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Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

LYS228

CLYS228X2202

A randomized, controlled, evaluator-blinded, multi-center study to evaluate LYS228 pharmacokinetics, clinical response, safety, and tolerability in patients with complicated intra-abdominal infection

Statistical Analysis Plan (SAP)

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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 ***"CLYS228X2202"***.

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

1.2 Study reference documentation

This SAP has been developed using Clinical Trial Protocol version v01 dated 02-Nov-2017.

1.3 Study objectives

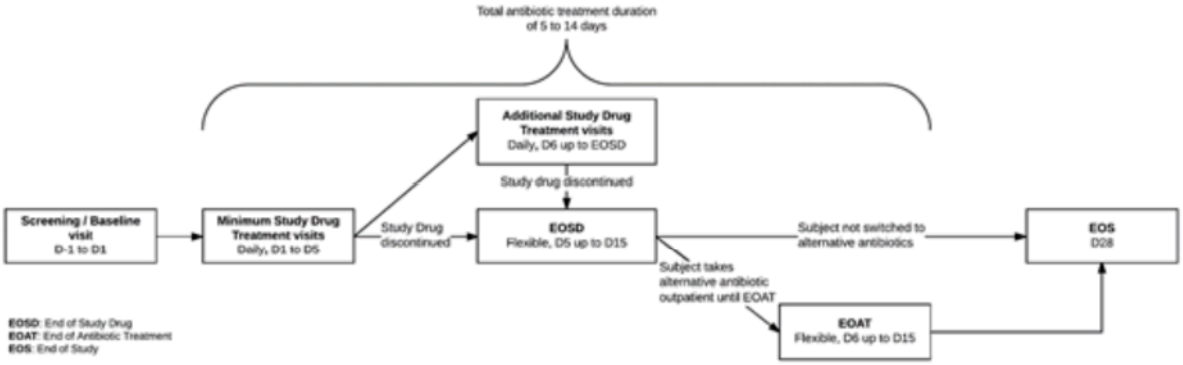
1.3.1 Primary objectives

Primary objectives	Endpoints related to primary objectives
• To evaluate the plasma pharmacokinetics of LYS228 in patients with complicated intra-abdominal infection (cIAI)	• Plasma PK on Day 5
• To evaluate the clinical response to LYS228 in combination with vancomycin and metronidazole compared to standard of care antibiotics for treating patients with cIAI	• Clinical success at 28 days after randomization (End of Study) determined by signs, symptoms, and the need for additional antibiotics, unplanned surgical procedures, or drainage

1.3.2 Secondary objectives

Secondary objectives	Endpoints related to secondary objectives
• To evaluate the safety and tolerability of LYS228 in combination with vancomycin and metronidazole in patients with cIAI	• Adverse events • Clinical laboratory tests • Vital signs
• To evaluate the microbiological response to LYS228 in combination with vancomycin and metronidazole compared to standard of care antibiotics for treating patients with cIAI	• Microbiologic success at 28 days after randomization (End of Study) determined by culture from the intra-abdominal focus of infection when available or presumed eradication based on clinical success

1.4 Study design and treatment



This is a randomized, comparator-controlled, evaluator-blinded, non-confirmatory study to evaluate the pharmacokinetics, clinical response, safety and tolerability of intravenous LYS228 in patients with complicated intra-abdominal infection (cIAI). The study will enrol approximately 60 patients with cIAI who have not yet been treated for their current infection and will be randomized to receive LYS228 in combination with vancomycin and metronidazole or standard of care antibiotic therapy for cIAI for no less than 5 days and up to 14 days. The study treatment will be administered in an open-label basis. There will be no placebo-treated patients. A blinded evaluator at each site will perform safety and clinical response assessments.

The study consists of a Screening and Baseline Period (D-1 to D1), a Treatment Period of variable duration (D1 to D5, and possibly up to D15), a Follow-up period of at least 14 days and an EOS visit on Day 28. A patients' flowchart is provided in Section 17 of the protocol.

Patients will be randomized to one of the following two treatment arms in a ratio of 2:1.

- Arm 1: LYS228 in combination with vancomycin and metronidazole (n=40). LYS228 dose for each patient will be based on the renal function as described in Section 3.3 of the protocol.
- Arm 2: Standard of care intravenous antibiotic therapy for the treatment of cIAI (n=20)

Adjustment of the non-LYS228 Study Drug components of treatment arms may be permitted based on microbiologic data as detailed in the SOM.

Change of treatment from Study Drug to alternative antibiotics is permissible in the following circumstances:

1. Change to oral antibiotics after completing 5 days of intravenous Study Drug if a patient is clinically improved and discharged, or
2. Patient requires additional therapy or change to rescue therapy in the case of clinical failure, or adverse event that merits discontinuation of Study Drug as detailed in Section 7.2 of the protocol.

Alternative antibiotics must be effective against the relevant clinical isolates. The total antibiotic treatment duration, including Study Drug and any alternative antibiotic, will be no less than 5 days and up to 14 days, unless discussed with sponsor.

During the treatment period all patients will complete a minimum of 5 visits (V101 -V105) and up to 15 visits (V101-V116), depending on the duration of hospitalization. All patients

that change treatment to an alternative antibiotic must have an EOSD visit prior to antibiotic change.

The follow-up period spans the period after completion of antibiotic treatment (EOAT visit) up to 28 days after randomization, at which time all patients will have an EOS visit. This visit is considered the Test of Cure (TOC) visit for evaluation of clinical response. A post-study safety phone call will be conducted 30 days after the last administration of study treatment.

2 First interpretable results (FIR)

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

4 Statistical methods: Analysis sets

For patients for which the actual treatment received does not match the randomized treatment the treatment actually received will be used for the analysis.

The following are considered the definitions for the statistical analysis populations:

- Safety (or modified intent-to-treat, mITT) population: All patients that received at least one dose of Study Drug, and experienced no protocol deviations with relevant impact on clinical data.
- Pharmacokinetics (PK) population: All patients in mITT that have at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, and experienced no protocol deviations with relevant impact on PK data.
- Microbiological modified intent-to-treat (micro-mITT) population: All patients in mITT who have a baseline bacterial pathogen known to cause cIAI.
- Clinically evaluable (CE) population: All patients in mITT with cIAI confirmed by operative or percutaneous drainage findings, with sufficient information to determine clinical outcome at the TOC visit (EOS) (i.e. data relating to the same signs and symptoms

recorded at both screening/baseline and the TOC visit), and have no other protocol deviation with relevant impact on clinical data. Patients who received < 5 days of Study Drug due to clinical failure will NOT be excluded from the clinically evaluable population.

- Microbiologically evaluable (ME) population: All patients in micro-mITT who also have at least one clinically relevant pathogen (Enterobacteriaeceae) suspected to be susceptible to the study treatment isolated in the initial specimen collected from the intra-abdominal focus of infection, and experienced no protocol deviations with relevant impact on clinical data.

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Patients are excluded from all *(safety, mITT)* analysis in case of these PDs:		Exclude patient completely from all ***(safety, mITT)*** poulations
None		
Patients are excluded from PK analysis in case of these PDs:		Exclude patient from PK population
TRT01	*Study treatment deviations*	Yes
Patients are excluded from micro-mITT analysis in case of these PDs:		Exclude patient from micro-mITT population
None		
Patients are excluded from CE analysis in case of these PDs:		Exclude patient from CE population
INCL03	*Deviation from inclusion criterion 3 (Expectation that, in the judgment of the Investigator, the patient will survive with effective antibiotic therapy and appropriate supportive care for the anticipated duration of the study.)*	Yes
EXCL02	*Deviation from exclusion criterion 2 (Any excluded diagnoses)*	Yes
EXCL03	*Deviation from exclusion criterion 3 (Received more than 24 hours of total prior antibiotic therapy (based on dosing interval) in the 72 hours prior to the planned dosing of Study Drug)*	Yes
EXCL04	*Deviation from exclusion criterion 4 (Received long-acting antibiotic (≥24 hours dosing interval) intra- or post-operatively.)*	Yes
EXCL05	*Deviation from exclusion criterion 5 (Received any non-study antibiotic more than 6 hours post-procedure.)*	Yes

Category Deviation code	Text description of deviation	Data exclusion
EXCL06	*Deviation from exclusion criterion 6 (Concomitant bacterial infection at time of enrollment requiring non-Study Drug antibiotics and that may interfere with the evaluation of clinical response to the study antibiotic.)*	Yes
EXCL07	*Deviation from exclusion criterion 7 (Known non-abdominal source of infection, including endocarditis, osteomyelitis, abscess, meningitis, or pneumonia diagnosed within 7 days prior to enrollment.)*	Yes
EXCL08	*Deviation from exclusion criterion 8 (Patient has APACHE II score > 30 or is considered, in the judgment of the investigator, unlikely to survive 4 weeks.)*	Yes
EXCL09	*Deviation from exclusion criterion 9 (Patients that meet sepsis criteria as defined by the quick sequential sepsis-related organ failure assessment (qSOFA).)*	Yes
WITH01	*Withdrawal criteria met but subject not discontinued*	Yes
COMD01	*Use of prohibited medication during the study*	Yes
TRT02	*Patients who received <80% of study drug doses (includes comparator SOC as well as LYS228 + vancomycin + metronidazole)*	Yes
TRT03	*Patients who missed two consecutive doses*	Yes
Patients are excluded from ME analysis in case of these PDs:		Exclude patient from ME population
INCL03	*Deviation from inclusion criterion 3 (Expectation that, in the judgment of the Investigator, the patient will survive with effective antibiotic therapy and appropriate supportive care for the anticipated duration of the study.)*	Yes
EXCL02	*Deviation from exclusion criterion 2 (Any excluded diagnoses)*	Yes
EXCL03	*Deviation from exclusion criterion 3 (Received more than 24 hours of total prior antibiotic therapy (based on dosing interval) in the 72 hours prior to the planned dosing of Study Drug)*	Yes
EXCL04	*Deviation from exclusion criterion 4 (Received long-acting antibiotic (≥24 hours dosing interval) intra- or post-operatively.)*	Yes
EXCL05	*Deviation from exclusion criterion 5 (Received any non-study antibiotic more than 6 hours post-procedure.)*	Yes

Category Deviation code	Text description of deviation	Data exclusion
EXCL06	*Deviation from exclusion criterion 6 (Concomitant bacterial infection at time of enrollment requiring non-Study Drug antibiotics and that may interfere with the evaluation of clinical response to the study antibiotic.)*	Yes
EXCL07	*Deviation from exclusion criterion 7 (Known non-abdominal source of infection, including endocarditis, osteomyelitis, abscess, meningitis, or pneumonia diagnosed within 7 days prior to enrollment.)*	Yes
EXCL08	*Deviation from exclusion criterion 8 (Patient has APACHE II score > 30 or is considered, in the judgment of the investigator, unlikely to survive 4 weeks.)*	Yes
EXCL09	*Deviation from exclusion criterion 9 (Patients that meet sepsis criteria as defined by the quick sequential sepsis-related organ failure assessment (qSOFA).)*	Yes
WITH01	*Withdrawal criteria met but subject not discontinued*	Yes
COMD01	*Use of prohibited medication during the study*	Yes

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

5 Statistical methods for Pharmacokinetic (PK) parameters

5.1 Primary objective

To evaluate the plasma pharmacokinetics of LYS228 in patients with complicated intra-abdominal infection (cIAI).

5.2 Variables

The primary PK variables are LYS228 plasma concentration and the following PK parameters:

- AUCtau, Cmax, Tmax, CL, Vss, T1/2, %fT>MIC in plasma on Day 5.

Noncompartmental PK analysis will be performed on the LYS228 plasma concentration-time profiles and the PK parameters listed above characterizing the disposition of LYS228 will be generated using WinNonlin Phoenix (Version 6.4 or higher, Pharsight, Mountain View, CA). Additional PK parameters may be determined and compartmental PK modeling may be performed where appropriate.

5.3 Descriptive analyses

LYS228 plasma concentration data will be listed by patient and visit/sampling time-point. Descriptive summary statistics will be provided by visit/sampling time-point. Descriptive summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum values.

PK parameters will be calculated as described above and will be listed by patient, and will be summarized by dose and renal category. Descriptive summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum values. An exception to this is Tmax where median, minimum and maximum will be presented.

Additionally, 95% confidence intervals will be computed for log-transformed primary PK parameters (AUCtau and Cmax). These intervals will be reported on the original exponential scale.

A population PK/PD analysis combining all data from this study and from other studies will be performed for target attainment analysis and will be reported separately.

5.3.1 Handling of missing values/censoring/discontinuations

All concentrations below the limit of quantification or missing data will be labeled as such in the concentration data listings. All drug concentrations below the lower limit of quantification (LLOQ) will be treated as zero in summary statistics and for the calculation of PK parameters. A geometric mean will not be reported if the dataset includes zero values.

5.4 Graphical presentation

Arithmetic mean (SD) plasma concentration data will be plotted across time, with separate line types for dose.

Graphical presentation will be used to display the trough concentrations versus the study visit days.

Overlaying individual plasma concentration-time profiles will be generated.

Individual plasma concentration-time profiles will be generated.

Graphical presentation will be used to explore the relationship between the quartile exposure parameters and clinical response. Individual clinical response vs AUCtau, Cmax, and %fT>MIC will be explored, respectively.

6 Statistical methods for Pharmacodynamic (PD) parameters/clinical response

6.1 Primary objective

To evaluate the clinical response to LYS228 in combination with vancomycin and metronidazole compared to standard of care antibiotics for treating patients with cIAI.

6.1.1 Variables

The primary clinical response variable is clinical success at 28 days after randomization. Clinical success and clinical failure are defined as follows:

- **Clinical success** is defined as resolution, or substantial improvement (i.e. reduction of severity of all baseline signs and symptoms and worsening of none) of all or most (i.e. >50%) baseline signs and symptoms of cIAI infection without the need for additional antibiotic therapy other than any oral antibiotics given to complete treatment at home following discontinuation of Study Drug and no drainage or surgical reintervention required 96 hours after the start of Study Drug.
- **Clinical failure** is defined as lack of response to study therapy as documented by persistence or worsening of baseline symptoms and/or signs of cIAI infection, such that alternative or additional antibiotic therapy or surgical interventions are required

These primary variables will be assessed separately in the micro-mITT, CE and ME populations.

Each sign will be assessed as “new”, “improved”, “unchanged” or “worsened”.

Each symptom will be assigned a CTCAE grade. If the CTCAE grade increases, the symptom is worsening. If the CTCAE grade decreases, the symptom is improving.Clinical success or failure will be evaluated at the end of Study Drug therapy (EOSD), at the end of all antibiotic therapy (EOAT), and at 28 days post-randomization (EOS).

6.1.2 Descriptive analyses

The primary clinical response variables will be summarized with descriptive statistics by treatment arm.

6.1.3 Statistical model, assumptions and hypotheses

Clinical success or failure will be evaluated at the end of Study Drug therapy (EOSD), at the end of all antibiotic therapy (EOAT), and at 28 days post-randomization (EOS).

The proportion of patients who achieved clinical success or failure will be computed for each treatment arm and provided along with an 80% two-sided confidence interval based on the Clopper-Pearson method. The 80% confidence interval for the difference in clinical success between treatment arms will be computed according to the Wilson score method without continuity correction.

Bayesian methods will be implemented based on the Beta-Binomial model to compare the clinical success rate in micro-mITT population at 28 days post-randomization. Informative prior on LYS228 and control will be used as follows: Meta-analytic-predictive (MAP) informative prior (Spiegelhalter et al 2004, Neuenschwander et al 2010 and Schmidli et al 2014) for the clinical success rate in micro-mITT population on active control was obtained based on the evaluable historical data (FDA guidance, 2015): 0.67*Beta(172,38)+0.23*Beta(9,3)+0.1*Beta(1,1), where median=0.81, sd=0.144, 95% CI=[0.25, 0.93] and the quantified information is equivalent to an effective sample size of 7.

Denote by p_T and p_C the event probabilities for the LYS228 treatment arm and the active control arm, respectively.

For p_T:

Prior: $p_T \sim [0.67 \text{ x Beta}(172, 38)] + [0.23 \text{ x Beta}(9, 3)] + [0.1 \text{ x Beta}(1, 1)]$

Observed: y_T events in n_T patients (binomial distribution with event probability p_T)

Posterior: $p_T \mid y_T \sim [w_1 \text{ x Beta}(172 + y_T, 38 + n_T - y_T)]$
$+ [w_2 \text{ x Beta}(9 + y_T, 3 + n_T - y_T)]$
$+ [w_3 \text{ x Beta}(1 + y_T, 1 + n_T - y_T)]$

where

$$w_1 = \frac{0.67c_1}{0.67c_1 + 0.23c_2 + 0.1c_3}$$
$$w_2 = \frac{0.23c_2}{0.67c_1 + 0.23c_2 + 0.1c_3}$$
$$w_3 = \frac{0.1c_3}{0.67c_1 + 0.23c_2 + 0.1c_3}$$

and

$$c_1 = \frac{\Gamma(172+38)}{\Gamma(172)\Gamma(38)} \frac{\Gamma(172+y_T)\Gamma(38+n_T-y_T)}{\Gamma(172+38+n_T)}$$
$$c_2 = \frac{\Gamma(9+3)}{\Gamma(9)\Gamma(3)} \frac{\Gamma(9+y_T)\Gamma(3+n_T-y_T)}{\Gamma(9+3+n_T)}$$
$$c_3 = \frac{\Gamma(1+1)}{\Gamma(1)\Gamma(1)} \frac{\Gamma(1+y_T)\Gamma(1+n_T-y_T)}{\Gamma(1+1+n_T)}$$

For p_C:

Prior: $p_C \sim [0.67 \text{ x Beta}(172, 38)] + [0.23 \text{ x Beta}(9, 3)] + [0.1 \text{ x Beta}(1, 1)]$

Observed: y_C events in n_C patients (binomial distribution with event probability p_C)

Posterior: $p_C \mid y_C \sim [w_1 \text{ x Beta}(172 + y_C, 38 + n_C - y_C)]$
$+ [w_2 \text{ x Beta}(9 + y_C, 3 + n_C - y_C)]$
$+ [w_3 \text{ x Beta}(1 + y_C, 1 + n_C - y_C)]$

where

$$w_1 = \frac{0.67c_1}{0.67c_1 + 0.23c_2 + 0.1c_3}$$
$$w_2 = \frac{0.23c_2}{0.67c_1 + 0.23c_2 + 0.1c_3}$$
$$w_3 = \frac{0.1c_3}{0.67c_1 + 0.23c_2 + 0.1c_3}$$

and

$$c_1 = \frac{\Gamma(172+38)}{\Gamma(172)\Gamma(38)} \frac{\Gamma(172+y_C)\Gamma(38+n_C-y_C)}{\Gamma(172+38+n_C)}$$

$$c_2 = \frac{\Gamma(9+3)}{\Gamma(9)\Gamma(3)}\frac{\Gamma(9+y_C)\Gamma(3+n_C-y_C)}{\Gamma(9+3+n_C)}$$
$$c_3 = \frac{\Gamma(1+1)}{\Gamma(1)\Gamma(1)}\frac{\Gamma(1+y_C)\Gamma(1+n_C-y_C)}{\Gamma(1+1+n_C)}$$

An 80% posterior credible interval of the clinical success rate at TOC visit in the micro-mITT population will be provided for each treatment arm as well as the treatment difference.

6.1.3.1 Graphical presentation of results

All posterior distributions will be summarized graphically.

6.1.3.2 Sensitivity analyses

Additional sensitivity analyses may be performed in which adjustments are made for factors that cannot be controlled at randomization, such as delays in surgical intervention, presence of bacterial resistance at baseline, age, total duration of therapy. Any sensitivity analyses will be conducted by Novartis.

6.2 Secondary objectives

To evaluate the microbiological response to LYS228 in combination with vancomycin and metronidazole compared to standard of care antibiotics for treating patients with cIAI.

6.2.1 Variables

The secondary clinical response variable is microbiological outcome. Microbiological success and microbiological failure are defined as follows:

- **Microbiological success** is defined as documented microbiological eradication of all baseline intra-abdominal pathogens following at least 5 days of Study Drug, or presumed microbiological eradication is defined as a clinical success (see section 6.1.1 above).
- **Microbiological failure** is defined as i) culture of the intended to treat baseline Gram negative (Enterobacteriaceae) pathogen from a specimen obtained from the site of abdominal infection following at least 5 days of Study Drug, or ii) presumed microbiological failure if no cultures obtained and there is clinical failure.

Microbiological outcome will be considered indeterminate when no post-baseline specimen culture results are obtained for patients with indeterminate clinical response.

Microbiological outcome will be evaluated at the EOSD, at the EOAT, and at 28 days postrandomization (EOS) in the micro-mITT and ME populations.

6.2.2 Descriptive analyses

The secondary clinical response variables will be summarized with descriptive statistics by treatment arm.

Subgroup summaries will also be provided by bacterial genetic characterization including beta-lactamase identification (i.e ESBLs, KPCs, MBLs) and in a subset of patients with cIAI caused by drug resistance mechanisms including CRE.

The distribution of bacterial isolates and bacterial response by treatment arm will be provided.

6.2.3 Statistical model, assumptions and hypotheses

Microbiological success will be evaluated at the EOSD, at the EOAT, and at 28 days post randomization (EOS).

The proportion of patients who achieved microbiological success will be computed for each treatment arm and provided along with an 80% two-sided confidence interval based on the Clopper-Pearson method. The 80% confidence interval for the difference between treatment arms will be computed according to the Wilson score method without continuity correction.

6.2.4 Pharmacokinetic / pharmacodynamics/clinical response interactions

Graphical presentation will be used to explore the relationship between the quartile exposure parameters and clinical response. Individual clinical response vs AUCtau, Cmax, and %fT>MIC will be explored, respectively.

The analysis results will be reported in a separate document.

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 patient demographics, baseline characteristics, and treatment information.

7.2 Descriptive analyses

Subject demographics and other baseline characteristics

All data for background (underlying inclusion diagnosis, type of surgical intervention) and demographic variables will be listed by treatment arm and patient. Summary statistics will be provided by treatment arm.

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

Treatment

Data for Study Drug administration, rescue medication, alternative antibiotics and concomitant therapies will be listed by treatment arm and patient.

Vital signs

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

ECG evaluations

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

Clinical laboratory evaluations

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

The number of patients with treatment-emergent CTCAE grade 2 or higher in clinical laboratory evaluations will be summarized by CTCAE grade and treatment.

Adverse events

All information obtained on adverse events will be displayed by treatment arm and patient.

The number and percentage of patients with adverse events will be tabulated by body system and preferred term with a breakdown by treatment arm and also by body sytem, preferred term and maximum severity with a breakdown by treatment arm. A patient with multiple adverse events within a body system is only counted once towards the total of this body system and treatment arm. Tabulations will also be provided for special interest adverse events (e.g. hypersensitivity reaction, hepatotoxicity, nephrotoxicity, local infusion reactions, gastrointestinal discomfort, *Clostridium difficile*-associated diarrhea, seizure, thrombocytopenia).

Summaries will be provided for all treatment adverse events and also for treatment adverse events suspected to be related to study drug.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than 5% and on 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 (mITT) population. These tables will be produced by Novartis.

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.

7.3 Graphical presentation

Boxplots to visualize trends in longitudinal safety data (vitals, ECG, lab parameter) will be created.

Fever curves will be created as overlaying individual profiles of the highest temperature entered in the clinical evaluation page.

9 Reference list

Neuenschwander B, Capkun-Niggli G, Branson M, et al (2010) Summarizing historical information on controls in clinical trials. Clin Trials p. 5-18.

Schmidli H, Gsteiger S, Roychoudhury S, et al (2014) Robust meta-analytic-predictive priors in clinical trials with historical control information. Biometrics p. 1023-32.

Spiegelhalter DJ, Abrams KR, Myles JP (2004) Bayesian Approaches to Clinical trials and Health-Care Evaluation.