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Statistical Analysis Plan

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Title: A Superiority Phase 3 Study to Compare the Effect of Panzyga Versus Placebo in Patients with Paediatric Acute-Onset Neuropsychiatric Syndrome (PANS/PANDAS)

Study Number: NGAM-13

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Statistical Analysis Plan

Study ID	NGAM-13
Study title	A Superiority Study To Compare The Effect of Panzyga Versus Placebo in Patients with Pediatric Acute-Onset Neuropsychiatric Syndrome
Study phase	3

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Approved by

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Document History

Version	Date	Author	Description
Final 1.0	18-Mar-2020	[redacted]	New Document
Final 2.0	27-May-2020	[redacted]	Incorporation of the following aspects to reflect changes introduced in protocol version 2: Addition of a double-blind, crossover safety and efficacy follow-up phase, extension of total observation period to 18 weeks, PK analysis of Total IgG, Durability of clinical benefit as secondary endpoint, Prospective assessment of suicidality as exploratory endpoint Clarification of analysis details: Details on possible patient enrichment, Clarification of critical alpha levels for the interim analysis and for the analyses of secondary endpoints in case of early study termination, Primary analysis based on ITT, Additional sensitivity analysis for primary endpoint, Test details for secondary endpoints, Patient groups for safety reporting
Final 3.0	26-Jan-2021	[redacted]	Adjust wording to reflect revised eligibility criteria, unified use of term patient rather than subject, safety review of first 6 patients added, collection of non treatment-emergent AEs, introduction of the MINI-KID assessment, specific biomarker panel (autoimmune encephalopathy) replaced by backup blood sample for later analysis
Final 4.0	28-Jul-2021	[redacted]	Update based on Protocol Version 4.0: correct the number of items in SNAP-IV Scale; Correct the item score in CY-BOCS; Clarify the significance level for the interim analysis; Adjust wording in sample size estimation; Add covariates for multiple imputation.
Final 5.0	21-Jul-2023	[redacted]	Update based on Protocol Version 5.0 and 6.0: Add correlation analysis between CYBOCS and CGI-I. Add exploratory analysis for the percentage of patients with PANS improvement. Add interim review after 20 patients have completed blinded treatment.

Abbreviations

ADHD	Attention-Deficit Hyperactivity Disorder
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BW	Bodyweight
CD	Conduct Disorder
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression – Severity
CI	Confidence Interval
COIS	Parent & Child OC Impact Scale – Revised
COIS-RC	Child Obsessive-compulsive Impact Scale - Revised – Child
COIS-RP	Child Obsessive-compulsive Impact Scale - Revised – Parent
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CY-BOCS	Children's Yale-Brown Obsessive Compulsive Scale
DB	Database
DSM	American Psychiatric Association's Diagnostic and Statistical Manual
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice

HTR	Hemolytic Transfusion Reaction
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
ITT	Intention-To-Treat
IVIG	Intravenous Immunoglobulin
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MINI-KID	Mini International Neuropsychiatric Interview for Children and Adolescents
OC	Obsessive–Compulsive
ODD	Oppositional Defiant Disorder
PANDAS	Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection
PANS	Patients with Acute-onset Neuropsychiatric Syndrome
PP	Per Protocol
PTQ	Parent Tic Questionnaire
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SNAP-IV	Swanson, Nolan, and Pelham Rating Scale
SSRI	Selective Serotonin Reuptake Inhibitors
TEE	Thromboembolic Event
WHO	World Health Organization

Table of Contents

1. Preface

The purpose of this Statistical Analysis Plan (SAP) is to describe the statistical methods to be deployed for the collection and analysis of data for the study with protocol number NGAM-13. The SAP will be finalized prior to database lock and any statistical analysis. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

This phase 3 study is conducted in pediatric patients with acute-onset neuropsychiatric syndrome (PANS) to confirm that Panzyga is superior to placebo (saline solution) in reducing severity of symptoms associated with PANS in this patient group. It is designed as a prospective, multicenter, randomized, double-blind, parallel group, placebo-controlled, Phase 3 superiority study, with an additional double-blind, crossover safety and efficacy follow-up phase.

Efficacy will be evaluated by comparison of the observed changes in neuropsychiatric symptomatology and behavior, determined by the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), between the randomized treatment groups:

- Panzyga (Immune Globulin Intravenous, Human 10%)
- Placebo (saline solution)

In addition to this primary endpoint, secondary efficacy and exploratory evaluations will cover the durability of the clinical benefit, and behavioral changes by means of the following standardized assessments: Clinical Global Impression (CGI), Parent & Child OC Impact Scale – Revised (COIS-RP and COIS-RC), Swanson, Nolan, and Pelham Rating Scale (SNAP-IV, 26 item), Parent Tic Questionnaire (PTQ).

Furthermore safety assessments (adverse events, vital signs, physical examinations, laboratory parameters) will be performed throughout the study period, and the pharmacokinetics of Panzyga in PANS patients will be investigated. A blood sample will be collected at Screening and Week 18/Early Termination Visit for later analyses (assessments to be determined).

Because the available knowledge on the effect of intravenous immunoglobulin (IVIG) in the PANS population is limited, this study will deploy an adaptive enrichment design with an interim analysis after [redacted] patients have completed the initial 9-week treatment period, at which time a decision will be made based on prespecified criteria whether to continue enrollment in the overall population (PANS) or to restrict future enrollment on a targeted subpopulation, including e.g. the subgroup of patients diagnosed with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS); please refer to section 5.1 for details on the interim analysis.

The possible design adaptations at the interim analysis will also include a sample size re-assessment on basis of the observed changes in CY-BOCS.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the FDA and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials[1].

The following documents were reviewed in preparation of this SAP:

- Clinical Study Protocol NGAM-13, Version 3.0, dated 25-Jan-2021

[1] International Conference on Harmonization. (1998). Guidance on Statistical Principles. ICH Topic E9 (Statistical Principles for Clinical Trials), and its Addendum on Estimands and Sensitivity Analysis, E9(R1), 2019-11-20.

The reader of this SAP is encouraged to also read the clinical protocol for details on the planned conduct of this study. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant for the specification of the planned analyses.

2. Purpose

This SAP outlines the statistical analyses to be performed on data collected in study NGAM-13, and the resulting output that will be compiled to support the completion of the CSR.

The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts. Exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc or unplanned analyses performed that are not identified in the final SAP will be clearly identified in the respective CSR.

The statistical output provided to the medical writer of the CSR will closely follow the ICH guideline for industry on topic E3 (Structure and Content of Clinical Study Reports[2]) to facilitate the subsequent compilation of the CSR.

This statistical output will consist of tables, figures, and listings, including

- Tables, figures, and listings used or referenced in, or appended to the CSR as detailed in the remainder of this SAP (section 14 of the CSR)
    - Demographic data summary figures and tables
    - Efficacy data summary figures and tables
    - Safety data summary figures and tables
- Listings provided as appendices to the CSR
    - Patient data listings (section 16.2 of the CSR)
    - Individual patient data listings (section 16.4 of the CSR) will be covered by inclusion of SAS datasets into the electronic submissions to the authorities

A detailed list of all tables, figures and listings will be supplied in a separate document later when all feedback from authorities will be available.

If relevant aspects of the study design are adapted following the interim analysis, this SAP will be updated accordingly.

[2] International Conference on Harmonization. (1996). Structure and Content of Clinical Study Reports. Structure and Content of Clinical Study Reports (Guideline for Industry) (S. 37). London: International Conference on Harmonization.

3. Study Objectives and Endpoints

3.1. Study Objectives

3.1.1. Primary Objective

The primary objective of this study is to confirm that Panzyga is superior to placebo (0.9% w/v sodium chloride) for reducing the severity of symptoms associated with PANS in pediatric patients.

3.1.2. Secondary Objectives

The secondary objectives of this study are

- to verify the sustainability of the reduction of the severity of symptoms in pediatric patients treated with Panzyga, and
- to assess the efficacy of Panzyga treatment in reducing functional impairment associated with PANS.

3.1.3. Exploratory Objectives:

The exploratory objectives of this study are to:

- assess the safety parameters of Panzyga administration
- characterize the pharmacokinetic (PK) exposure and the fluctuation thereof throughout the treatment course

Additional exploratory objectives of this study are to:

- assess the correlation between CGI-I and CY-BOCS
- assess the PANS improvement in pediatric patients

3.2. Study Endpoints (Target Variables)

This section defines the target variables collected or derived for the evaluation of the endpoints; please refer to sections 8 to 12 for analysis details.

3.2.1. Primary Target Variables

The primary endpoint is defined as:

Improvement of neuropsychiatric symptomatology and behavior in PANS patients determined by clinician-rated CY-BOCS score. The mean changes in the total CY-BOCS score from Baseline to Week 9 will be compared between Panzyga and Placebo treatment groups to demonstrate superiority.

The primary target variable to assess impairments associated with PANS symptoms is thus the clinician-rated CY-BOCS score.

The total CY-BOCS score is the sum of items 1 -10 of the assessment form; each of the item's score is an integer between 0 and 4. Consequently the total CY-BOCS score ranges between 0 (no impairment) to 40 (maximum impairment). For participation in the study, patients must have a total CY-BOCS score of at least 16 based on specific criteria defined in the protocol.

3.2.2. Secondary Target Variables

Efficacy:

CY-BOCS score at the end of the follow-up period at Week 18 will be compared to the Week 9 scores within the (Panzyga – Placebo) treatment group to assess the durability of the clinical benefit associated with Panzyga treatment.

The protocol specifies the following standardized instruments for the assessment of behavioral changes as secondary efficacy endpoints:

- Clinical Global Impression (CGI) – For the confirmatory endpoint analysis the CGI-I (CGI – Improvement) total score will be used
- Parent & Child OC Impact Scale – Revised (COIS-RP and COIS-RC) – For the confirmatory endpoint analysis the COIS-RP total score will be used
- The Swanson, Nolan, and Pelham Rating Scale (SNAP-IV, 26 item)
- Parent Tic Questionnaire (PTQ)

These scores are therefore considered as secondary target variables; please refer to the protocol for details on these instruments.

3.2.3. Exploratory Target Variables

- Columbia Suicide Severity Rating Scale (C-SSRS) for the prospective assessment of suicidality
- All adverse events (AEs) throughout the study period, with particular emphasis on thromboembolic events (TEEs) and hemolytic transfusion reactions (HTRs).
- Vital signs (blood pressure, heart rate, body temperature and respiratory rate).
- Physical examinations
- Laboratory parameters (hematology, clinical chemistry)
- Total IgG plasma levels for pharmacokinetic assessments

Additional exploratory target variables are:

- Correlation between change in CY-BOCS from baseline to Week 9 and CGI-I assessment at Week 9
  Note: the change in CY-BOCS will be measured by ratio of the CYBOCS at Week 9 to that at Baseline.
- Correlation between change in CY-BOCS from Week 9 to Week 18 and CGI-I assessment at Week 18
- The percentage (%) of pediatric patients with PANS improvement at Week 9 and Week 18.

PANS improvement will be defined as improvement of PANS symptoms based on CGI-I ratings at Week 9 since Week 3, and at Week 18 since Week 12. Patient will be evaluated as PANS improvement if the CGI-I score is 3 (Minimally Improved) or better at the evaluated visit.

3.2.4. Important Covariates and Patient Characteristics

The following variables have been identified as important patient characteristics and will be used for stratification as detailed in section 4.3:

[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]

Additionally, the effect of the following variables on the endpoints will be assessed in an exploratory manner:

- Age: considered as continuous variable and to define the following subgroups:
  - Children (6 to 12 years) and Adolescents (13 to 17 years) (predefined)
  - < median age and ≥ median age for possible population enrichment (interim data)
- Sex
- Onset of PANS symptoms:
  - "< 6 months": Onset of initial symptoms within 6 months prior to screening
  - "≥ 6 months": Patients with relapsing symptoms: initial symptoms may not have been more than 12 months prior to the screening and must have fully resolved, their recurrence must be within 6 months prior to screening
- Baseline CY-BOCS score: considered as continuous variable and to define 2 subgroups:
  - Moderate (16 to <24) and Severe (≥24)

4. Study Methods

4.1. Overall Study Design and Plan

Study NGAM-13 is designed as a prospective, multicenter, randomized, double-blind, parallel group, placebo-controlled, phase 3 superiority study, with an additional double-blind, crossover safety and efficacy follow-up phase.

In the first phase of the study, from enrolment to Week 9, patients will receive Panzyga or placebo administered 3 times within 9 weeks in 3-week intervals, according to their randomized treatment sequence. After Week 9 all patients will be switched to the alternative for another 3 treatments in the crossover phase of the study. Dosing and dosing intervals will be the same for all study drug administrations in both study phases, namely Panzyga 2 g/kg bodyweight (BW), administered as 1 g/kg BW daily for two consecutive days) or placebo (0.9% w/v sodium chloride infusion equivalent in volume to 1 g/kg BW Panzyga daily for two consecutive days).

Up to [redacted] sites (USA and rest of the world) are projected to participate.

After the first [redacted] patients have been enrolled, the study enrollment will be put on hold until the Independent Data Monitoring Committee (IDMC) has reviewed unblinded safety and PK data of these [redacted] patients and given the green light to pursue the study.

The duration of the initial parallel-group phase will be 9 weeks, plus up to 28 days from screening to randomization, the duration of 2nd phase after the crossover will also be 9 weeks. After the initial phase patients will directly continue with the second phase without any wash-out time.

Patients eligible after screening will be randomized in a balanced 1:1 ratio to one of two treatment sequences:

- (Panzyga – Placebo): 3 administration cycles with Panzyga, followed by 3 administration cycles with placebo
- (Placebo – Panzyga): 3 administration cycles with placebo, followed by 3 administration cycles with Panzyga

The study population will be prospectively balanced according to the stratification factors specified in section 3.2.4 above. Psychological and behavioral evaluations, in particular the CY-BOCS, will be conducted at every visit, i.e. every 3 weeks during the initial parallel-group phase and at Week 18 / Final Visit; please refer to the protocol for the complete flow chart of assessments.

It is important to keep in mind that the primary efficacy evaluation of this study will be based on changes in the total CY-BOCS score from Baseline to Week 9, no data collected in the cross-over phase will be considered. Patients dropping out after Week 9 are not considered as withdrawals for the primary objective of the study.

As the first secondary endpoint is to assess the durability of the clinical benefit, this analysis will be based on data collected throughout the whole study on patients receiving Panzyga in the initial, parallel-group phase (baseline to Week 9) of the study, i.e. on patients randomized to treatment sequence Panzyga – Placebo.

Analyses of all subsequent secondary endpoints will be based on data collected during the parallel-group phase of the study only, i.e. up to Week 9.

After [redacted] patients have completed blinded treatment (Visit Week 9), an interim review of the preliminary safety and efficacy data will be conducted by Independent Data Monitoring Committee (IDMC). At this timepoint, the IDMC will independently evaluate all data accrued in this pivotal study to provide a statement on whether emerging data confirm the prospect of direct benefit and positive risk-benefit ratio for PANS patients treated with Panzyga. IDMC confirmation will justify the submission to concerned Health Authorities of additional study protocol(s) evaluating other dose regimens of Panzyga treatment in patients with PANS. The actual numeric results will not be shared with the Sponsor or Investigators to ensure that bias will not affect subsequent study decisions since the data of the first [redacted] patients will be included in the final statistical analysis.

An interim analysis will be performed by an independent statistician after [redacted] patients have completed the initial 9-week treatment period, to verify the initial assumptions, and to allow for the following adaptations in study design:

1. Adaptive enrichment in the study population

   The CY-BOCS scores at Visit 9 will be analyzed with respect to the following covariates/sub-groups in order to identify those that exhibit a promising treatment effect. It will then be determined whether future enrollment will be restricted to any (or a combination) of these:

[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

2. Sample size re-estimation to achieve the desired power of 80% while maintaining the overall type 1 error rate of 2.5%. Please refer to section 6 for details on the sample size determination.

Study enrollment will continue while enough patient data is accrued to conduct the interim analysis. In case the sample size re-assessment does not result in a required total of more than the number of patients already enrolled at the time, enrollment will be stopped but patients already randomized will continue in the study until the planned end, i.e. for 18 weeks.

4.2. Selection of Study Population

Patients will be aged 6–17 years, with moderate to severe PANS with prominent and stable obsessive-compulsive disorder (OCD) symptoms. All patients will meet criteria for PANS, including the abrupt dramatic onset of OCD meeting DSM-5 diagnostic criteria for OCD as confirmed by the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID), and at least two of seven additional associated neuropsychiatric symptoms. Please refer to the protocol for a complete list of inclusion/exclusion criteria.

As a possible consequence of the adaptations mentioned in section 4.1 the selection criteria for the study population may be adapted based on the recommendations of the IDMC. In such a case the study protocol will be amended to reflect the different selection criteria.

4.3. Randomization, Stratification and Blinding

All patients qualified to participate in the study at Baseline (Week 0) will be randomized to one of two treatment sequences, (Panzyga – Placebo) or (Placebo – Panzyga), as detailed in section 4.1 above.

The randomization procedure will consider the following variables as stratification factors to balance the randomization also with respect to these patient characteristics of interest:

[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

5. Sequence of Planned Analyses

5.1. Interim Analysis

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

5.2. Final Analyses and Reporting

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

5.3. Control of type 1 error probability

Although neither changes of the endpoints nor the stated hypotheses are planned after the interim analysis the study will be using the combination pf p-values approach according to Bauer & Köhne [4] to maintain the overall type 1 error level.

In combination with the enrichment aspect of study this approach seems to better account for the potential differences in study cohorts between the two stages.

As recommended by Liu & Chi [3] an adjusted p-value will be calculated and presented in the final analysis in addition to the separate p-values p_1 and p_2 from the two study stages for better interpretability.

6. Sample Size Determination

The main endpoint of interest is the reduction of the total CY-BOCS score from Baseline to Week 9.

[redacted]

[redacted]

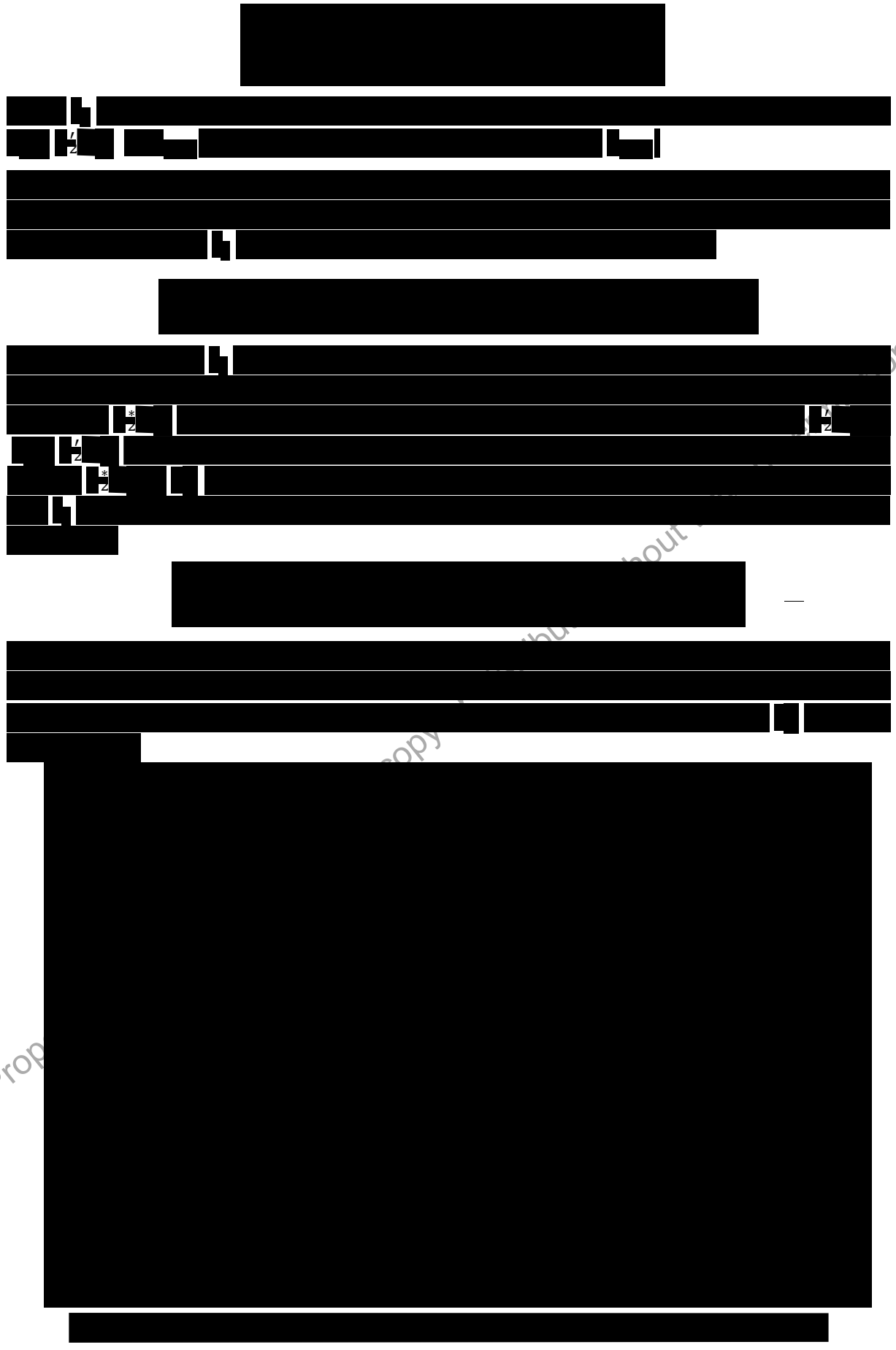
[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

[redacted]

[redacted]

References

[1] Mehta CR, Pocock SJ. Adaptive increase in sample size when interim results are promising: A practical guide with examples. *Statist Med* 2011; 30: 3267-3284

[2] Cui L, Hung HM, Wang SJ. Modification of sample size in group sequential clinical trials. *Biometrics* 1999; 55: 853-857

[3] Liu Q, Chi GYH. On Sample Size and Inference for Two-Stage Adaptive Designs. *Biometrics* 2001; 57: 172-177

[4] Bauer P, and Köhne K. Evaluations of experiments with adaptive interim analyses. *Biometrics* 1994; 50, 1029-1041.

6.1. Patient Replacement Policy

There will be no patient replacement in this study, but enrollment will continue until it is foreseeable that the number of patients required (according to the possible adaptations and the revised sample size determined at the interim analysis) for the evaluation of the primary endpoint will be achieved with the currently enrolled patients. 'Foreseeable' in this context means that the required number of evaluable patients will be achieved if the drop-out rate at the time remains unchanged for the remainder of the study.

6.2. Premature Termination of the Study

Both the Investigator and the Sponsor reserve the right to terminate the study at any time. In this event, any necessary procedure will be arranged on an individual study basis after review and consultation by both parties. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the patients' interests.

Regulatory authorities and IECs/IRBs should be informed in accordance with national regulations. Please refer to the protocol (sections 4.3.1 and 6.2.3) for further details on premature termination, in particular for the exact stopping criteria triggering temporary suspension/early termination of the entire study for an unacceptable increased venous TEE or acute renal failure risk in the Panzyga group compared to the placebo group.

In case the study is terminated prematurely, the SAP will be revised to address all issues arising from such special circumstances, and to confirm or redefine the scope of the analysis if necessary.

7. Analysis Populations

The following populations will be considered for the statistical analysis:

The **Intent-to-Treat set (ITT)** will include all randomized patients, regardless of whether the patient actually received study drug.

The **full analysis set (FAS)** will include all randomized patients who received at least part of one infusion of Panzyga or placebo

The **per-protocol set (PP)** consists of all patients of the FAS, excluding those with protocol deviations which may have an impact on the evaluation of the primary study outcome parameter(s). Only important protocol deviations with the potential to affect the study results substantially, or to invalidate the interpretation of the data obtained, will lead to exclusion of patients from the PP set; protocol deviations to be considered will include (but will not be limited to):

- Violations of the study entry criteria
- Withdrawal criteria that developed during the study
- Wrong treatment or incorrect dose
- Prohibited concomitant medication
- Incorrect completion of the CY-BOCS which affects the scoring

All protocol deviations documented during the conduct of the study or identified at the data review process prior to DB lock will be reviewed and classified as minor or major, and with respect to their importance for the planned analyses. This classification of protocol deviations is the joint responsibility of the clinical study manager, the study statistician, and Octapharma's responsible medical expert, and will be agreed and documented before the database is locked or unblinded.

For this study no separate safety population is defined as the FAS coincides with all patients who received at least part of one infusion of Panzyga or placebo. All safety data will thus be analyzed using the FAS. In the event that a patient takes the wrong study drug (i.e., did not take the randomized study drug), the actual treatment received will be used for safety analyses.

All efficacy analyses will primarily be based on the ITT population. In addition, analyses of the primary and secondary endpoints will be repeated on basis of the FAS, unless FAS and ITT coincide. All efficacy analyses will follow the intent-to-treat principle, i.e. patients will be analyzed according to the group they were originally assigned, regardless of what treatment they actually received.

Selected efficacy analyses, but at least the primary and secondary efficacy analyses, will be repeated for the PP population.

Screening failures will only be accounted for in the overall patient disposition, and individual data will be listed.

The assignment of each patient into the respective analysis populations will be determined before the statistical analysis in a data review meeting by a panel consisting of a medical expert from the sponsor, the clinical project manager, the data manager and the study statistician.

8. General Issues for Statistical Analysis

The primary target variable in this study is the CY-BOCS, the mean changes in the total CY-BOCS from Baseline to Week 9 will be compared between Panzyga and Placebo by a confirmatory statistical test to demonstrate superiority.

Descriptive summaries will be presented for each of the primary, secondary, and exploratory variables. In general, summaries will be presented by treatment group in a side-by-side fashion, using a set of standard summary statistics according to the different types of data:

Binary data (whether or not an event has occurred): counts and proportions

Count data (the frequency of an event in a set time period): rate (count per unit time)

Continuous data (measurements on a continuous scale, including quasi-continuous variables): arithmetic mean, standard deviation, median, minimum, maximum

Scales data (Ordinal and Non-ordinal): absolute and relative frequencies

Time-to-event data (how long it takes to observe the outcome of interest: time to event or last evaluation (censored data in case patients are lost to follow-up) and event rate). These parameters might not be tabulated separately, but can be included as an inset into a Kaplan-Meier plot of the product-limit survival function estimates.

Additional descriptive and exploratory statistics, such as geometric means, quartiles or confidence intervals, are included as appropriate. If not mentioned otherwise, confidence intervals are to be understood as two-sided, 95% confidence intervals.

Categorical data will generally be summarized with counts and percentages of patients. The denominator used for the percentage calculation will be clearly defined.

8.1. Analysis Software

Statistical analysis will be done with the statistical package SAS (version 9.4 or later).

8.2. Withdrawals

All patients enrolled in the trial will be accounted for, and withdrawals will be listed in full detail, including the reasons for withdrawal. Patients who withdraw from the study prematurely will be considered in all data presentations for which they contribute data in the ITT analysis populations.

All patients of the ITT will be included in the primary efficacy analysis, according to the intent-to-treat principle. Patients with missing data, including withdrawals, will be included in the analysis of the primary endpoint by means of the multiple imputation method assuming missing at random (MAR).

8.3. Handling of Missing Data

For the primary efficacy analysis, missing CY-BOCS results at Week 9 will be subjected to the multiple imputation method assuming missing at random, to include all randomized patients into the analysis.

In an additional sensitivity analysis such missing primary endpoint data will be replaced with the median change observed in the placebo group.

In case of missing weight measurements the last available body weight will be used for calculations related to dosing. In individual patient data listings missing data will however not be replaced by imputed values.

Missing data in secondary analysis variables will not be replaced by any method of imputation; instead, the frequency of missing values will be presented.

For adverse events the following will be applied:

AEs will be reported from the moment that informed consent has been given throughout the complete observation period; AEs with onset after start of the first IMP administration will be considered to be 'treatment-emergent' with respect to the treatment group of the patient at time of onset as defined in section 8.4 below.

If the start date and time of an AE are partially or completely missing, the AE will be considered as treatment-emergent in the analysis if it cannot be definitely shown that the AE did not occur or worsen after first IMP administration (worst case approach). Missing dates and times will not be replaced.

For medications the following will be applied:

A medication will be assumed to be concomitant if it cannot be definitely shown that the medication was not administered after the first IMP administration. Missing dates will not be replaced.

8.4. Derived and Computed Variables

The following derived/computed variables have been initially identified as important for the analysis of the primary and secondary target variables. It is expected that additional variables and flags will be required. The SAP will not be amended for additional variables that are not related to the primary target or key secondary target variables. Any additional derived or computed variables will be identified and documented in the SAS programs that create the analysis files. If the SAP is not amended, further derivations related to primary and secondary target variables will be described in the CSR.

- The age of a patient is defined according to the usual definition that a person is n years old until she or he has completed her or his (n+1)th year of life, using the date of informed consent as the reference date. This is also the definition that will be applied for evaluation of the age related inclusion criteria. [Unit: years]
- Body Mass Index: BMI = (Body weight) / Height^2 [Unit: kg/m^2]
- Treatment group for safety analyses: Because of the cross-over follow-up phase in this study, safety data will be summarized in 3 groups:
    1. 'Panzyga': Patients with either
        - Panzyga as the first IMP administered, from start of treatment and up to 21 days after the end of the last Panzyga infusion, or with
        - Panzyga as their 2nd treatment, from start of Panzyga treatment until the end of the observation period.
    2. 'Placebo': Patients with Placebo as their first IMP administered, from start of treatment until the first administration of Panzyga.
    3. 'Placebo after Panzyga': Patients who received Panzyga in the first period and are now treated with Placebo, from 22 days after the last Panzyga administration until the end of the observation period.

Derivations with respect to evaluation/scoring of the standardized assessment tools/questionnaires used in this study (CY-BOCS, CGI, COIS, SNAP-IV, PTQ, C-SSRS) will be done according to the respective scoring manuals and are therefore not detailed in this SAP.

9. Study Patients and Demographics

9.1. Disposition of Patients and Withdrawals

All subjects screened for the study will be accounted for. For screening failures the reasons for not being enrolled in the study will be listed and summarized.

For all patients enrolled in the study, descriptive summaries of population data will be provided overall and by randomized treatment group; these will include

- The number and percent of patients in each analysis population, overall, by randomized treatment group, and by the variables used for stratification (prophylactic use of antibiotics, PANDAS disease subtype).
- Number of patients enrolled, randomized, treated, and the number of completers
- Study withdrawals by reason of withdrawal

Individual patient assignments to the analysis populations will be listed, including the reasons for any exclusion from an analysis population.

9.2. Protocol Deviations

Protocol deviations will be checked on complete data for all patients prior to defining the analysis populations. The final decision regarding inclusion/exclusion of patients from the analysis sets will be made based on data listings and reports during data review meetings before database lock, data release and final analysis, applying the definitions in section 7.

Major/important protocol deviations will be summarized by type of deviation. All individual protocol deviations will be listed.

9.3. Demographics and Other Baseline Characteristics

Descriptive summaries of the demographic and other baseline characteristics will be completed for the populations specified below, overall and by randomized treatment group; these include:

- Demographics [redacted]

  (ITT/FAS, PP)
- Medical History (ITT/FAS)

  Medical history will be coded with the Medical Dictionary for Regulatory Activities (MedDRA, according to the version specified in the Data Management Plan). Incidences of findings in medical history will be summarized by MedDRA system organ class and preferred term
- Prior and Concomitant Medications (ITT/FAS)

  Medications will be coded using the WHO Drug Dictionary (according to the version specified in the Data Management Plan). Incidences of prior and concomitant medications will be summarized by ATC level 2 and ATC level 4
- Baseline Physical Examination (ITT/FAS)
- Baseline CY-BOCS (ITT/FAS)

9.4. Measurement of Treatment Compliance

The following parameters will be listed and summarized for each treatment group, per patient and/or per infusion:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Deviations from the planned treatment schedule will be summarized by counting the number of infusions that deviate from the scheduled intervals by more than the allowed intervals, and by listing all such cases individually.

10. Efficacy Analysis

10.1. Primary Endpoint

Primary Analysis

The primary endpoint parameter in this study is reduction of neuropsychiatric symptomatology in PANS patients, measured by the ratio of the total CY-BOCS after 3 cycles of Panzyga treatment (2 g/kg every 3 weeks) at Week 9 to that at Baseline. [redacted]

Secondary Analysis

In addition to this primary analysis approach, alternative statistical methods may be applied if the underlying assumption of normally distributed measurements cannot be verified. [redacted]

Sensitivity Analyses

Missing endpoint data will be replaced with the median change observed in the placebo group, regardless of the actual group assignment; this sensitivity analysis is considered to be conservative as it will diminish the difference in treatment effect between the treatment groups.

Supportive Analyses

The primary analysis will be repeated for the per-Protocol Population.

10.2. Secondary efficacy endpoints

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10.3. Exploratory analyses

The impact of the stratification variables mentioned in section 4.3 on the primary and secondary endpoints will be assessed in an exploratory manner. [redacted]

[redacted]

[redacted]

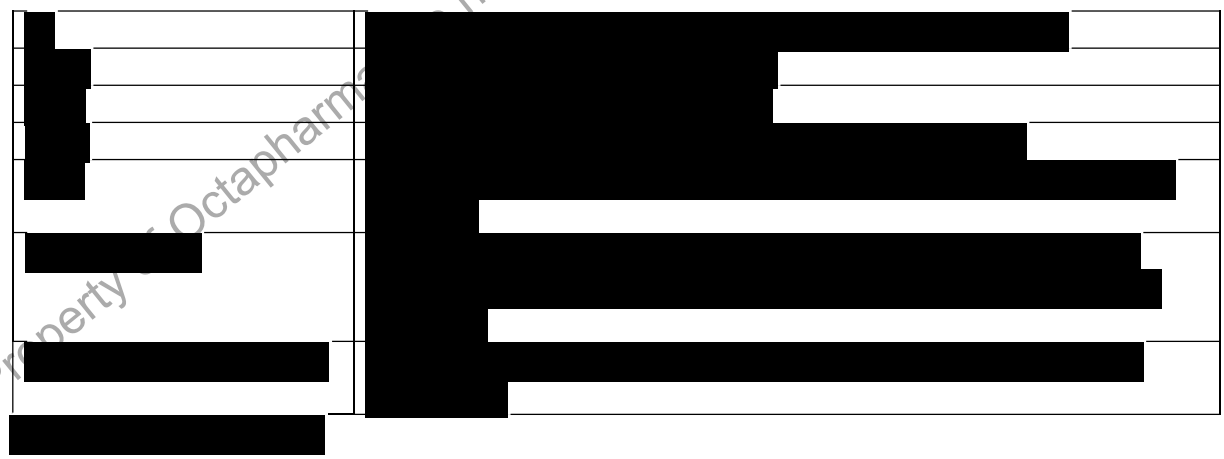
[redacted]

10.3.1. Pharmacokinetics

Blood for the determination of IgG in plasma will be sampled at the following times:

- [redacted]
- [redacted]

[redacted]



[redacted]

[redacted]

- [redacted]
- [redacted]

- [redacted]

[redacted]

[redacted]

10.3.2. Correlation between CY-BOCS and CGI-I

The correlation analysis between CY-BOC and CGI-I will be performed based on ITT Population for the following exploratory endpoints:

- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10.3.3. Pediatric Patients with PANs improvement

PANS improvement will be defined as improvement of PANS symptoms based on CGI-I ratings at Week 9 since Week 3, and at Week 18 since Week 12. Patient will be evaluated as PANS improvement if the CGI-I score is 3 (Minimally Improved) or better at the evaluated visit.

The descriptive statistics (n and percentage %) for patients with PANS improvement will be summarized by treatment groups at Week 9 and Week 18. [redacted]

11. Safety and Tolerability Analyses

The safety analysis will comprise descriptive statistics, tabulations and listings of all adverse events (AEs), safety laboratory results, and physical examination findings. The safety analysis will be made with the FAS, including all randomized patients who received at least part of one infusion of Panzyga or placebo. In the event that a patient received the wrong study drug (i.e. did not take the randomized study drug), the actual treatment will be used for safety analyses.

To account for the cross-over follow-up phase in this study, safety tabulations will differentiate between 3 patients groups according to their treatment status as defined in section 8.4 above.

In particular, AEs in patients with treatment sequence (Panzyga – Placebo) that start more than 21 days after the last administration of Panzyga will be reported separately, and an additional medical review will be performed to identify any possible signal of events with long latency.

11.1. Adverse Events

All reported AEs will be coded according to MedDRA.

All AEs with first onset or worsening during the treatment period, i.e. after first IMP administration, are accounted for in the analysis.

In general AE frequency tables will feature columns for each treatment group (as defined in section 8.4) and a total column in a side-by-side fashion.

All reported events will be listed and tabulated in full detail; in particular the following key figures will be presented:

- Total number of AEs reported by severity and overall
- Number of related AEs by severity and overall
- Number of TEEs and HTRs
- Number of SAEs
- Number of AEs leading to withdrawal
- Infusional AEs (AEs that occur during or within: (a) 1 hour, (b) 24 hours, and (c) 72 hours following an infusion, regardless of other factors that may impact the causality assessment

Narratives will be prepared describing each death, other SAEs, and other significant AEs that are judged to be of special interest because of clinical importance, including all TEEs and HTRs reported.

11.2. Clinical Laboratory Evaluations

All laboratory data will be converted to standard units during the Data Management process. The laboratory data will be listed with suitable flags indicating abnormal values (L=Lower than reference range, H=Higher than reference range).

Summary statistics for the laboratory values as well as their changes from baseline will be tabulated for all laboratory parameters. The tables on changes in lab parameters will again feature columns for each treatment group as defined above and a total column in a side-by-side fashion.

11.3. Retention samples

Retention samples will be taken at Screening and at Week 18/Early Termination. Not all samples might be analyzed, but all available viral test results will be listed, and a dedicated table will be prepared in case any seroconversion occurs at any time after administration of Panzyga.

11.4. Vital Signs

To evaluate short-term tolerance, monitoring of vital signs including blood pressure, body temperature, pulse and respiratory rate will be performed before, during and after end of each infusion at time points specified in the protocol. Vital sign abnormalities that qualify as AEs will be reported as such in the eCRF.

All available vital sign measurements will be listed and summarized by time-point by means of standard descriptive statistics, by actual treatment administered at the infusion in question as well as in total.

11.5. Physical Examination

General and targeted physical examinations respectively will be performed throughout the study at visits specified in the protocol. All documented abnormalities will be listed, and any clinically relevant worsening from the status at baseline will be documented as an AE.

12. Reporting Conventions

The following reporting conventions will be adopted for the presentation of study data. These conventions will enhance the review process and help to standardize presentation with common notations.

12.1. General Reporting Conventions

- All tables and data listings will be developed in landscape orientation, unless presented as part of the text in a CSR.
- Figures will in general also be presented in landscape orientation, unless presented as part of the text in a CSR.
- Legends will be used for all figures with more than one variable or item displayed.
- Figures will be in black and white, unless color figures have been identified as useful for discriminating presentation in the figure. Lines in figures should be wide enough to view the line after being photocopied.
- 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, α, β).
- The ICH numbering convention is to be used for all tables, figures, and data listings.
- All footnotes will be left justified and placed at the bottom of a page. Footnotes must be present on the page where they are first referenced. Footnotes should be used sparingly and must add value to the table, figure, or data listing. If more than four footnote lines are planned then a cover page may be used to display footnotes.
- Missing values for both numeric and character variables will be presented as blanks in a table or data listing. A zero (0) may be used if appropriate to identify when the frequency of a variable is not observed.
- All date values will be presented as DDMMMYYYY (e.g., 29AUG2001) format.
- All observed time values will be presented using a 24-hour clock HH:MM format (e.g. 15:26).
- Time durations will be reported in HH:MM notation. The use of decimal notation to present (display) time durations should be avoided (e.g. 0.083h = 5min) unless it is necessary to show the computation of time differences in a table, figure, or data listing, in which case both notations may be used to display the time duration.
- All tables, figures and data listings will have the name of the program, and a date stamp on the bottom of each output.

12.2. Population Summary Conventions

- Population(s) represented on the tables or data listings will be clearly identified in the title as “Population: <name of population>” where <name of population> is any of the analysis population names or abbreviations defined in section 7 (full analysis set (FAS), per-protocol set (PP), etc.).

- Sub-population(s) or special population(s) descriptions will provide sufficient detail to ensure comprehension of the population (e.g., FAS Females, Per-Protocol Patients with prophylactic use of antibiotics) used for analysis in a table or figure.
- Population sizes may be presented for each treatment or dosing category as totals in the column header as (N=xxx), where appropriate.
- Population sizes shown with summary statistics are the samples sizes (n) of patients with non-missing values.
- All population summaries for continuous variables will include: N, mean, SD, median, Q1, Q3, minimum and maximum.
- All percentages are rounded and reported to a single decimal point (xx.x%).

13. Tables, Listings and Figures

To be supplied in a separate document later when all feedback from authorities will be available.