHODOLOGY

All parameters will be presented by treatment and visit using summary statistics. Additional statistical analyses are specified below.

7.1 Primary endpoint(s) Analysis

The primary endpoint will be the mean number of confirmed UTIs during six months from start of intervention, as compared to placebo.
The mean number of UTIs per intervention group will be estimated based on the total number of UTIs by subject.
An additional analysis will be made to include the subjects who have been used prohibited medications, long term antibiotics and Hiprex during the study.

7.1.1 Main analytical approach

The mean number of UTIs will be analysed using analysis of covariance with intervention, UTI history and age as independent variables. Sexual activity will only be used in the analysis if it is possible.

7.1.2 Sensitivity analysis

No sensitivity analysis for primary endpoint(s) will be performed.

7.1.3 Supplementary analyses

No supplementary analysis for primary endpoint(s) will be performed.

7.1.4 Presentation

All graphs and tables will be presented in demographic data, section 13.

7.2 Secondary Endpoint(s) Analysis

7.2.1 Definition of endpoint(s)

7.2.1.1 Number of confirmed UTIs

The number of confirmed UTIs for both the:

- Mean number of confirmed UTIs during the three months' intervention period, as compared to placebo.

and

- Mean number of confirmed UTIs during the three months' follow-up period, as compared to placebo.

will be analysed using the same methods as for the primary endpoint.

7.2.1.2 Time to first relapse of UTI

Time to first relapse of UTI will be defined as the time from delivery of intervention (*i.e.* start of intervention) to date of first confirmed UTI ((Confirm date – Intervention date) + 1).
Subjects with no UTI will be censored at last known date within the study period.
The time to first relapse will be analysed using Cox regression analysis and presented by Kaplan-Meier graphs.

7.2.1.3 Relapse rate

The relapse rate for both:

- Proportion of subjects (%) who experienced at least one confirmed UTI during three months from start of intervention, as compared to placebo.

and

- Proportion of subjects (%) who experienced at least one confirmed UTI during six months from start of intervention, as compared to placebo.

will be analysed using Chi-square test without continuity correction and presented using frequency tables.

7.2.2 Analysis safety endpoint(s)

7.2.2.1 Adverse events

Adverse events and SAEs will be recorded from start of IP intervention. Medical events occurring between screening and start of IP intervention will be reported separately.

7.2.3 Main analytical approach

The mean number of UTIs will be analysed using analysis of covariance with intervention, UTI history and age as independent variables. Sexual activity will only be used in the analysis if it is possible. No intervention by centre interaction will be possible to apply in this analysis. The estimated intervention difference will be presented by LSMeans and a 95% confidence interval. The time to first relapse of UTI will be analysed using Cox regression analysis and presented by Kaplan-Meier graphs.

7.2.4 Sensitivity analysis

No sensitivity analysis for secondary endpoint(s) will be performed.

7.2.5 Supplementary analyses

No supplementary analysis for secondary endpoint(s) will be performed.

7.2.6 Presentation

The p-values will be included in the summary tables.

7.3 Tertiary/Exploratory Endpoint(s) Analysis

No tertiary/exploratory analysis will be performed.

7.4 Discontinuation

Patients who discontinue from IMP treatment will be tabulated. The reason for discontinuation will be given. For discontinuation due to AE, the AEs will be given.

7.5 Other Analyses

No other analysis will be performed.

7.6 Interim Analysis

No interim analysis will be performed.

8 CHANGES FROM THE CSP

The following have been adjusted regarding to the CSP:

- Sexual activity will only be used in the analysis if it is possible.
- The definition of confirmed and unique UTI's have been added.
- Specify the definition of compliance for PPS.
- Subjects who have been used prohibited medications, long term antibiotics or Hipex during the study will be excluded from PPS.
- Subjects not participated at visit 4 and 7 (3 month and 6 month) will not be included in the PPS population.

9 STATISTICAL DELIVERABLES

The following documents will be delivered:

- SAP
- Statistical analyses and summary tables

10 SOFTWARE

All statistical analyses will be performed using SAS Version 9.4 (SAS institute, Cary, NC).

11 APPROVAL

Issued by:

Fredrik Hansson, Director Biometrics
CTC Representative

03 SEP 2019
Date (dd-Mmm-yyyy)

Approved by:

Kerstin Nilsson

4 SEP 2019
Date (dd-Mmm-yyyy)

Kerstin Nilsson, Clinical Research Manager
BioGaia AB Representative

12 SUPPORTIVE DOCUMENTATION

12.1 Appendix 1. – List of Abbreviations

Abbreviation of term	Explanation
AE	Adverse Event
ATC	Anatomical-Therapeutic-Chemical
BMI	Body Mass Index
CF	Clean File
cfu	Colony-forming units
CRF	Case Report Form
CSP	Clinical study protocol
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
DMP	Data Management Plan
DSM	*Deutsche Sammlung von Mikroorganismen*
DVP	Data Validation Plan
eCRF	Electronic Case Report Form
EEA	European Economic Area
FAS	Full Analysis Set
GI	Gastro-intestinal
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IP	Investigational Product
N	Number
MedDRA	Medical Dictionary for Regulatory Affairs
PAC	Proanthocyanidin
PPS	Per Protocol Set
RCT	Randomized Clinical Trials
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SAS	Statistical Analysis System
SD	Standard Deviation
SDV	Source Data Verification
SOP	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
UTI	Urinary Tract Infection
Enrolled subject	Subject who has signed the Informed Consent Form (ICF)
Screening failure	Enrolled subject not included
Included subject	Subject randomized
Withdrawn subject	Subject randomized but not completed
Completed subject	Subject completed both the intervention and the follow-up periods

12.2 Appendix 2. – Changes to Protocol-Planned Analyses

13 Demographic data

13.1 Demographic information

TABLE 14.1.1.1 SUMMARY OF DEMOGRAPHIC DATA AND OTHER BASELINE CHARACTERISTICS (FULL ANALYSIS SET)

		Treatment A (N=xx)	Treatment B (N=xx)	Total (N=xx)
Age (years)	n/nmiss	xx/x	xx/x	xx/x
	Mean (SD)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)
	Median (Min, Max)	xx.x (x, xx)	xx.x (x, xx)	xx.x (x, xx)
Weight (kg)	n/nmiss	xx/x	xx/x	xx/x
	Mean (SD)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)
	Median (Min, Max)	xx.x (x, xx)	xx.x (x, xx)	xx.x (x, xx)
Height (cm)	n/nmiss	xx/x	xx/x	xx/x
	Mean (SD)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)
	Median (Min, Max)	xx.x (x, xx)	xx.x (x, xx)	xx.x (x, xx)
BMI (M2)	n/nmiss	xx/x	xx/x	xx/x
	Mean (SD)	xx.x (x.x)	xx.x (x.x)	xx.x (x.x)
	Median (Min, Max)	xx.x (x, xx)	xx.x (x, xx)	xx.x (x, xx)

13.2 Medical/Surgical history

TABLE 14.1.4 MEDICAL HISTORY EVENTS BY SYSTEM ORGAN CLASS AND PREFERRED TERM (FULL ANALYSIS SET)

	Treatment A N=xx		Treatment B N=xx		Total N=xx	
System organ class Preferred term	n(%)	m	n(%)	m	n(%)	m
Total	**x(xx%)**	**x**	**x(xx%)**	**x**	**x(xx%)**	**x**
Psychiatric disorders	**x(xx%)**	**x**	**x(xx%)**	**x**	**x(xx%)**	**x**
Anxiety	x(xx%)	x	x(xx%)	x	x(xx%)	x
Depression	x(xx%)	x	x(xx%)	x	x(xx%)	x
Insomnia	x(xx%)	x	x(xx%)	x	x(xx%)	x
Immune system disorders	**x(xx%)**	**x**	**x(xx%)**	**x**	**x(xx%)**	**x**
Hypersensitivity	x(xx%)	x	x(xx%)	x	x(xx%)	x
Seasonal allergy	x(xx%)	x	x(xx%)	x	x(xx%)	x
Metabolism and nutrition disorders	**x(xx%)**	**x**	**x(xx%)**	**x**	**x(xx%)**	**x**
Type 1 diabetes mellitus	x(xx%)	x	x(xx%)	x	x(xx%)	x
General disorders and administration site conditions	**x(xx%)**	**x**	**x(xx%)**	**x**	**x(xx%)**	**x**
Chronic fatigue syndrome	x(xx%)	x	x(xx%)	x	x(xx%)	x
Nervous system disorders	**x(xx%)**	**x**	**x(xx%)**	**x**	**x(xx%)**	**x**
Narcolepsy	x(xx%)	x	x(xx%)	x	x(xx%)	x
Reproductive system and breast disorders	**x(xx%)**	**x**	**x(xx%)**	**x**	**x(xx%)**	**x**
Premenstrual syndrome	x(xx%)	x	x(xx%)	x	x(xx%)	x
Respiratory, thoracic and mediastinal disorders	**x(xx%)**	**x**	**x(xx%)**	**x**	**x(xx%)**	**x**
Asthma	x(xx%)	x	x(xx%)	x	x(xx%)	x
Vascular disorders	**x(xx%)**	**x**	**x(xx%)**	**x**	**x(xx%)**	**x**
Hypertension	x(xx%)	x	x(xx%)	x	x(xx%)	x

n, number of subjects; m, number of events. Percentages are based on the number of subjects in the full analysis set

13.3 Subject disposition and exposure

TABLE 14.1.1.2 SUBJECT DISPOSITION

	Treatment A	Treatment B	Total
Screened subjects	xx	xx	xx
Subjects that entered the study	xx	xx	xx
Withdrawn subjects	xx	xx	xx
Completed subjects	xx	xx	xx
Included in FAS	xx	xx	xx
Included in PPS*	xx	xx	xx
Subjects at Screening	xx	xx	xx
Subjects at Visit 2	xx	xx	xx
Subjects at Visit 3	xx	xx	xx
Subjects at Visit 4	xx	xx	xx
Subjects at Visit 5	xx	xx	xx

13.4 CONCOMITANT MEDICATIONS

LISTING 16.2.5.2.1. CONCOMITANT MEDICATIONS, INDICATIONS (FULL ANALYSIS SET)

Gender	Subject Identifier for the Study	Sequence Number	Reported Name of Drug, Med, or Therapy	Standardized Medication Name	Medication Class Code	Category for Medication	Dose Description	Dose Units	Route of Administration	Dosing Frequency per Interval
Female	xxx	x	xx«	xxx	XXX	Medical/ surgical history	xx	mg	Oral	Daily
Female	xxx	x	xx«	xxx	XXX	Medical/ surgical history	xx	mg	Oral	Daily
Female	xxx	x	xx«	xxx	XXX	Medical/ surgical history	xx	mg	Oral	As needed

13.5 Primary Endpoint: XXXX

TABLE 14.2xx XXXX (µg/l)

Variable	Result Category	Visit Name		Treatment A	Treatment B
XXXXX	Measured value	Visit 1 Baseline	N	xx	xx
			Mean (SD)	xx (xxx)	xx (xxx)
			Median (Min, Max)	xx (xx, xx)	xx (xx, xx)
			95% CI	xx;xx	xx;xx
		Visit 2	N	xx	xx
			Mean (SD)	xx (xxx)	xx (xxx)
			Median (Min, Max)	xx (xx, xx)	xx (xx, xx)
			95% CI	xx;xx	xx;xx
	Absolute change from baseline	Visit 2	N	xx	xx
			Mean (SD)	xx (xxx)	xx (xxx)
			Median (Min, Max)	xx (xx, xx)	xx (xx, xx)
			95% CI	xx;xx	xx;xx
			Between groups p-value (Wilcoxon)	0.xxxx	0.xxxx
			Within group p-value (Wilcoxon)	0.xxxx	0.xxxx
	Percent change from baseline (%)	Visit 2	N	xx	xx
			Mean (SD)	xx (xxx)	xx (xxx)
			Median (Min, Max)	xx (xx, xx)	xx (xx, xx)
			95% CI	xx;xx	xx;xx
			Between groups p-value (Wilcoxon)	0.xxxx	0.xxxx
			Within group p-value (Wilcoxon)	0.xxxx	0.xxxx

13.6 Continuous variables measured over time

TABLE 14.2.xx Variables over time

Variable	Result Category	Visit Name		Treatment A	Treatment B
XXXXX	Measured value	Visit 1 Baseline	N	xx	xx
			Mean (SD)	xx (xxx)	xx (xxx)
			Median (Min, Max)	xx (xx, xx)	xx (xx, xx)
			95% CI	xx;xx	xx;xx
		XX	N	xx	xx
			Mean (SD)	xx (xxx)	xx (xxx)
			Median (Min, Max)	xx (xx, xx)	xx (xx, xx)
			95% CI	xx;xx	xx;xx
	Absolute change from baseline	XX	N	xx	xx
			Mean (SD)	xx (xxx)	xx (xxx)
			Median (Min, Max)	xx (xx, xx)	xx (xx, xx)
			95% CI	xx;xx	xx;xx
			Between groups p-value (Wilcoxon)	0.xxxx	0.xxxx
			Within group p-value (Wilcoxon)	0.xxxx	0.xxxx
	Percent change from baseline (%)	XX	N	xx	xx
			Mean (SD)	xx (xxx)	xx (xxx)
			Median (Min, Max)	xx (xx, xx)	xx (xx, xx)
			95% CI	xx;xx	xx;xx
			Between groups p-value (Wilcoxon)	0.xxxx	0.xxxx
			Within group p-value (Wilcoxon)	0.xxxx	0.xxxx

13.7 Continuous variables measured at one occasion

TABLE 14.2.xx Variables at one occasion

Variable	Result Category	Visit Name		Treatment A	Treatment B
XXXXX	Measured value	XXX	N	xx	xx
			Mean (SD)	xx (xxx)	xx (xxx)
			Median (Min, Max)	xx (xx, xx)	xx (xx, xx)
			95% CI	xx;xx	xx;xx
			Between groups p-value (Wilcoxon)	0.xxxx	0.xxxx

13.8 Categorical variables at different visits

TABLE 14.2.xx categorical variables over time

		Treatment A (N=xx)	Treatment B (N=xx)	Total (N=xx)
Prevalence of XXXXXXX visit x	No	xx (xx%)	xx (xx%)	xx (xx%)
	Yes	xx (xx%)	xx (xx%)	xx (xx%)
	Chi-Square p-value			0.xxxx
Prevalence of XXXXXXX visit x	No	xx (xx%)	xx (xx%)	xx (xx%)
	Yes	xx (xx%)	xx (xx%)	xx (xx%)
	Chi-Square p-value			0.xxxx
Prevalence of XXXXXXX visit x	No	xx (xx%)	xx (xx%)	xx (xx%)
	Yes	xx (xx%)	xx (xx%)	xx (xx%)
	Chi-Square p-value			0.xxxx
Prevalence of XXXXXXX visit x	No	xx (xx%)	xx (xx%)	xx (xx%)
	Yes	xx (xx%)	xx (xx%)	xx (xx%)
	Chi-Square p-value			0.xxxx

13.9 Adverse events

TABLE 14.3.1.1 OVERVIEW OF ADVERSE EVENTS, FAS

	Treatment A N=XX n(%)	Treatment B N=XX n(%)	Total N=XX n(%)
Any AE	x(xx%)	x(xx%)	x(xx%)
Any SAE	x(xx%)	x(xx%)	x(xx%)
Any AE leading to withdrawal	x(xx%)	x(xx%)	x(xx%)
Any AE leading to death	x(xx%)	x(xx%)	x(xx%)
Causality			
Not Related	x(xx%)	x(xx%)	x(xx%)
Possible	x(xx%)	x(xx%)	x(xx%)
Probable	x(xx%)	x(xx%)	x(xx%)
Severity			
Mild	x(xx%)	x(xx%)	x(xx%)
Moderate	x(xx%)	x(xx%)	x(xx%)

n, number of subjects; m, number of events
Percentages are based on the number of subjects in the treatment period included in the full analysis set.
Adverse events that occurred during follow-up are omitted from summary.

TABLE 14.3.1.2 ADVERSE EVENTS BY SYSTEM ORGAN CLASS AND PREFERRED TERM, FAS

	Treatment A N=XX		Treatment B N=XX		Total N=XX	
System organ class Preferred term	n(%)	m	n(%)	m	n(%)	m
Gastrointestinal disorders	**x(xx%)**	**y**	**x(xx%)**	**y**	**x(xx%)**	**y**
Dry mouth	**x(xx%)**	**y**	**x(xx%)**	**y**	**x(xx%)**	**y**
Gingival blister	**x(xx%)**	**y**	**x(xx%)**	**y**	**x(xx%)**	**y**
Lip pain	**x(xx%)**	**y**	**x(xx%)**	**y**	**x(xx%)**	**y**
Nausea	**x(xx%)**	**y**	**x(xx%)**	**y**	**x(xx%)**	**y**
Infections and infestations	**x(xx%)**	**y**	**x(xx%)**	**y**	**x(xx%)**	**y**
Diarrhoea infectious	**x(xx%)**	**y**	**x(xx%)**	**y**	**x(xx%)**	**y**
Gastroenteritis viral	**x(xx%)**	**y**	**x(xx%)**	**y**	**x(xx%)**	**y**
Influenza	**x(xx%)**	**y**	**x(xx%)**	**y**	**x(xx%)**	**y**
Nasopharyngitis	**x(xx%)**	**y**	**x(xx%)**	**y**	**x(xx%)**	**y**
Nervous system disorders	**x(xx%)**	**y**	**x(xx%)**	**y**	**x(xx%)**	**y**
Dizziness	**x(xx%)**	**y**	**x(xx%)**	**y**	**x(xx%)**	**y**

n, number of subjects; m, number of events
Percentages are based on the number of subjects in the treatment period included in the full analysis set.
Adverse events that occurred during follow-up are omitted from summary.

TABLE 14.3.1.3 ADVERSE EVENTS: SEVERITY AND RELATION, WITH PATIENT IDENTIFICATIONS, FAS

			Mild --- NR	Mild --- Related	Moderate --- NR	Moderate --- Related	Total --- NR	Total --- Related	Total --- R+NR
Treatment A (N=xx)	Gastrointestinal disorders	Nausea		x (xx%)				x (xx%)	x (xx%)
				xxx **					
				xxx					
	Infections and infestations	Gastroenteritis viral			x (xx%)		x (x%)		x (xx%)
					xxx				
		Nasopharyngitis	x (xx%)				x (x%)		x (xx%)
			xxx						
	Nervous system disorders	Dizziness		x (xx%)				x (xx%)	x (xx%)
				xxx					
Treatment B (N=xx)	Gastrointestinal disorders	Dry mouth		x (xx%)				x (xx%)	x (xx%)
				xxx					
		Gingival blister				x (xx%)		x (xx%)	x (xx%)
						xxx			
		Lip pain	x (xx%)				x (xx%)		x (xx%)
			xxx						
	Infections and infestations	Diarrhoea infectious			x (xx%)		x (xx%)		x (xx%)
					xxx				
		Influenza	x (xx%)				x (xx%)		x (xx%)
			xxx						

**: Subject randomisation number
R: Related. NR: Not related. AEs judged as 'Possibly Related' or 'Problably Related' are grouped as 'Related'.
Adverse events that occurred during follow-up are omitted from summary.