Title: An Open-Label Study of the Safety, Pharmacokinetics, and Pharmacodynamics of ABX464 in HIV-1 Seronegative and Seropositive adult subjects.

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Statistical Analysis Plan

ABX464-005

An Open-Label Study of the Safety, Pharmacokinetics, and Pharmacodynamics of ABX464 in HIV-1 Seronegative and Seropositive adult subjects

ABIVAX
5 rue de la Baume
75008 Paris, France
Tel: +33 (0) 1 53 83 08 41
Fax: +33 (0) 1 53 83 07 48

CONFIDENTAL

Version	Author
Final	Sandor Fritsch

Statistical Analysis Plan

ABX464-005

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1 Introduction

This document outlies the Statistical Analysis Plan (SAP) for the ABIVAX sponsored ABX464. PHASE Ib, STUDY CODE: ABX464-005.

2 Study Objectives

2.1 Primary Objectice

To evaluate the distribution of ABX464 and its main metabolite (N-Glu) in various compartments in HIV-1 Seronegative and Seropositive adult subjects.

2.2 Secondary Objectives

To evaluate the safety of ABX464 administered once daily at one dose, alone in HIV-uninfected subjects and in combination with ARTs in HIV-1 infected adult subjects;

To evaluate the systemic and mucosal immunological response to ABX464 in HIV-uninfected and or in HIV-infected adult subjects;

To evaluate the effect of ABX464 on the HIV reservoir cells in HIV-infected adult subjects;

To evaluate the effect of ABX464 on the control of the viral load and the CD4+/CD8+ in HIV-infected adult subjects;

To evaluate the effect of ABX464 on the microbiome in HIV-1 Seronegative and Seropositive adult subjects;

To evaluate the effect of ABX464 on the rectal transcriptome & proteome in HIV-1 Seronegative and Seropositive adult subjects.

3 Study Design

3.1 Overwiev

The purpose of the ABX464-005 study is to characterize the systemic and mucosal immunological sequelae associated with exposure to ABX464 and to explore selected immunological endpoints, compartmental pharmacokinetics, and pharmacodynamics. The site will screen and enroll 12 HIV-infected subjects who will receive 150 mg ABX464 orally once daily for 28 days (Cohort 1). Following completion of this cohort a further 24 subjects will be enrolled: 12 HIV-uninfected subjects will receive 50 mg ABX464 orally once daily for 28 days (Cohort 2) and 12 HIV-infected subjects (Cohort 3) will receive 50 mg ABX464 orally once daily for 84 days.

Following screening, eligible subjects in both cohorts will undergo a baseline visit during which blood and tissue samples will be collected. All subjects will have additional blood and tissue samples

collected on Day 28 of dosing (and on Day 84 for subjects enrolled in cohort 3) and four weeks after completion of dosing. The HIV infected subjects should be receiving a stable combination antiretroviral regimen for 12 months and be fully virally suppressed (plasma viral load < 50 copies/mL) during the last 6 months prior to enrolment.

Dose limiting toxicity (DLT) is defined as a grade 3 or higher adverse event as defined by the Division of AIDS table for grading the severity of adult and pediatric adverse events (including signs/symptoms, lab toxicities and/or clinical events) considered by the Data Safety Monitoring Board as probably or definitely related to study treatment.

If more than 2 DLTs occur during the treatment period of the first four treated subjects, then the enrolment of additional subjects will be stopped. In addition, in case of a life threatening (grade 4) adverse reaction enrolment and treatment of ongoing subjects will be immediately discontinued. In both cases, enrolment will only be resumed upon the decision of the sponsor if the Data Safety Monitoring Board can conclude that the causality of the event was unrelated or unlikely related to study treatment.

3.2 Inclusion and Exclusion Criteria

To be eligible for inclusion into this study, each patient must fulfil all inclusion criteria and not violate any exclusion criteria (for the protocol under which they are entered) during screening. Details of the inclusion and exclusion criteria are presented in the protocol.

3.3 Study Treatment

HIV infected Subjects must be on a stable antiretroviral regimen for 12 months and have a plasma viral load of < 50 copies/mL for at least 6 months prior to enrolment into the study and be willing to continue their antiretroviral regimen for the duration of the ABX464-005 study

12 HIV-infected subjects are screened and enrolled. They receive 150 mg ABX464 orally once daily for 28 days (Cohort 1). Following completion of this cohort a further 24 subjects are to be enrolled: 12 HIV-uninfected subjects receive 50 mg ABX464 orally once daily for 28 days (Cohort 2) and 12 HIV-infected subjects (Cohort 3) who receive 50 mg ABX464 orally once daily for 84 days.

3.4 Study Timepoints

From a subject standpoint, the study participation is defined as

- Two to four weeks of screening period;
- Four weeks (Cohorts 1 & 2) or twelve weeks (Cohort 3) as the treatment period (ABX464);
- Follow-up visits at 1 week and 4 weeks after cessation of study medication.

Overall, the minimal study duration is approximately 70 days and up to 140 days depending on the subject Cohort.

Visits and visit windows are defined as follows:

Visit	Study Day	Window

Screening	-21	± 7 days
Baseline	1	
Control (Cohort 2 only)	7	± 2 days
Control (Cohort 2 only)	14	± 2 days
Control (Cohort 2 only)	21	± 2 days
Day 28 (Cohort 3 only)	28	± 2 days
End of Study Treatment (Cohort 1 & 2)	28	± 2 days
Follow-up (Cohort 1 & 2)	35	± 2 days
End of Study (Cohort 1 & 2)	56	± 7 days
Day 56 (Cohort 3 only)	56	± 2 days
End of Study Tretment (Cohort 3 only)	84	± 2 days
Follow-up (Cohort 3 only)	91	± 2 days
End of Study (Cohort 3 only)	112	± 7 days

3.5 Sample Size Considerations

No formal sample size calculations were performed. 36 subjects (24 HIV infected and 12 HIV uninfected subjects) are deemed sufficient to fulfil the study objectives.

3.6 Randomization

36 Subjects will be enrolled in this study. These subjects will be enrolled at one site in Spain.No randomizations were performed.

4 Study Endpoints

4.1 Primary Endpoint

Main pharmacokinetic parameters (C_{max}, AUC) after first dose of ABX464 (Day 1),

- Cohort 1: at Day 28 and at Day 56 for plasma, PBMC and rectal tissue.
- Cohort 2: at Day 28 and at Day 56 for plasma and PBMC. Rectal tissue only at Day 28.
- Cohort 3: at Day 28, Day 84 and Day 112 for plasma, PBMC and rectal tissue.

4.2 Secondary Endpoints

Number and grade of treatment-emergent adverse events, including treatment-emergent serious adverse events, adverse events leading to investigational product discontinuation, during the study;

Change in GALT HIV reservoirs in rectal tissue from Baseline to Day 28 and Day 56 in HIV-infected subjects (Cohort 1) and from Baseline to Day 28, Day 84 and Day 112 (Cohort 3);

Change in total viral DNA in the reservoir cells from Baseline to Day 28 and Day 56 in HIV-infected subjects (Cohort 1) and from Baseline to Day 28, Day 84 and Day 112 (Cohort 3);

Change in inflammatory markers in plasma from Baseline including IL-4, IL-6, IL-8, IL-12, IP-10, G-CSF, IFNg, D-dimer, CRP, sCD14 to Day 28 and Day 56 in subjects enrolled in Cohort 1 & 2 and to Day 28, Day 84 and Day 112 in subjects enrolled in Cohort 3;

Change in immunephenotype and assessment of cell-activation markers from Baseline in PBMCs and MMC, using an 11-colours panel, including: CD3, CD8, CD4, CD45RA, CCR7, CD27, CD28, CD38, HLA-DR, PD-1, viability to Day 28 and Day 56 in subjects enrolled in Cohort 1 & 2 and to Day 28, Day 84 and Day 112 in subjects enrolled in Cohort 3;

Change in HIV-1 RNA, CD4+ and CD8+ counts from Baseline to Day 28 and Day 56 in HIV-infected subjects (Cohort 1) and from Baseline to Day 28, Day 84 and Day 112 (Cohort 3);

Change of rectal microbiota using taxonomic markers from Baseline to Day 28 and Day 56 in subjects enrolled in Cohort 1 & 2 and to Day 28, Day 84 and Day 112 in subjects enrolled in Cohort 3;

Change in the transcriptome & proteome from Baseline to Day 28 and Day 56 in subjects enrolled in Cohort 1 & 2 and to Day 28, Day 84 and Day 112 in subjects enrolled in Cohort 3.

4.3 Pharmacokinetic Endpoint

ABX464 has a very short t1/2 (1 to 2 h) and generally no drug could be quantified after 10h post-dose, so steady-state is virtually reached at the second administration.

NGlcABX464 (main ABX464 metabolite) has a t1/2 of 90 to 110 h, meaning that steady-state is reached after 19 to 22 days of administration.

Pharmacokinetic parameters are assessed in plasma, in PBMC and in rectal mucosa.

Intensive Pharmacokinetic runs are conducted after the first dose of ABX464 (Day 1) and for

- Cohort 1: at Day 28 and at Day 56 for plasma, PBMC and rectal tissue.
- Cohort 2: at Day 28 and at Day 56 for plasma and PBMC. Rectal tissue only at Day 28.
- Cohort 3: at Day 28, Day 84 and Day 112 for plasma, PBMC and rectal tissue.

Following PK parameters will be derived for ABX464 and ABX464-N-glucuronide

- C_{max}, t_{max}: the maximum plasma concentration (C_{max}) and the time taken to reach C_{max} (t_{max}) will be obtained directly from the concentration-time data.
- $AUC_{0-\tau}$: the area under the concentration-time curve from time zero to the time of dosing interval τ (24 h post-dose for ABX464 and ABX464-N-glucuronide). If no concentration can be measured at this time point, AUC_{0-last} (from time zero to the last quantifiable concentration)

will be calculated. Both parameters will be presented independently. For both parameters, a linear trapezoidal method will be used.

In addition, five rectal biopsies at each time point will be sent to ALTANBIO for tissue PK determination.

4.4 Safety endpoint

Analysis of safety will be performed on the safety data set consisting in all subjects who received at least one dose of ABX464 in the study. The assessment of safety will be based on the frequency of adverse events (with and without regard to causality) graded according to the Division of AIDS table for grading the severity of adult and pediatric adverse events (Version 2.0 November 2014) and also, the review of individual values for clinical laboratory data, vital signs and ECG focusing on the detection of abnormal values and PCSAs [potentially clinically significant abnormalities (PCSAs) determined upon investigator considerations].

Adverse events will be tabulated (counts and percents) by group and dose. All adverse events will be listed and the data will be tabulated by body system/organ class. Adverse event tabulations will include all treatment emergent adverse events, which will be further classified by severity, and relationship to treatment and dose level.

Clinical laboratory parameters, vital signs, ECG will be summarized by using descriptive statistics (n, mean, SD, SEM, median, minimum and maximum). Number of subjects with at least one abnormal values will be tabulated (counts and percents) for each parameter in summary shift tables, by group and dose.

5 Definitions

Study Drug. Study drug in this study is ABX464.

Baseline. Baseline is defined by patient and by variable as the last non-missing value before the first dose of study drug.

Study Day. Study day is the number of days since start of treatment where the date of first dose is counted as Day 1.

Protocol Deviation: a deviation related to study inclusion or exclusion criteria, conduct of the trial, patient management or patient assessment. This refers to any change, divergence, or departure from the study design or procedures defined in the protocol.

Major Protocol Deviation: These are defined as protocol deviations that are liable to bias the evaluation of the main study endpoints. The following deviations will be considered as major (non-exhaustive list):

- Non-compliance with the inclusion or exclusion criteria;
- Non-compliance with the study treatment
- Intake of prohibited medication;

Non-compliance with time windowThe actual major protocol violations are identified by the study team and documented in an Excell file.

6 Analysis DatasetsSafety dataset (SAF population)

The Safety dataset (SAF population) is defined as those subjects included in the study, who have received at least one dose of the study treatment.

6.1 Full Analysis dataset (FAS population)

The Full Analysis dataset (FAS population) is defined as those subjects included in the study, who have received at least one dose of the study treatment, and who have at least baseline data.

6.2 Per Protocol dataset (PP population)

The Per Protocol dataset (PP population) is defined as those subjects of the FAS population without any major protocol deviation.

7 Safety Monitoring

No safety monitoring reports are planned.

A Data Safety Monitoring Board with expertise and experience in the management in HIV will review the safety of the trial, every 4 patients are recruited, in order to recommend, if appropriate, the continuation of the study.

8 Interim Analysis

An interim analysis have been produced when the first 12 HIV-positive subjects (Cohort 1) reached day 56 of follow-up. The interim analysis includes the following data:

- Safety and clinical parameters;
- HIV-1 RNA, CD4+ and CD8+ counts;
- Hematology and biochemistry parameters;
- Pharmacokinetic parameters in plasma, PBMCs and rectal tissue;
- Total HIV-1 DNA reservoir in PBMC and rectal tissue.

9 Data

10 Statistical Methods

10.1 General Principles

All statistical methods will be based on the International Conference on Harmonisation (ICH) E9 document "Statistical Principles for Clinical Trials".

Data will be summarised by cohort. A total column showing all patients will be included for baseline and safety summaries. Where appropriate, data will also be summarised by visit with summaries for each visit attended as scheduled and an additional summary for final (last scheduled visit or early withdrawal). The format of the summaries is defined in the shells in a separate document.

All summary tables will be made up of the following three columns:

- Cohort 1: Hiv infected subjects receiving the 150mg dose of ABX464 for 28 days;
- Cohort 2: Hiv uninfected subjects receiving the 50mg dose of ABX464 for 28 days;
- Cohort 3: Hiv infected subjects receiving the 50mg dose of ABX464 for 84 days.

In addition, summary tables for total DNA will be made up with an additional column of ohort 1 and Cohort 3 pooled.

In summary and analysis tables of continuous variables, standard descriptive statistics (N, mean, standard deviation [SD], median, quartiles, minimum, maximum) will be presented when relevant. 95% confidence Intervals (CI) will be presented in the statistical analysis outputs as appropriate. For PK summaries, arithmetic mean (AM), geometric mean (GM) and coefficient of variation (%CV) will be used to summarise the data. The minimum and maximum statistics will be presented in summary tables to the same number of significant figures as the original data. The mean/AM, median, GM, CI, SD and will be presented to one more significant than the original data.

For numeric data which includes non-numeric values (e.g. PK data reported as BLQ or lab results reported as < 10 or >100) the following principles will be applied when summarising the data:

- BLQ will be replaced with a value that is ½ of the lower limit of quantification (LLQ)
- Results reported as < x will be treated in the same way as BLQ with LLQ=x
- Otherwise AM, GM, SD, CI and %CV will not be calculated
- Whenever meaningful, minimum, median and maximum will be presented based on the reported data (e.g. minimum = <10, median = 20, maximum = >100)

In summary tables of categorical variables, the number of non-missing observations by category will be presented with percentages. The number of missing observations will also be presented when the count is non-zero. Unless otherwise specified, the denominator for each percentage will be the number of non-missing observations within the column. All percentages will be presented to one decimal place.

If changes in severity for the same TEAE have been reported separately but with the same AE number, they will be collapsed to a single AE with maximum severity for the summary tables, but listed as reported.

Classifications of medical history, concomitant medication and adverse events will be sorted alphabetically within the summary tables.

If any laboratory assessments are repeated at the same visit, the result from the repeat assessment will be used in summaries. Both values will be listed.

Data collected on the eCRF will be presented within data listings. The data listings will be sorted by treatment group, country, centre number, patient number and visit/week/day. Treatment group will be as treated. If any patients receive the wrong treatment this will be flagged in all listings. Visits outside the visit windows will be identified within the listings.

The date format for all output presentations will be 'ddMMMyyyy'.

All statistical analysis will be performed using SAS 9.3 or higher.

If any of the assumptions underlying the formal statistical methods proposed are violated during the analysis of the final data, alternative statistical methods will be used and any changes documented in the statistical methods section of the clinical study report (CSR), including the rationale for use.

10.2 Missing Data

There will be no imputation of missing data in this study.

11 Statistical Output

General principles for layout of the statistical output are described in Section 10.1, including specification of the table columns, and these are illustrated for each unique table in the table shells (separate document). For clarity and brevity in this document the phrase "by treatment group" or "by study cohort" is understood for all summaries and is not included within the text of this section.

The study analysis will be performed following database lock upon the completion of the last patient or upon its early discontinuation whichever occurs first.

11.1 Patient Disposition

A patient is considered to be a baseline failure if the patient signs the informed consent but withdraws before the screening visit. Reasons for exclusion will be recorded for patients who do not enter the study and presented in a data listing.

A summary of the number of screened patients, baseline failures, screening failures and reasons for screening failure will be produced for all enrolled patients.

The number (%) of patients who complete or withdraw from the study and the main reason for withdrawal will be summarised for all randomised patients.

The patient disposition table will summarise the following data for all randomised patients:

- The number (%) of patients in the FAS
- The number (%) of patients in the SAF
- The number (%) of patients in the PP set

A data listing presenting the eligibility for the analysis sets for each patient will also be presented.

Protocol deviations will be reviewed and classed as major or minor during the blind DRM. A listing of all patients with protocol deviations will be presented.

11.2 Patient Characteristics at Baseline

11.2.1 Demographic and Baseline Characteristics

Age will be calculated using Date of Birth (DOB) and date of informed consent and presented as age at last birthday as an integer.

BMI is the patient's body weight in kilograms divided by the square of the patient's height in metres.

Age, gender, race, height, weight and BMI will be summarised.

11.2.2 Medical History and Current Medical Conditions

All conditions will be coded using the version of the Medical Dictionary for regulatory Activities (MedDRA). Past medical/surgical history (conditions that stopped prior to or at the screening visit) and current medical conditions (classified as 'ongoing') will be summarised by system organ class (SOC) and preferred term (PT). The number (%) of patients reporting each condition will be presented.

11.2.3 Procedures / Non-Drug Therapies

All procedures/non-drug therapies recorded on the CRF will be listed only.

11.3 Analysis of Endpoints

The main analysis set for PK and efficacy analyses will be the FAS, and the primary analysis will be repeated for the PP Set if applicable.

Safety endpoints will be summarized on the SAF dataset

11.3.1 Analysis of the primary endpoint

The primary endpoint (Main pharmacokinetic parameters (C_{max}, AUC) after first dose of ABX464 (Day 1) and for

- Cohort 1: at Day 28 and at Day 56 for plasma, PBMC and rectal tissue.
- Cohort 2: at Day 28 and at Day 56 for plasma and PBMC. Rectal tissue only at Day 28.
- Cohort 3: at Day 28, Day 84 and Day 112 for plasma, PBMC and rectal tissue.

will be descriptively summarised on the FAS set.

The primary endpoint analysis will be repeated for the PP set if applicable.

11.3.2 Analysis of secondary endpoints

11.3.2.1 Number and grade of treatment-emergent adverse events

Number and grade of treatment-emergent adverse events, including treatment-emergent serious adverse events, adverse events leading to investigational product discontinuation, during the study.

Treatment-emergent adverse events will be summarized on the SAF dataset. Definition of tretment emergent AEs are found in General Safety Analysis Section (Section 14.4.1).

11.3.2.2 Change in GALT HIV reservoirs

Change in GALT HIV reservoirs in rectal tissue from Baseline to Day 28 and Day 56 in HIV-infected subjects (Cohort 1) and from Baseline to Day 28, Day 84 and Day 112 (Cohort 3).

Change in GALT HIV reservoirs will be descriptively summarised on the FAS set.

11.3.2.3 Change in total viral DNA

Change in total viral DNA in the reservoir cells from Baseline to Day 28 and Day 56 in HIV-infected subjects (Cohort 1) and from Baseline to Day 28, Day 84 and Day 112 (Cohort 3).

Change in total viral DNA will be descriptively summarised on the FAS set.

11.3.2.4 Change in inflammatory markers

Change in inflammatory markers in plasma from Baseline including IL-4, IL-6, IL-8, IL-12, IP-10, G-CSF, IFNg, D-dimer, CRP, sCD14 to Day 28 and Day 56 in subjects enrolled in Cohort 1 & 2 and to Day 28, Day 84 and Day 112 in subjects enrolled in Cohort 3.

Change in inflammatory markers will be descriptively summarised on the FAS set.

11.3.2.5 Change in immunephenotype

Change in immunephenotype and assessment of cell-activation markers from Baseline in PBMCs and MMC, using an 11-colours panel, including: CD3, CD8, CD4, CD45RA, CCR7, CD27, CD28, CD38, HLA-DR, PD-1, viability to Day 28 and Day 56 in subjects enrolled in Cohort 1 & 2 and to Day 28, Day 84 and Day 112 in subjects enrolled in Cohort 3.

Change in immunephenotype will be descriptively summarised on the FAS set.

11.3.2.6 Change in HIV-1 RNA, CD4+ and CD8+ counts

Change in HIV-1 RNA, CD4+ and CD8+ counts from Baseline to Day 28 and Day 56 in HIV-infected subjects (Cohort 1) and from Baseline to Day 28, Day 84 and Day 112 (Cohort 3).

Change in HIV-1 RNA, CD4+ and CD8+ counts will be descriptively summarised on the FAS set.

11.3.2.7 Change of rectal microbiota

Change of rectal microbiota using taxonomic markers from Baseline to Day 28 and Day 56 in subjects enrolled in Cohort 1 & 2 and to Day 28, Day 84 and Day 112 in subjects enrolled in Cohort 3.

Change of rectal microbiota will be descriptively summarised on the FAS set.

11.3.2.8 Change in the transcriptome & proteome

Change in the transcriptome & proteome from Baseline to Day 28 and Day 56 in subjects enrolled in Cohort 1 & 2 and to Day 28, Day 84 and Day 112 in subjects enrolled in Cohort 3.

Change in the transcriptome & proteome will be descriptively summarised on the FAS set.

11.4 Safety Analysis

In addition to the analysis of the secondary safety endpoint the following safety assessments will also be presented.

11.4.1 Adverse Events

All adverse events (AE) will be classified using the version of the MedDRA coding dictionary.

Events will be classified as treatment-emergent if they started or increased in severity on or after the first date and time of medication dosing at Day 1 and up to End of Rx, or withdrawal date if the

patient discontinues before End of Rx. If an event start date is partial, then the start day, month, year or stop date will be used to determine if the event is treatment-emergent. If the classification of the AE cannot be determined from the data available, then the event will be considered treatment-emergent.

Any adverse event which occurs after End of Rx will be classified as post-treatment-emergent.

An overall summary table will be presented using the safety set for adverse events occurring from baseline to the end of the study in the following categories:

- Any adverse event;
- Any treatment-emergent adverse event (TEAE);
- Any post-treatment-emergent adverse event;
- Any serious adverse event;
- Any severe adverse event (Common Toxicity Criteria [CTC] grade 3 or 4);
- Death

TEAEs will be further classified and summarised as follows:

Severe TEAEs: Severity classified as 'Grade 3', 'Grade 4' or missing.

Serious TEAEs: Seriousness classified as 'yes' or missing.

Drug-related TEAEs: Relationship to study drug classified as 'yes' or missing.

Serious drug-related TEAEs: Both serious and drug-related, as specified above.

TEAEs leading to study drug discontinuation: Action taken classified as 'permanent discontinuation'.

Summaries by system organ class (SOC) and preferred term (PT) will also be presented for treatment-emergent events. Similar tables will be presented for each of the classifications of treatment-emergent events above.

A summary of the mean duration (days) of treatment-emergent events will also be presented by SOC and PT, along with the number of events. Duration of an event is calculated as (stop date of event - start date of event) + 1. If an AE is ongoing then use the end of study date (or last known visit date for early termination) as the stop date.

All AE summary tables, unless otherwise specified, will show the number (%) of patients having at least one event and the number of events in each treatment group and overall. Note: If a patient has multiple AEs with the same preferred term, these will be summarised once within the count for N (%) of patients, but each event will be counted within the number of reports E of each AE. Changes in severity of the same AE (if collected) will be counted only once within the number of reports E of each AE.

All adverse events recorded on the CRF will be listed by SOC and PT within the data listings.

11.4.2 Laboratory Data

Routine clinical laboratory results will be carried out at screening, all visits during the treatment period. The laboratory parameters include:

- Haematology: hemoglobin, hematocrit, WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count , INR, PT
- Biochemistry: sodium, potassium, chloride, calcium, phosphate, glucose, BUN or urea, creatinine, AST, ALT, alkaline phosphatase, total bilirubin, GLDH, total protein, lipase, albumin, LDH, gGT, CRP,

Laboratory parameters will be summarised at each visit using descriptive statistics on the SAF set. Laboratory parameters classified as normal/ abnormal non clinically significant (NCS)/ abnormal clinically significant (CS) will be presented in a shift table showing changes from baseline to each visit for patients with at least one abnormal CS value. Baseline is defined as the last non-missing value before the first dose of study drug, which is Day 0.

If laboratory results are repeated at the same visit, the repeated result will be used in summaries (instead of the original one) provided the sample was taken within the visit window, otherwise the original result will be used. All results will be listed.

Laboratory results at unscheduled visits will be included in the listings but will not be summarised.

For all female patients of childbearing potential, a blood pregnancy test (β-HCG) will be performed at Day 0 and then a urine pregnancy test will be performed at each visit until VR. Results of all pregnancy testing will be listed only.

11.4.3 Vital Signs

Measurements of vital signs will be done at each visit (blood pressure, heart rate, body temperature and weight).

Vital signs, including body mass index (BMI), will be summarised for each visit using descriptive statistics on the safety set. Height is collected at screening and will be summarised within the demography data only.

11.4.4 Physical Examination

Physical examinations will be done at each visit.

Physical examination data will be listed only.

11.4.5 Electrocardiogram

A 12-lead ECG will be completed at Screening, Day 0, End of Rx, and End of Study visit.

The number and percentage of the patients with Normal / Abnormal NCS / Abnormal CS ECG results will be summarised at each visit.

A shift table will be presented, for patients with at least one Abnormal CS value, showing changes from baseline to each visit. Baseline is defined as the last non-missing value before the first dose of study drug, which is Day 0.

11.5 Study Drug Exposure and Compliance

Study drug exposure: Exposure is the number of days during the treatment period that the patient was exposed to the study treatment and is calculated as:

- (Date of last dose) – (Date of first dose) + 1

Compliance. Compliance is derived for each patient from their date of first dose to last dose as:

- Compliance (%) = (number of administered doses / scheduled number of doses) x 100%

Number of administered doses, study drug exposure and compliance (%) will be summarised using descriptive statistics for the FAS.

11.6 Prior and Concomitant Medication

All medications taken by patients on entry to the study or during the study will be recorded in the CRF. Medications will be classified using the version of the World Health Organisation Drug Dictionary (WHODD) coding dictionary defined in the DMP. The Anatomical Therapeutic Chemical (ATC) Classification and WHO-DRUG PT will be used to list and summarise the data.

Prior medications are defined as all medications that started and stopped before date of first dose. Only medications where the stop date is prior to date of first dose will be considered prior. If the stop date is unknown or incomplete and the medications cannot definitely be considered as stopped prior to date of first dose then the medications will be considered as maintained medications.

Maintained medications are defined as all medications that started before date of first dose and their stop date is either ongoing at the end of the study or the stop date is on or after date of first dose. Partial start dates where the medication cannot definitely be considered as starting prior to date of first dose will lead to a categorisation of the medications as concomitant medications.

Concomitant medications are defined as all medications that started on or after date of first dose.

The number (%) of patients reporting the use of any prior medications and the number (%) of patients taking each drug by ATC classification (1st, 2nd and 4th levels) and PT will be summarised using the safety set.

This table will be repeated for maintained and concomitant medications.

12 Validation

All tables, figures and listings will be subject to visual review by the Head of Statistics.

13 Literature Citations / References

None