STATISTICAL ANALYSIS PLAN

Clinical Trial to Assess Onset of Action of Azelastine Hydrochloride and Fluticasone Propionate Nasal Spray Delivered in a Single Spray (Dymista) in the Treatment of Allergen-Induced Allergic Rhinitis Symptoms in Comparison to Placebo in an Environmental Exposure Unit (EEU).

Clinical Study Protocol No. AZFL-AES-4-001
(Version 3.0, dated 27 Jul 2021)

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List of Abbreviations and Definition of Terms

ANCOVA	Analysis of Co-Variance
AE	Adverse Event
BDR	Blinded Data Review
CI	Confidence Interval
COVID	Corona Virus Disease
CRF	Case Report Form
CRO	Contract Research Organization
CTP	Clinical Trial Protocol
DBL	Data Base Lock
EDC	Electronic Data Capture
EEU	Environmental Exposure Unit
EOS	End of Study
EOT	End of Treatment
ET	Early Termination
FAS	Full Analysis Set (Population)
ICH	International Council for Harmonization
IMPs	Investigational Medicinal Products
ITT	Intent-to-Treat (Population)
LSM	Least Square Means
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
OOW	Out Of Window
PP	Per Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAF	Safety (Population)
SAR	Seasonal Allergic Rhinitis
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
T7SS	Total 7 Symptom Score (TNSS + TOSS)
TEAE	Treatment Emergent Adverse Event
TLFs	Table Listing Figures
TNSS	Total Nasal Symptom Score
TOSS	Total Ocular Symptom Score
OTC	Over the Counter
WHODrug	World Health Organization Drug Global

1. Introduction to the Statistical Analysis Plan

This Statistical Analysis Plan (SAP) provides a thorough description of statistical analysis methods and presentation of the study data from the clinical trial described in Study Protocol AZFL-AES-4-001, (Version no. 3.0) dated 27 Jul 2021.

The SAP will be finalized prior to database lock (DBL) and statistical methods described in this document supersede the statistical section mentioned in the study protocol. Deviations to the protocol are described in section 3.6, if any.

Mock shells for Table, Listing & Figure (TLFs) are only for template purpose, modifications might be done in final TLFs as identified during the review of data to have meaningful presentation of data.

2. Objective of the Study

The objectives of this study are:

2.1 Primary Objective:

- To assess the onset of action of a fixed combination of azelastine hydrochloride and fluticasone propionate nasal spray (Dymista) in relieving the nasal symptoms of seasonal allergic rhinitis (SAR) induced by an allergen challenge in an Environmental Exposure Unit (EEU)

2.2 Secondary Objectives:

- To assess onset of action of Dymista in relieving the ocular symptoms of SAR induced by an allergen challenge in an EEU
- To assess onset of action of Dymista in relieving the combined nasal and ocular symptoms of SAR induced by an allergen challenge in an EEU
- To compare overall efficacy (0-4 hours after dosing) of Dymista in relieving the nasal symptoms (TNSS) with that of placebo
- To compare overall efficacy (0-4 hours after dosing) of Dymista in relieving the ocular symptoms (TOSS) with that of placebo
- To compare overall efficacy (0-4 hours after dosing) of Dymista in relieving the combined nasal and ocular symptoms (T7SS) with that of placebo
- To compare overall efficacy (0-4 hours after dosing) of Dymista in relieving the individual nasal and ocular symptoms with that of placebo
- To evaluate time to relevant response to therapy (30% and 50% reduction of TNSS)

3. Investigational Plan

3.1 Overall Study Design

This study is a therapeutic study performed as a single-center, randomized, placebo-controlled, double-blind, and two-period cross-over trial.

The aim of the current study is to replicate the results of the fast onset of action for Dymista from study X-03065-3311 in a second onset of action study using an EEU model with a similar design but without an active control.

An EEU is used to promote a uniform aerosolization of allergen over time in a highly controlled manner. As the assessments will be conducted with limited confounding environmental factors and with consistent allergen exposure, the use of an EEU model is expected to provide a more effective method to assess the onset of efficacy of Dymista compared to a field trial.

3.2 Investigational Medicinal Products:

Subjects were randomized to receive either one of the treatment sequence as AB or BA.

Period 1 (Visit 3)	**Period 2 (Visit 5)**
Treatment A: One spray in each nostril of Dymista nasal spray for a total dose of 274 mcg azelastine hydrochloride plus 100 mcg of fluticasone propionate	Treatment B: One spray in each nostril of placebo nasal spray
Treatment B: One spray in each nostril of placebo nasal spray	Treatment A: One spray in each nostril of Dymista nasal spray for a total dose of 274 mcg azelastine hydrochloride plus 100 mcg of fluticasone propionate

The blinded study treatment was given to suitable subjects on Visits 3 and 5 approximately 2.5 hours after the start of the EEU session.

3.3 Randomization Procedure

To be eligible for Randomization (Visit 3) a subject must comply with all inclusion criteria and must not meet any of the exclusion criteria for randomization mentioned in protocol sections # 4.2.1 and 4.2.2.

3.4 Sample Size Justification

[redacted]

[redacted]

[redacted] a total of 216 randomized subjects should be included in this study.

[redacted]

3.5 Schedule of Events

The study visit schedule can be found in Table 0-1 of the protocol (Version 3.0: 27 Jul, 2021).

3.6 Change to Analysis from Protocol

The following minor changes from the CTP were decided during the blind data review meeting:

- It was decided to draw the figures with absolute values with standard deviation as error bar instead of standard error of means. The reason is, that SEM will be displayed already at the change from baseline figures and different error bars will provide more information.
- Additional to the specification of the protocol, all symptom score assessments, which are out of the defined time windows as defined in the CTP, should be excluded from the per protocol analysis for the respective timepoint (compare also section 5.7).
- Additional to the specification of the protocol, all patients, who do not have assessments for both periods in this cross over study (e.g., due to early discontinuation), should be excluded from the per protocol population.

3.7 Analysis Populations

3.7.1 Safety (SAF) population

All subjects having received at least one dose of the study treatment. The SAF will be used for the analysis of safety data and subjects will be categorized according to the treatment that they actually received. In case the actually received treatment is not documented or could not unambiguously stated, the corresponding treatment period will be assigned to the active treatment and all safety analyses will be done with this classification. The denominator for incidences of AEs will not be changed.

3.7.2 Full Analysis Set (FAS) Population

This will be the intention to treat (ITT) population. These are all randomized subjects including subjects who receive incorrect treatment, do not complete the study or do not comply to the protocol, and who are randomized but did not take any study medication.

3.7.3 Per-Protocol (PP) Population

The per-protocol (PP) set of subjects will be a subset of the FAS population excluding the subjects with major protocol violations that may affect the results of the primary efficacy endpoint. For out-of-window assessments see also section 5.7.
Additionally, all patients who do not have assessments for both periods in this cross over study will be excluded from per protocol population.

3.7.4 FAS Subset with Moderate/Severe Ocular Symptoms

All FAS subjects with baseline TOSS at Visit 3 ≥4 (moderate or severe).

3.8 Population Derivation

Conditions for the population derivation:

1) Has the subject been randomized? = "Yes"

Subjects who satisfy conditions # 1 will be considered in FAS population.

2) Subjects with baseline TOSS at Visit 3 is ≥4.

Subjects who are in FAS population and satisfy condition # 2 will considered in FAS subgroup population.

3) Date of dosing must be available for at least one visit (visit 3 and/or visit 5).

Subjects who satisfy condition # 3 will be considered in Safety (SAF) population.

4) Subjects should not have major protocol violations that may affect the results of the primary variables (as discussed in the blind data review meeting and stated in the blind data review report). Subjects should have data for both treatment periods of this cross over study.

Subjects who are in the FAS population and satisfy conditions # 4 will be considered in PP population.

4. Efficacy and Safety Variables

4.1 Primary Efficacy Endpoint

For onset of action assessment:

- Changes from baseline in TNSS at each post-dose assessment time point (0 to 4 hours p.a.)

4.2 Secondary Efficacy Endpoints

4.2.1 Efficacy:

- Changes from baseline in TOSS and total 7 symptoms score (T7SS) at each post-dose assessment time point (0 to 4 hours p.a.).
- Absolute values (time courses) of TNSS, TOSS, and T7SS during the 6.5-hour EEU session.
- Change from baseline in individual nasal symptom scores (itchy nose, nasal congestion, runny nose, sneezing) and ocular symptom scores (itchy eyes,

watery eyes, eye redness) at each post-dose assessment time point (0 to 4 hours p.a.).

4.2.2 Safety and tolerability:

- Adverse events (AEs)
- Vital signs

4.3 Safety Variables

Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs).

5. Statistical Considerations

5.1 General Considerations

General considerations are as follows:

- Continuous variables will be summarized by descriptive statistics (Number of subjects, number of subjects with missing data, mean, median, standard deviation (SD) and range) and for categorical variables will be summarized as frequencies and percentages.
- For all endpoints, baseline is defined per period as the average of the last 2 assessments (105 and 120 min) in the EEU prior to dosing with study treatment. In case one of these two assessments is missing, the baseline will be the remaining value.
- All the statistical analyses will be conducted at 5% alpha level of significance unless specified.
- For Tables, Listings and Figures preparation, SAS® software (SAS institute, Inc. Cary, USA) version 9.4 or higher will be used.

5.2 Derived Variable

Following derivations will be utilized throughout the study. Formula used for calculation will be displayed in footnote of the table.

- Change from baseline = Post Baseline value – Baseline value
- TNSS = Itchy nose + nasal congestion + runny nose + sneezing
- TOSS = Itchy eyes + watery eyes + eye redness
- T7SS = TNSS + TOSS
- %Reduction in TNSS = (change from baseline for TNSS / Baseline TNSS value)*100
- Time to 30% reduction in TNSS = first time point when the %Reduction is equal or more than 30%

- Time to 50% reduction in TNSS = first time point when the %Reduction is equal or more than 50%
- Prior Medication = Medication consumed by subject prior to screening (Visit 1).
- Concomitant Medication = Medication consumed by subject from signing informed consent to post-study follow-up.
- Prior & Concomitant Medication = Medication consumed by subject prior to screening (Visit 1) and/or during the study period.

5.3 Reporting Precision

All outputs will be generated based on the specifications mentioned in the document of Mock TLFs.

Summary statistics will be presented to the following degree of precision:

Statistic	Degree of Precision
Mean and Median	One more decimal place than the raw data
Minimum and Maximum	Same as the raw data
Standard deviation, Standard error	Two more decimal places than the raw data
Percentage	One decimal places
p-value	Four decimal places or as <.0001

Examples for the Decimal Places:

If percentage value is 0 or 100, it will be reported as '0' and '100' respectively.

Ratios and/or Confidence Interval (CI) will be reported with at least 2 decimal places (e.g. xx.xx, (xx.xx, xx.xx)).

5.4 Multiple Comparison/ Multiplicity

[redacted]

5.5 Handling of missing data

In case of a missing value at time point 105 min or 120 min which are required for baseline calculation, please see section 5.1.

In an event of a single missing symptom item (1 out of 4 nasal symptoms per assessment or 1 out of 3 ocular symptoms missing), this will be replaced by the average of the previous and the following time point of this symptom item, if these two were present for the patient. In an event that before this replacement, two or more symptom items were missing or after this replacement one or more symptoms were still missing, the TNSS/TOSS at this time point will be regarded as missing.

This rule is not applicable for values used for baseline calculation and first assessed timepoint post dose (105 min, 120min pre-dose, 5 min post dose).
T7SS will be calculated as the sum of the TNSS and TOSS. In an event that one or both of these is missing, the T7SS at this time point will be missing, too.

5.6 Interim Analysis

There is no interim analysis planned for the study.

5.7 Out of window assessments

Definition of out of window deviations.
The primary endpoint of this study is the Total Nasal Symptom score (TNSS) including 4 nasal symptoms. All scheduled assessments should be conducted during the time windows specified in the CTP.

However, as there are some assessments outside the defined windows a more precise definition of out-of-window-deviations is given in the following:

If at least one of the 4 nasal symptoms is assessed inside the defined windows, which is specified in the CTP for the respective time point, the complete assessment of the TNSS (all 4 symptoms) is regarded as inside the window. In other words, only if all 4 nasal symptoms are assessed outside the defined window for the respective time point the TNSS score will be classified as out-of-window (OOW). This is applicable for all nasal symptoms, all time points and irrespective if the assessment is before or after the defined window.

Handling of out-of-window assessments:
It is regarded, out-of-window assessments for single time points are considered minor in the sense, that this does not justify an exclusion of all assessments of this patient from per protocol analysis who otherwise assessed scores within the assessment windows at other timepoints.
However, as the primary endpoint is a time-related assessment it is not deemed justified, that out of window deviations should be included in the per protocol analysis. Therefore, all OOW assessments will be excluded from the per protocol analysis of TNSS for the affected time points. Within window assessments of the same patient will be included for the analyses of other time points.
The OOW assessments for a specified timepoint will be handled like missed assessments for the per protocol analysis of TNSS at this timepoint.

Missed assessments:

It is regarded, that missed assessments of single time points are considered minor and that it is not regarded as violation, which justifies the exclusion of the patient from the per protocol analysis. However, as there is no replacement of missing data, the missing timepoint will be kept as missing in the analysis of this specified time point.

6. Statistical Analysis

6.1 Subject Disposition and Withdrawals

Frequency only of the following categories will be displayed as overall:

- Number of screening events (provided informed consents, since study protocol allows rescreening, a unique subject may have 1 to 2 screening events).
- Number of unique subjects screened
- Number of screen failure events by reason

Following categories will be presented as overall using frequency and percentages:

- Number of subjects in FAS Population
- Number of subjects in Safety (SAF) Population
- Number of subjects in PP Population
- Number of subjects in FAS Subset Population
- Number of subjects who completed the study
- Subjects who discontinued early, as well as reasons for subject discontinuation

The denominators for the percent calculations will be overall number of randomized subjects.

Subjects' discontinuation status will be listed by last administered treatment and will include subject number, date of completion or discontinuation and specific reason for discontinuation.

6.2 Demographic Characteristics

Demographic characteristics will be collected at screening.

Demographic characteristics (age, sex, ethnic origin, race, height, body weight and BMI) will be summarized by number of subjects (n), mean, standard deviation, median, minimum and maximum for the continuous variables and number of subjects and percent of subjects for categorical variables.

Demographic characteristics data will also be listed and summarized for Safety and FAS population.

6.3 Primary Efficacy Analysis

The primary endpoint of the study is,

- Changes from baseline in TNSS at each post-dose assessment time point (0 to 4 hours p.a.)

[redacted]

The onset of action is defined as the first time point after initiation of treatment when the product demonstrates a greater change from baseline compared to the placebo, which proves durable from this time point until the end of the last assessed time point (4h) of this study.

Primary efficacy analysis will be performed on FAS population and sensitivity analysis of the primary efficacy endpoint will be performed on PP population. For PP analysis see also section 5.7.

[redacted]

6.4 Secondary Efficacy Analysis

6.4.1 Efficacy:

- Changes from baseline in TOSS and total 7 symptoms score (T7SS) at each post-dose assessment time point (0 to 4 hours p.a.)

- Change from baseline in individual nasal symptom scores (itchy nose, nasal congestion, runny nose, sneezing) and ocular symptom scores (itchy eyes, watery eyes, eye redness) at each post-dose assessment time point (0 to 4 hours p.a.)

The analysis for these two secondary endpoints will be the same as for the primary endpoint analysis.

Overall change from baseline in TNSS, TOSS, and T7SS and all individual symptoms (0 to 4 hours after dosing) will be performed using all time points together and a mixed model repeated measurements analysis [redacted]

All secondary endpoints will be analysed on FAS population.

[redacted]

[redacted]

Time courses: Time courses of TNSS, TOSS, and T7SS during the 6.5-hour EEU session. Time courses will be displayed graphically. Time course arithmetic mean ± SE curves for raw values (0-6.5 hours) and for change from baseline in TNSS, TOSS, and T7SS for the post-dose time points 0 to 4 hour will be presented by treatments overlaid each other using the FAS Population.

Responder analysis: Time to relevant response to therapy (30% and 50% reduction of TNSS) will be analysed by means of Kaplan Meier analysis.

- 30% reduction in TNSS
- 50% reduction in TNSS

The time to 30% and 50% reduction in TNSS will be analysed using the survival analysis method. For a subject during a treatment period, if the time to 30% reduction in TNSS is not achieved before completion of 4 hour post dose time point in EEC or subject discontinue or withdrawn earlier than 4 hour post dose time point in EEC, the 30% reduction time is unknown and will be considered as right-censored for the analysis of 30% reduction time. Similarly, the unknown response time for 50% reduction in TNSS will be considered as right-censored for the analysis of 50% reduction time. The censored observations from this study will be considered as random and uninformative type.

The Kaplan-Meier method of calculation will be used for the cumulative survival probabilities. Cox proportional hazard model using the treatment and baseline TNSS scores will be used to evaluate and compare the treatments and the effect of baseline symptom score for the response time. The Efron method will be used to compute the partial likelihood estimates in case there are event times that are tied.

The reported study results will include:

- The Kaplan-Meier cumulative survival probabilities.
- Summary of estimates of rate of change in log of the hazard corresponding to a one-unit change as well as the hazard ratio for each predictor variable Treatment and baseline TNSS. The hazard ratio for baseline TNSS will be expressed as percentages.

- Percentage of subjects with 30% and 50% reduction in TNSS figures by predictor variable Treatment groups from Cox proportional hazard model analysis.

6.4.2 Subgroup Analysis:

The subgroup analysis on FAS population for TOSS and T7SS with baseline TOSS at Visit 3 ≥4 (moderate or severe) will be performed.

The onset of action and overall change from baseline in TOSS and T7SS for this subgroup will be analysed same as defined in section 6.3 and 6.4.1.

6.5 Safety and Tolerability Assessment

Following will be covered under safety assessment.

AE: Any untoward medical occurrence reported by subject during study period (i.e. screening to end of study) and which does not necessarily have to have a causal relationship with this treatment.

TEAE: The AE start date and treatment dosing dates are compared to attribute an AE to the last treatment just before the adverse event. An AE is considered treatment emergent when occurring in the period from administration of study medication until 5 days (120 h) thereafter. Otherwise, the AE is not considered a Treatment Emergent Adverse Event.

SAE: The adverse events which are Serious

Adverse events will be coded using the latest version of Medical Dictionary for Regulatory Authorities (MedDRA). The occurrence of treatment emergent AEs (TEAEs) and SAEs will be summarized in terms of incidence, as well as in terms of total number of AEs. Analysis of AEs in terms of incidence by severity and by relatedness will also be provided.

6.5.1 Overall Summary of AEs and TEAEs

Following categories will be displayed considering Adverse Event, TEAE and SAE for each treatment and overall.

- Total number of AE/TEAE/SAE (Counts only)
- Number of subjects with at least one TEAE/SAE
- Subjects discontinued due to TEAE
- Number of subjects Died

All subjects in Safety (SAF) population will be included while preparing the tables.

6.5.2 Summary of TEAEs by SOC, PT

Incidences of TEAE will be presented by number and percentages of subjects experience the TEAE and total number of events for SOC & PT by treatment.

If a subject has more than one occurrence of the same preferred term (PT) for an AE then the PT will be counted only once for that subject under the SOC at which it was experienced.

6.5.3 Summary of SAE by SOC, PT

A summary of number and percent of subjects who experienced at least one serious AE or TEAE as well as the number of events, number and percent of subjects who experienced each specific SOC and PT will be presented by treatment.

If a subject has more than one occurrence of the same preferred term (PT) for an AE then the PT will be counted only once for that subject under the SOC at which it was experienced.

6.5.4 Summary of TEAE leading to discontinuation by SOC, PT

Incidences of TEAE leading to discontinue will be presented by number and percentages of subjects experienced TEAE and total number of occurrence.

6.5.5 Summary of TEAE leading to death by SOC, PT

Incidences of TEAE leading to death will be presented by number and percentages of subjects experienced TEAE and total number of occurrence.

6.5.6 Summary of incidence of TEAE by relatedness to study drug

All TEAE will be presented by relationship categories, in case any adverse event observed more than once in same subject then highest relationship only will be counted once for that subject and TEAE. Table will be presented for TEAE and Serious TEAE.

6.5.7 Summary of incidence of TEAE of any causality by treatment, SOC, PT and Severity

All TEAE will be presented by severity categories, in case any adverse event observed more than once in same subject then highest severity only will be counted once for that subject and TEAE.

Adverse events listing and summary will be presented using safety (SAF) population.

6.5.8 Vital Signs

Summary statistics like n, mean, SD, median, minimum and maximum of vital signs will be presented for non-treatment days (Visit 1, Visit 2, Visit 4 and EOS/ET Visit). For vital signs during the treatment periods, the Pre-EEU observation will be considered as baseline. During treatment periods, summary statistics for the observed data at Pre- and Post-EEU session as well as the change at Post-EEU session for Visit 3 and Visit 5 will be presented by treatments.

Blood Pressure and heart rate will be listed and summarised.

Vitals sign listing and summary will be presented by treatment and visit using Safety (SAF) population.

6.5.9 Laboratory Parameters

All laboratory parameters will be listed with the subject number, visit, treatment sequence, date and time of sample collection, test name and results of test and will be presented using Safety (SAF) population.

6.6 Physical Examination

Physical examinations will be listed with the subject number, visit, treatment sequence, date of physical examination, results and clinical significance, if applicable.

6.7 Protocol Deviation

The list of major protocol deviations will be finalized prior to database lock and unblinding as part of the final blind data review (BDR).

Potential violations that may result in the exclusion of the subject from the per-protocol population include, but are not limited to:

a) Not fulfilling all of the inclusion and none of the exclusion criteria during randomization.
b) Not receiving the treatment to which they were randomized.
c) Taking prohibited concomitant medications that may affect the primary variables.

A list of all protocol deviations will be produced. A summary of protocol deviations will also be produced as frequency and percentages by treatment groups along with total.

6.8 Medical and Social History

Clinically relevant medical history (including drug sensitivities and allergies, major surgeries) and any medical condition present at the time that the subject is screened will be documented under medical history and updated until first exposure to study treatment.

Medical and Social history term will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.1 or higher.

Listing of medical and social history will include the parameters as subject number, medical or surgical term, system organ class/preferred term, start date, end date, ongoing and medication ongoing of the term.

6.9 Prior and Concomitant Medication

Any medication other than study drug, either prescription drug or OTC will be treated as concomitant medication.

Medication/Therapy and indication code terms will be coded using the WHO Drug Dictionary (Version March 2019).

Listing of prior and concomitant medication will include Medication/Therapy, Indication, Dose per administration, Unit, Dosage form, Frequency, Route, Start date/Stop date (if applicable)/ongoing, Prior/ Conmed/ Prior & Conmed/ Post EOT.

Listing of prior and concomitant non-pharmacological treatments will include Treatment Name/Procedure/Diagnostic Measures, Indication, Start date/Stop date (if applicable), ongoing.

No summary table will be generated.

6.10 Rescue Medication

In case rescue medication was used, this will be documented as concomitant medication.

7. Summary of Analyses

Endpoint	Analyses	Population(s)
Primary Endpoint: For onset of action assessment: • Changes from baseline in TNSS at each post-dose assessment time point (0 to 4 hours p.a.)	ANCOVA model by timepoint	FAS and PP
Secondary Endpoints: • Changes from baseline in TOSS and total 7 symptoms score (T7SS) at each post-dose assessment time point (0 to 4 hours p.a.)	ANCOVA model by timepoint	FAS
• Time courses of TNSS, TOSS, and T7SS during the 6.5-hour EEU session and change from baseline (0-4h post dose)	Figure: mean and SEM	FAS
• Change from baseline in individual nasal symptom scores (itchy nose, nasal congestion, runny nose, sneezing) and ocular symptom scores (itchy eyes, watery eyes, eye redness) at each post-dose assessment time point (0 to 4 hours p.a.)	ANCOVA model by timepoint	FAS
• Overall change from baseline in TNSS, TOSS, and T7SS and all individual symptoms (0 to 4 hours after dosing)	MMRM model	FAS
• Subgroup analysis on FAS population for TOSS and T7SS with baseline TOSS at Visit 3 ≥4 (moderate or severe)	ANCOVA model by timepoint and MMRM model	FAS subset
• Time to relevant response to therapy (30% and 50% reduction of TNSS)	Kaplan Meier analysis	FAS
Safety variable: • Adverse events • Vital signs	Frequency (%) Summary Statistics	Safety Safety
Disposition	Frequency (%)	All Screened Subjects
Demographics	Summary Statistics	Safety FAS PP

Endpoint	Analyses	Population(s)
Protocol deviations	Frequency (%)	All randomized Subjects

8. Data Management Considerations

All data entry shall be performed by the site staff into the EDC system using CodeAngelo version 1.0. The ePDAT™ data will be transferred to the Cliantha Clinical Data Management group and integrated into the final database. Prior to performing the analyses, a series of checks will be performed to identify missing data, inconsistent data and errors in database. Protocol deviations will be identified. All reported adverse events (AEs) will be coded to standard 'Preferred Terms' and 'System Organ Class' using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.1 or higher.

After all the modifications to the database are made, protocol deviations identified, and adverse events coded, database will be locked. All request to modify the database after treatment assignment is added will require the written approval of the Head of biometrics (Viatris).

All summaries, statistical analyses, and individual subject data listings will be completed using Statistical Analytical System (SAS®) version 9.4, or higher SAS Institute, Cary, North Carolina, United States of America (USA).

9. Tables, Listings and Figures

The TLF shells for this study are provided in a separate document "SAP Mock Shells". These shells may not be reflective of every aspect of this study but are intended to show the general layout of the Tables, Listings and Figures that will be included in the final report.

TLFs are numbered following the ICH E3 "Structure and Content of Clinical Study Report".

10. References

- ICH E3: Structure and Content of Clinical Study Reports, July 1996, CPMP.
- ICH E9: Statistical Principles for Clinical Trials, September 1998, CPMP.