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Clinical Development

LIK066

Clinical Trial Protocol CLIK066B2203 / NCT03198767

Randomized, open label, two-part, three-period, cross-over study to investigate the effects of carbohydrate in diet and to evaluate supplements on the gastrointestinal tolerability of LIK066 in overweight or obese subjects

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
21-June-2017	Prior to DB lock	Creation of initial version	N/A – First version	NA
[redacted]				
21-Sep-2017	Prior to DB lock		Daily number of bowel movements is added as another variable for the primary endpoint, three-day total number of bowel movements is added as another variable for the secondary endpoint	Section 6.1
21-Sep-2017	Prior to DB lock	Study conduct issues	Method to impute missing urine volume is updated	Section 6.3.3.1

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1 Introduction

1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial ***"CLIK066B2203".***

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

1.2 Study reference documentation

Protocol version used for this SAP is final version v01 dated 08-Aug-2017.

1.3 Study objectives

The objectives of this study are: 1) to assess whether or not a meal containing low carbohydrate in the form of glucose and galactose is associated with less diarrhea compared to a high carbohydrate meal; 2) to assess the potential effects of supplements such as psyllium or calcium carbonate on alleviating diarrhea.

1.3.1 Primary objective(s)

Primary objective(s)	*Endpoints related to primary objective(s)*
• To assess the effects of meals with different carbohydrate content on diarrhea	• Diarrhea (consistency and incidence)
• To assess the effects of supplements (psyllium and calcium carbonate) on diarrhea	• Diarrhea (consistency and incidence)

1.3.2 Secondary objective(s)

Secondary objective(s)	*Endpoints related to secondary objective(s)*
• To assess the effects of LIK066 and carbohydrate in meal on fecal parameters	• Stool samples (timing, assessment of consistency with Bristol stool chart, stool weight, and stool pH)

1.4 Study design and treatment

This study employs a randomized, open-label, two-part, three-period, cross-over design.

This is a non-confirmatory study. Each part of the study will enroll approximately 24 overweight or obese subjects, thus, a total of approximately 48 subjects will be enrolled for the entire study. In each part of the study, each subject will be randomized to one of the 3 treatment sequences shown in Figure 1-1 (Part A) and Figure 1-2 (Part B). Blocked randomization within each study part will be used.

Part A of the study will assess the effects of % carbohydrate (50%, 25% and 0%) in the breakfast meals on diarrhea when LIK066 is administered immediately before the breakfast.

Part B of the study will assess the effects of a concomitant treatment with a supplement (calcium carbonate or psyllium) on diarrhea when LIK066 is administered immediately before a breakfast meal with 50% carbohydrate.

The study will consist of an up to 24 day screening period, a 3 day baseline/run in period, and three periods of treatment of 3 days each with a 5 day washout period in between each treatment period. Study completion will occur 3 days after the last dose of LIK066.

The baseline, treatment and washout periods will be conducted with subjects being domiciled for approximately 25 days (see Figure 1-1 and Figure 1-2).

Figure 1-1 Part A: Effects of Carbohydrate in the Breakfast Meals*

Screening Period Day-28 to -4	Baseline Day -3 to -1	Sequence	Treatment Period 1 Day 1-3	Washout 5 Days	Treatment Period II Day 9-11	Washout 5 Days	Treatment Period III Day 17-19	Washout EOS Day 20-22
	Run-In	1 (n=8)	50% CHO		25% CHO		0% CHO	
	Run-In	2 (n=8)	25% CHO		0% CHO		50% CHO	
	Run-In	3 (n=8)	0% CHO		50% CHO		25% CHO	

* CHO = % carbohydrate content in the standardized breakfast meal

LIK066 50mg QD will be given in the morning immediately before the breakfast meal

Figure 1-2 Part B: Effects of Supplements in the Breakfast Meals**

Screening Period Day-28 to -4	Baseline Day -3 to -1	Sequence	Treatment Period 1 Day 1-3	Washout 5 Days	Treatment Period II Day 9-11	Washout 5 Days	Treatment Period III Day 17-19	Washout EOS Day 20-22
	Run-In	I (n=8)	NS		Psyllium		CC	
	Run-In	II (n=8)	Psyllium		CC		NS	
	Run-In	III (n=8)	CC		NS		Psyllium	

** CHO = % carbohydrate content in the standardized breakfast meal (50%) for all groups
LIK066 (50 mg QD) and supplement will be administered immediately before the breakfast meal
NS = No supplement
CC = Calcium Carbonate (1 gram)
Psyllium = 6 grams

There will be no interim analyses planned for the study.

2 First interpretable results (FIR)

First interpretable results (FIR) will be provided for this trial.

The study FIR template (mock slides) can be found in CREDI in the study RAP folder Cabinets/CREDI Projects/L/LIK066/CREDI Studies/LIK066B2203/Administrative Files (study level)/RAP or RAMP Meeting/.

The template shows the analysis / results to be presented in the FIR. Study outputs required to be created at the time of the FIR will be highlighted in TFL shells document and marked as "Key" in the Programming Deliverables Tracker (PDT) output list.

3 Interim analyses

Not applicable.

4 Statistical methods: Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatments received.

The safety analysis set will include all subjects that received any study drug. All subjects in the safety analysis set will be included in the safety data analysis.

[redacted]

The PD analysis set will include all subjects in safety analysis set with available PD (diarrhea) data post baseline and no protocol deviations with relevant impact on PD data. All subjects in the PD analysis set will be included in the PD data analysis.

For subjects for which the actual sequence of treatments received does not match the randomized sequence of treatments, the actual sequence will be used for analysis involving a sequence component if the actual sequence is one of the sequences planned in the study design. If the actual sequence is not one of the sequences planned in the study design, the randomized sequence will be used for analysis involving a sequence component but data points from periods in which the subject has not received the randomized treatment will be excluded from the analysis.

The analysis sets and protocol deviation codes are related as follows:

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from PD and PK analysis in case of these protocol deviations:		Exclude subject from PD and PK analysis set
	All inclusion and exclusion criteria deviations	
TRT01	*Subject received treatment sequence that do not belong to ones specified for the study*	*Only data points from periods different from randomized sequence will be excluded*
TRT02	*Subject doesn't have sufficient wash out per protocol*	
COMD01	*Subject received prohibited concomitant medication*	

Summary of frequency of subjects in each analysis set will be provided and subjects excluded from each analysis set will be listed with reasons being excluded. All protocol deviation will be listed together with corresponding analysis set(s) being excluded when applicable.

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL.

6 Statistical methods for Pharmacodynamic (PD) parameters

All subjects within the PD analysis set will be included in the PD data analysis.

6.1 Primary objective

The primary objectives of this study are to assess the efficacy of:

- Meals with different carbohydrate content on diarrhea
- Supplements such as (psyllium and calcium carbonate) on diarrhea

when LIK066 is administrated immediately before the breakfast.

6.1.1 Variables

The primary endpoint diarrhea will be assessed by the below two variables

1. Daily number of stools with a BSC score of 6 or 7.

2. Daily number of bowel movements

6.1.2 Descriptive analyses

Daily number of stools with a BSC score of 6 or 7 and daily number of bowel movements will be listed by treatment sequence, subject, and visit/sampling time point. Descriptive summary statistics for the observed value and change from baseline will be provided by treatment and visit. Summary statistics will include mean (arithmetic), SD, median, minimum and maximum.

Observed Mean (SD) plot and spaghetti plot of individuals' observed data will be produced by treatment.

6.1.3 Statistical model, assumptions and hypotheses

The primary efficacy hypotheses are that the mean daily number of stools with a BSC score of 6 or 7 /change from baseline in daily number of bowel movements in:

1. the 50% carb group is higher than other groups with lower carbs
2. the no supplement group is higher than other groups with supplement.

The primary analysis will be performed by study part. The daily number of stools with a BSC score of 6 or 7 will be analyzed using a negative binomial mixed effects model with fixed effects of period, treatment, day, the period-by-day interaction, and the treatment-by-day interaction, and a random subject effect. An unstructured covariance matrix will be specified for the repeated observations on a subject within the same period. The least-squares mean and associated 80% CI for the daily number of stools with a BSC score of 6 or 7 for each treatment, and the estimated mean difference between each treatment, the p-value, and corresponding two-sided 80% CI, will be extracted from the model for each day, and summarized. Mean difference will then be exponentiated as ratio between treatments means. Conclusions from the analysis will be based on treatment differences from all 3 days, collectively.

Change from baseline in daily number of bowel movements will be analyzed by a linear mixed effects model with fixed effects of baseline daily number of bowel movements, period, treatment, day, the period-by-day interaction, and the treatment-by-day interaction, and a random subject effect. An unstructured covariance matrix will be specified for the repeated observations on a subject within the same period. Baseline is defined by the last daily measurement before dosing. If day -1 measurement is missing, day -2 or day -3 measurements will be used instead. The least-squares mean and associated 80% CI for each treatment, and the estimated mean difference between each treatment, the p-value, and corresponding two-sided 80% CI, will be extracted from the model and summarized.

6.1.3.1 Model checking procedures

Missing data will be assumed to be missing at random and thus the above analysis will be performed on all available data. There will be no imputation of missing data.

The interaction between treatment and day will be assessed, and if non-significant, the results from the 3 days will be averaged and corresponding model-based quantities extracted.

The model assumption of negative binomial distribution will be examined, especially if over-dispersion (i.e. variance>mean) exist. If the data doesn't fit negative binomial distribution or over-dispersion doesn't exist, other models such as Poisson regression will be explored.

The model assumption of no first-order carry-over effect may be evaluated by incorporating first-order carry-over effects into the above statistical models, and performing a type 3 test for the first order carry-over effect. In addition, descriptive summary statistics will also be provided by treatment sequence and visit in order to assess carry-over effect.

6.1.3.2 Graphical presentation of results

Least-square mean and least-square mean difference between treatments with 80% confidence intervals will be plotted by treatment for daily number of stools with a BSC score of 6 or 7 and daily number of bowel movements.

6.2 Secondary objectives

6.2.1 Variables

- Three-day total number of stools with a BSC score of 6 or 7 per period
- Three-day total number of bowel movements per period

Over each 24 hour collection period:

- Average stool consistency with Bristol stool chart

  It is defined as arithmetic average of consistency for all stools collected during 24 hour period.

- Average stool pH

  It is defined as arithmetic average of PHs for all stools collected during 24 hour period.

- Average stool weight

  It is defined as arithmetic average of weights for all stools collected during 24 hour period.

6.2.2 Descriptive analyses

All secondary endpoints will be listed by treatment sequence, subject, and visit/sampling time point. Descriptive summary statistics will be provided for the observed values and change from baseline by treatment and visit/period. Summary statistics for the three-day total number of episodes of diarrhea, average stool consistency, pH, and weight will include mean (arithmetic), SD, median, minimum and maximum. Observed Mean (SD) plot will be produced for all secondary endpoints.

6.2.3 Statistical model, assumptions and hypotheses

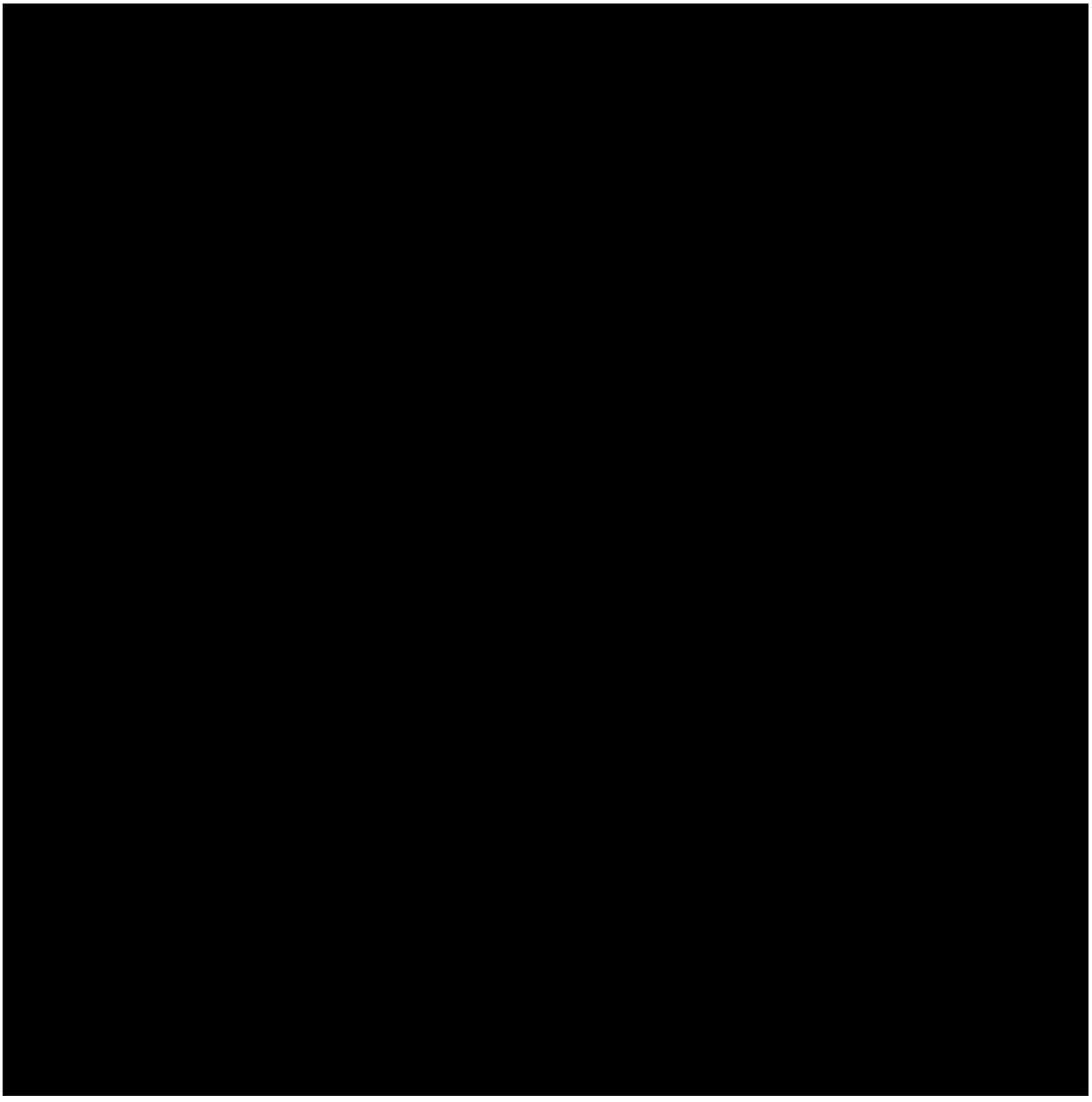
Three-day total number of stools with a BSC score of 6 or 7 per period will be analyzed by a negative binomial mixed effects model with random effect of subject and fixed effects of period and treatment. Change from baseline in three-day total number of bowel movements per period will be analyzed by a linear mixed effects model with random effect of subject and fixed effects of period, treatment and baseline three-day total number of bowel movements. Secondary endpoints including average stool consistency, PH and weight will be analyzed by a linear mixed effects model with random effect of subject and fixed effects of period, treatment, and baseline measurement. The least-squares mean and associated 80% CI for each treatment, and the estimated mean difference between each treatment, the p-value, and corresponding two-sided 80% CI, will be extracted from the model, and summarized.

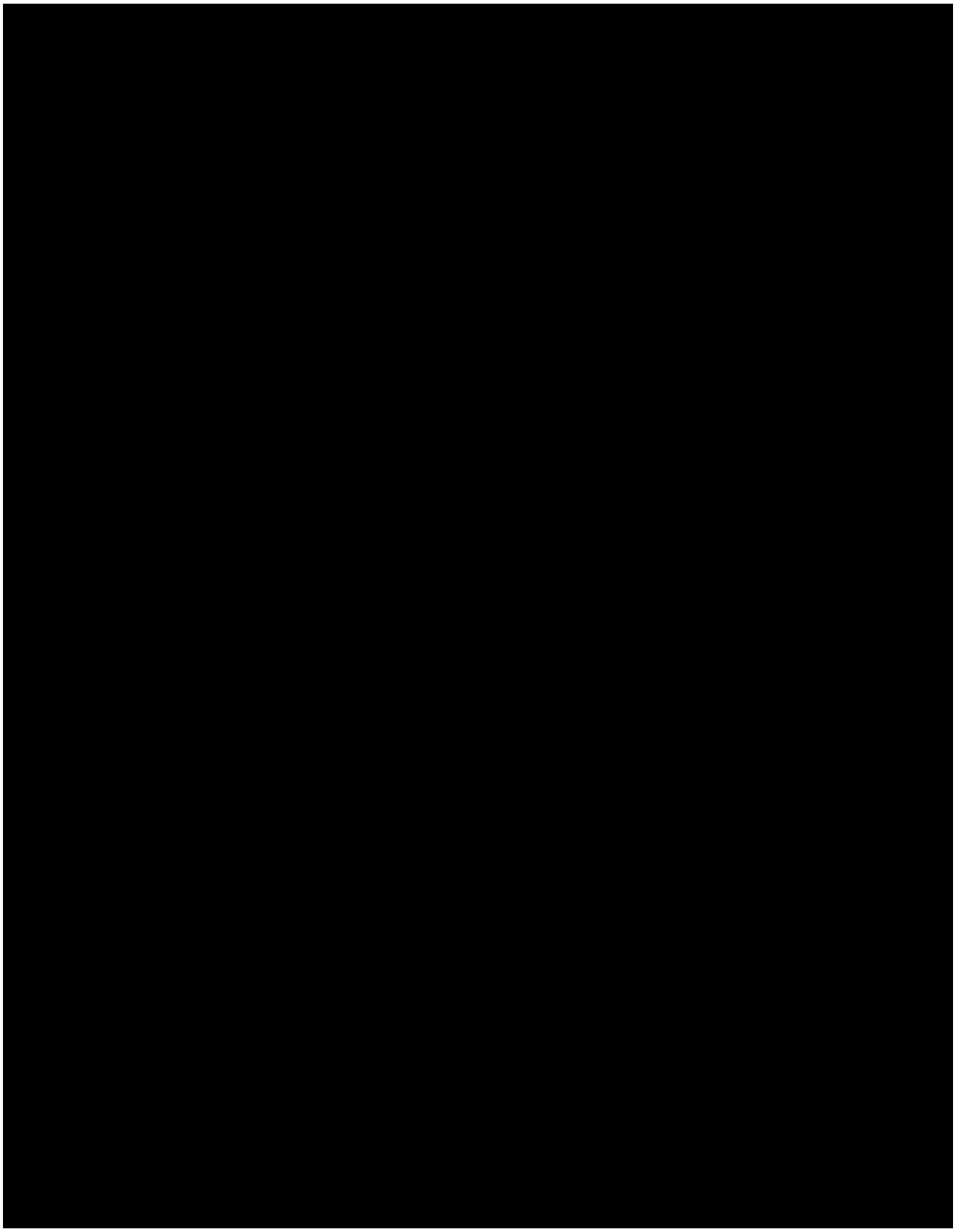
6.2.3.1 Model checking procedures

The model assumption of no first-order carry-over effect and negative binomial distribution will be examined for three-day total number of stools with a BSC score of 6 or 7 per period and three-day total number of bowel movements per period similarly to the primary endpoint. Missing data will be assumed to be missing at random and thus the above analyses will be performed on all available data. There will be no imputation of missing data.

6.2.3.2 Graphical presentation of results

Least-square mean and least-square mean difference between treatment groups with 80% confidence intervals will be plotted for all secondary endpoints by treatment.





7 Statistical methods for safety and tolerability data

7.1 Variables

Adverse events, vital signs (blood pressure, pulse rate, body temperature), ECG intervals, laboratory measurements, as well as subject demographics, baseline characteristics, and treatment information.

7.2 Descriptive analyses

Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment sequence and subjects in the safety analysis set. Summary statistics will be provided for all subjects in the safety analysis dataset, as well as for each treatment sequence.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment sequence and subject.

Subject disposition (frequency of completion/discontinuation and reasons for early discontinuation) will be summarized by epoch and treatment sequence.

Treatment

Data for study drug administration and meal/supplement dosing and concomitant therapies will be listed by treatment sequence and subject. Number of dose administration will be summarized by treatment.

Vital signs

All vital signs data will be listed by treatment sequence, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

ECG evaluations

All ECG data will be listed by treatment, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment, subject, and visit/time and if normal ranges are available abnormalities will be flagged. A separate listing is provided presenting all parameters in a subject with any abnormal values. Summary statistics will be provided by treatment and visit/time.

Adverse events (AEs)

All information obtained on adverse events will be listed by treatment sequence and subject.

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. An adverse event starting in one period/epoch and continuing into the next period/epoch is counted only in the onset period. A subject with multiple adverse events within a body system and treatment period/epoch is only counted once towards the total of this body system and treatment. If AE dates are needed to assign onset period and the dates are missing, AE date will be imputed by the following rule: if year is missing there will be no imputation of date. Otherwise missing month will be imputed by January, and missing day will be imputed by 1st.

Serious adverse events and adverse events leading to early discontinuation will be listed by treatment sequence and subject.

Adverse events leading to death will be listed by treatment sequence and subject.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on on-treatment/treatment emergent adverse events which are not serious adverse events with an incidence greater than 1% and on on-treatment/treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE.

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

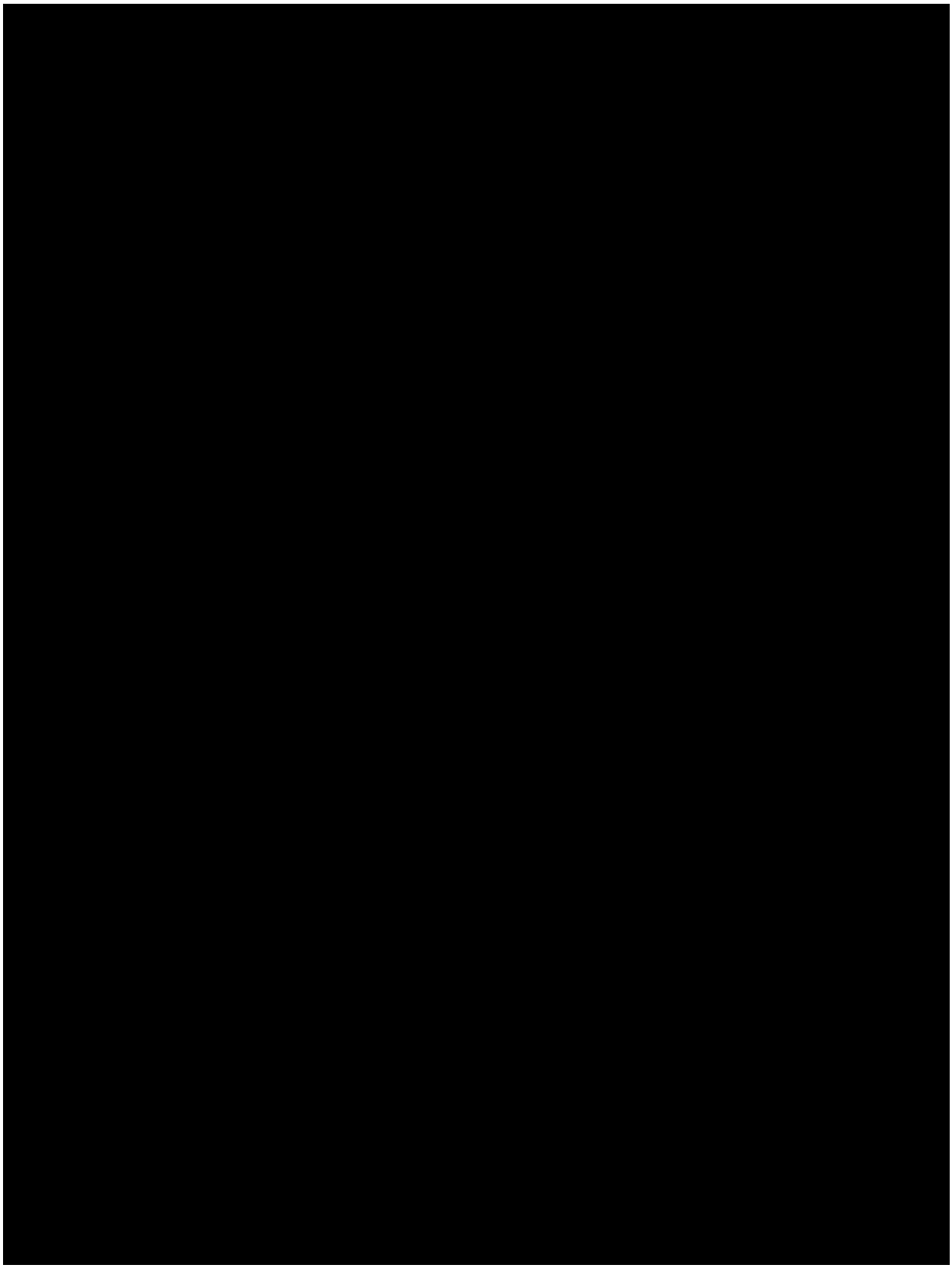
The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

Immunogenicity

Not applicable

7.3 Graphical presentation

There will be no graphic presentation of the safety data.



[redacted]

9 Reference list

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