STATISTICAL ANALYSIS PLAN

1407-0037

PARTIALLY-BLIND, RANDOMIZED, PARALLEL GROUP, PLACEBO AND ACTIVE COMPARATOR-CONTROLLED PHASE I CLINICAL TRIAL TO EVALUATE THE PHOTOSENSITIVITY POTENTIAL OF BI 730357

AUTHOR: [redacted]

VERSION NUMBER AND DATE: V2.0, 23JUL2020

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MODIFICATION HISTORY

Listed below are modifications made to the SAP after the signed approval(s).

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	26FEB2020	[redacted]	Not Applicable – First Version
2.0	23JUL2020		Updated to describe the statistical analysis of the 300 mg BID dose group (BI 730357 or placebo) which was added as an additional dose group via the Protocol Version 3.0 (ie, Amendment 2) dated 01 APR 2020.

TABLE OF CONTENTS

1. INTRODUCTION

As per ICH E9, the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data. This trial statistical analysis plan (TSAP) assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 "Statistical Methods and Determination of Sample Size". Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomization

This TSAP Version 2.0 is based on Protocol Version 3.0, (ie, Amendment 2) dated 01 April 2020 and is an amendment to the TSAP Version 1.0 which was finalized on 26 February 2020. This TSAP amendment adds a description of the statistical analysis of the additional dose group of 300 mg BID (subjects randomized to BI 730357 300 mg BID or placebo 300 mg BID) added to the study by the above mentioned protocol.

For the assessment of photosensitivity, statistical analyses for both the double-blind randomized 400 mg QD dose group (subjects randomized to BI 730357 400 mg QD or placebo) and the double-blind randomized 300 mg BID dose group (randomized to BI 730357 300 mg BID or placebo) will be identical but will be performed separately.

[redacted]

This TSAP is developed using the [redacted] statistical analysis plan templates. The operating procedures (SOPs) and programming standards of the Sponsor will be followed for this study.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective of this trial is to evaluate the photosensitivity potential of BI 730357 compared to placebo and a mild photosensitizer ciprofloxacin as positive control, assessed by the Photosensitivity Index (PI), changes in Minimum Erythema Dose (MED), erythema, and local skin reactions following exposure to UVA and UVB radiation. All endpoints are applicable for Treatment A and Treatment B parts.

2.1.1. PRIMARY ENDPOINTS

- Photosensitivity index at 24 hours under Condition 1 (i.e., under full range of UVB/UVA exposure)
- Photosensitivity index at 24 hours under Condition 2 (i.e., under UVA exposure only)

2.1.2. SECONDARY ENDPOINTS

- Photosensitivity index at 10 minutes under Condition 1
- Photosensitivity index at 1 hour under Condition 1
- Photosensitivity index at 10 minutes under Condition 2
- Photosensitivity index at 1 hour under Condition 2
- MED percent change from baseline at 10 minutes, 1 hour, and 24 hours measured under Condition 1 and Condition 2

[redacted]

[redacted]

[redacted]

2.3. SAFETY OBJECTIVES

Safety and tolerability objectives are to be assessed in terms of adverse events (AEs), including AEs of special interest (AESIs), laboratory assessments, vital signs, electrocardiograms (ECG), and physical examination.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

The trial will be performed as partially-blind, randomized, parallel group, placebo and active comparator controlled Phase I clinical trial in healthy male and female subjects aged ≥18 to ≤ 55 years. The subjects

will be randomized to one of the two treatments parts (Treatment Part A [Treatment A] or Treatment Part B [Treatment B]) in a 3:1 (A:B) manner first and then Treatment Part A will be conducted according to a randomized, double-blind, placebo-controlled design to assess the photosensitivity potential, safety and tolerability, and pharmacokinetics of multiple doses of BI 730357. In Treatment A, subjects enrolled under the original protocol Version 1.0 will be randomized in a 3:1 manner to receive 400 mg QD of BI 730357 or placebo and subjects enrolled under the protocol Version 3.0 will be randomized in a 3:1 manner to receive 300 mg BID of BI 730357 or placebo.

Treatment Part B will be conducted according to an open-label, observer-blinded design to assess the photosensitivity potential of ciprofloxacin (a mild photosensitizer) as a positive control.

In total, approximately 84 healthy male and female subjects (36 subjects in Treatment A for 400 mg QD; 36 subjects in Treatment A for 300 mg BID; 12 subjects in Treatment B) are planned to be randomized in this trial to allow for at least 74 completed subjects.

Treatment A:

Subjects enrolled under Protocol Version 1.0 will receive 400 mg of BI 730357 or placebo once daily over 8 days in order to reach pharmacokinetic steady state. Similarly, subjects enrolled under Protocol Version 3.0 will receive 300 mg of BI 730357 or placebo twice daily 12 hours apart over 7 days with a single dose on Day 8 in order to reach pharmacokinetic steady state. Photosensitivity assessments will occur at baseline and following the last dose of either BI 730357 or placebo.

Treatment B:

Subjects will receive 500 mg ciprofloxacin starting on the morning of Day 3. Twelve (12) hours later, subjects received their second dose of 500 mg ciprofloxacin. Subjects continued a twice-daily dosing regimen through to the morning of Day 8 to ensure they reached pharmacokinetic steady state. Photosensitivity assessments will occur at baseline and following the last dose of ciprofloxacin.

3.2. SCHEDULE OF EVENTS

Visit schedules can be found in the protocol (see Flow Chart for Treatment A and Flow Chart for Treatment B).

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

The further objective of [redacted] will not be performed for this study.

The primary, secondary [redacted] endpoints referred in the protocol as “Phototoxicity index” are changed to the appropriate name “Photosensitivity index” (see Sections 2.1.1, 2.1.2 and 2.2.1 above).

4. PLANNED ANALYSES

4.1. INTERIM ANALYSIS

There are no formal statistical interim analyses planned for this study. However, after completion of the 400mg dose group, the independent Investigator and BI medical representatives will review blinded photosafety data of treatment A group to determine the acceptability of photosafety. After the team review of these data, it may be recommended to terminate the trial based on favourable results of 400mg, or in case of unfavourable results - to test the lower dose in of 200mg for treatment A. However, primary analysis of ongoing PoC trial have shown higher exposures in Psoriasis patients than those of healthy volunteers; therefore, in order to investigate possible phototoxic effects in exposures which approximate those of patients treated with 200 mg BID, healthy volunteers should be treated with 300 mg BID. under fed conditions in this trial.

4.2. FINAL ANALYSIS

All final, planned analyses identified for non-PK data in this SAP will be performed by [redacted] Biostatistics following sponsor authorization of this Statistical Analysis Plan, identification of important protocol deviations requiring analysis exclusions, database lock, determination of analysis sets, and unblinding of treatment. All final, planned analyses for PK data will be performed by the Sponsor.

5. ANALYSIS SETS

Agreement and authorization of subjects included/ excluded from each analysis set will be conducted prior to the unblinding of the study.

5.1. ENROLLED SET (ES)

The enrolled set will contain all subjects who provide informed consent for this study. Subjects in this population will be used for disposition summaries and listings as appropriate.

5.2. TREATED SET (TS)

The treated set includes all subjects who were randomized and treated with at least one dose of study drug (BI 730357, Placebo or ciprofloxacin). The treated set will be used for safety analyses and randomized treatment will be used for safety analysis.

5.3. FULL ANALYSIS SET (FAS)

This set includes all subjects in the treated analysis set who provide at least one photosensitivity endpoint that was defined as primary or secondary and was not excluded due to an important protocol deviation relevant to the evaluation of photosensitivity. Descriptive and model based analyses of photosensitivity endpoints will be based on the FAS.

5.4. PHARMACOKINETIC SET (PKS)

The pharmacokinetic set includes all subjects who were randomized and treated with at least one dose of study drug BI 730357 and have at least one evaluable primary PK parameter, and are without important protocol deviations thought to have a relevant impact on the PK of BI730357. Whether a protocol deviation is relevant will be decided no later than in the report planning meeting.

6. GENERAL CONSIDERATIONS

Derivation of the PK parameters for BI 730357, in plasma, and generation of the PK analysis datasets, and statistical outputs (table, listing and figures), will be the responsibility of the sponsor. [redacted] biostatistics is only responsible for generating PK SDTM datasets PC and PP using the PK concentration and PK parameter data files received from the sponsor.

The summaries and data listings of all non-PK data as well as the statistical inferential analyses of the primary, secondary and further endpoints of photosensitivity variables will be the responsibility of the study biostatistician at [redacted]

Some minor modifications may be necessary to the planned design of tables, figures, and listings to accommodate data collected during the actual study conduct.

6.1. SUMMARY STATISTICS

For qualitative variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative variables will be summarized using descriptive statistics, including n, mean, standard deviation (SD), median, interquartile range (IQR calculated as third quartile [Q3] minus first quartile [Q1]), minimum, and maximum values. In addition, 10^{th} percentile (P10), 90^{th} percentile (P90), coefficient of variation (CV%), geometric mean (gMean) and geometric CV% (gCV%) will also be presented for PK concentration data and all PK parameters, where applicable.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment

group. The category missing will be displayed only if there are actually missing values.

6.2. TREATMENT SUMMARIZATION

In general, data will be presented for each treatment group (BI 730357 400 mg QD, Placebo QD, BI 730357 300 mg BID, Placebo BID and ciprofloxacin 500 mg BID). Data for subjects in the following combined treatment groups will also be presented when appropriate:

- All subjects combined, presented as Overall
- All BI 730357 treated subjects combined from the 2 dose groups, presented as BI 730357 Pooled
- All placebo treated subjects combined from the 2 dose groups, presented as Placebo Pooled

6.3. PRECISION

Non-PK variables (ie, primary, secondary, further endpoints and safety variables), including derivations thereof, will be reported to the same precision as the source data. Derived variables will be reported using the same precision to those from which they were derived. For the reporting of descriptive statistics, the minimum and maximum values will be presented to the same precision as the source data (base precision); base precision+1 for the mean, median and confidence intervals (CIs); and base precision+2 for the SD and IQR (see APPENDIX 1). Percentages will be presented with one decimal point.

[redacted]

6.4. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date, and will be used to show start/stop day of assessments and events.

Reference start date is defined as the day of the first dose of study medication (Day 1 is the day of the first dose of study medication), and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date then:

Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference date then:

  Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear partial or missing in the listings.

6.5. BASELINE

Unless otherwise specified, baseline is defined as the last scheduled non-missing measurement taken prior to dosing and will generally correspond to Day -1 or Day 1, predose for safety assessments. However, if a subject is missing the planned baseline collection, the previous non-missing scheduled evaluation will become the baseline value. In the case where the last scheduled non-missing measurement (except for AEs and concomitant medications [CMs]) and the date and/or time of study drug coincide, that measurement will be considered as collected prior to study drug administration.

Baseline for photosensitivity assessments will be the assessment collected on Day -2 (Conditions 1 and 2) or Day -1 (Condition 3) (see Section 15.1 for the definitions of baseline for photosensitivity assessment)

6.6. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

Unscheduled measurements will not be included in summary statistics, but will contribute to the best/worst case value where required (e.g. shift tables) and assessment of clinical outliers. Early termination results will be recorded as such, and included with the end-of-treatment (EOT) summaries.

In the case of a retest of a scheduled assessment, the earliest available measurement for that scheduled time (i.e. the original assessment) will be used for summaries unless flagged as invalid.

Listings will include all scheduled, unscheduled, retest and early discontinuation data.

6.7. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

- Value after baseline – Baseline Value

6.8. SOFTWARE VERSIONS

All derivations, statistical analyses, summaries and listings will be generated using SAS version 9.4 or

higher (SAS Institute, Inc., Cary, North Carolina). Non-compartmental pharmacokinetic parameter calculations will be performed using Phoenix® WinNonLin 64 Build 8.1.0.3530.

7. STATISTICAL CONSIDERATIONS

7.1. MISSING DATA

Missing safety data will not be imputed.

8. OUTPUT PRESENTATIONS

APPENDIX 1 shows conventions for presentation of data in outputs.

The templates provided with this TSAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by [redacted] Biostatistics.

9. DISPOSITION AND WITHDRAWALS

Subject disposition and withdrawals will be tabulated by treatment part/treatment for the enrolled set by summarizing the number (percent) of subjects:

- Enrolled
- Failed screening
- Randomized
- Treated
- Completed treatment
- Discontinued treatment prematurely, and the reason for early discontinuation
- Completed study
- Discontinued study prematurely, and the reason for early discontinuation.

The denominator for calculating percentages will be the number of subjects in the respective treatment group.

A listing of subject disposition data will be provided. In a separate listing, the inclusion/exclusion of subjects in the different analysis sets will be presented.

Listings of study eligibility, treatment randomization, and study treatment administration will be

provided.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The following demographic and baseline characteristics will be tabulated by treatment and overall for the treated set:

- Age (years)
- Sex
- Childbearing status
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)
- Fitzpatrick skin type.

Descriptive statistics (n, mean, SD, median, IQR, minimum, and maximum) will be presented for continuous variables. Frequency counts and percentages will be presented for categorical variables. No statistical testing will be carried out for demographic or other baseline characteristics.

Individual subject demographics and baseline characteristics will be presented in listings.

10.1. DERIVATIONS

- BMI (kg/m^2) = weight (kg)/ height $(m)^2$
- Age (years) = Integer value of [(Date of informed consent – date of birth + 1)/365.25]

11. PROTOCOL DEVIATIONS

11.1. DEVIATIONS RELATED TO STUDY CONDUCT

A protocol deviation is any noncompliance with the clinical trial protocol, good clinical practice (GCP), or Manual of Procedure requirements. The noncompliance may be either on the part of the subject, the site principal investigator, or the study site staff. Protocol deviations will be listed including a

classification of minor, major or critical as determined by clinical staff. Whether a protocol deviation is relevant for the statistical analysis will be decided no later than in the final blinded report planning meeting.

The reasons for exclusion of single data may include (but are not limited to):

- Incorrect trial medication taken
- Important violation of treatment compliance
- Use of restricted medications
- Important violation of inclusion/exclusion criteria
    - Inclusion Criteria 1 - Healthy male and female subjects according to the assessment of the Investigator, based on a complete medical history, physical examination (including dermatological skin type assessment), vital signs (blood pressure, pulse rate), 12-lead ECG, and clinical laboratory tests
    - Inclusion Criteria 4 - Fitzpatrick skin type I, II, or III (I: always burns easily, never tans; II: always burns easily, tans minimally; and III: burns moderately, tans gradually)
    - Inclusion Criteria 5 - No ultraviolet exposure of the test areas 4 weeks prior to baseline photo testing
    - Inclusion Criteria 6 - Normal skin response during preliminary photo testing
    - Exclusion Criteria 6 - Active skin disorders on the back where photosensitivity testing will be performed
    - Exclusion Criteria 7 - Subjects who must or wish to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial
    - Exclusion Criteria 12 - -History of hypersensitivity to ciprofloxacin, any member of the quinolone class of antibacterials
    - Exclusion Criteria 22 - -Unwillingness to adhere to the rules of UV-light protection as described in section 4.2.2 of the protocol

[redacted]

[redacted]

12. MEDICAL HISTORY AND PREVIOUS SURGICAL PROCEDURES

Medical History and previous surgical procedures coded using Medical Dictionary for Regulatory Activities (MedDRA) will be listed for the treated set.

13. MEDICATIONS

Medication usage will be coded using the WHO Drug Dictionary Global (Enhanced w/WHO Herbal Dictionary) B3 format. No Anatomical Therapeutic Chemical (ATC) class coding will be performed.

- 'Prior' medications are medications which started and stopped prior to the first dose of study medication.
- 'Concomitant' medications are medications which were taken during the treatment period, or specifically:
  - started on or after the first dose of study medication or
  - started prior to the first dose of study medication and were continued after the first dose of study medication
- 'Post' medications are medications which started after following the last dose of study medication.

See APPENDIX 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior, concomitant, or post treatment, the medication will be classified by the worst case; i.e. concomitant.

All medications will be displayed in a listing, with an additional flag to state if the medication is a 'Prior', 'Concomitant' or 'Post' medication will be provided for the treated set.

14. STUDY MEDICATION EXPOSURE

In 400 mg QD dose group, BI 730357 and matching placebo will be administered QD over 8 days from

Day 1 (total of 8 doses) in double-blind manner and ciprofloxacin will be administered BID over 5 days from Day 3 with a single dose on Day 8 (total of 11 doses) in an open-label manner. In 300 mg BID dose group, BI 730357 and matching placebo will be administered BID over 7 days from Day 1 with a single dose on Day 8 (total of 15 doses) in double-blind manner. Exposure to study medication as the number of doses administered will be presented by treatment for the treated set.

Study medication administration data will be provided in a data listing.

15. ANALYSIS OF PHOTOSENSITIVITY

For the assessment of photosensitivity, statistical analyses described below will be performed separately for the 400 mg QD dose group (randomized to 400 mg QD BI 730357 or placebo QD) and 300 mg BID dose group (randomized to 300 mg BID BI 730357 or placebo BID). The same ciprofloxacin group will be used as a positive control group in both analyses.

15.1. ASSESSMENT OF PHOTOSENSITIVITY

Skin irradiation will be performed with the following three different conditions, meant to simulate three different environmental sunlight exposure scenarios/conditions:

- Condition 1: Full range solar UVB/UVA (290 to 400 nm, UBV content ~10%), simulating midday summer outdoor sun exposure (assessed in $\mu w/cm^2$)
- Condition 2: UVA only (320 to 400 nm, UVB content <0.03%), simulating indoor exposure behind window glass with a secondary assessment of erythema and local skin reactions at 25 J cm^{-2} (assessed in mw/cm^2)

[redacted]

Subjects will be exposed to a series of 6 graded full range solar UVB/UVA exposures (Condition 1) and UVA only exposures (Condition 2), each 25% greater than the previous dose. Following irradiation, skin sites will be evaluated for erythema or skin darkening (for UVA-only exposure in the absence of additional, drug-induced phototoxicity).

The minimum erythema dose (MED) is defined as the lowest dose that produced uniform redness (Condition 1) or darkening (Condition 2) (assessed in joules (J) for UVA and millijoules (mJ) for UVB/UVA). The value of MED will be reported on electronic case report form (eCRF) at 10 minutes, 1 hour, and 24 hours post-irradiation on Day -3 ($MED_{preliminary}$ values) and Day -2 ($MED_{baseline}$ values) and at 10 minutes, 1 hour, 24 hours, 48 hours, and 72 hours post-irradiation on Day 10 ($MED_{on\ drug}$ values). For Conditions 1 and 2, MED assessments on Day -2 will provide precise baseline MED values (ie, $MED_{baseline}$) for determining the photosensitivity index (PI).

The PI is derived as the ratio of the $MED_{baseline}$ versus $MED_{on\ drug}$ (ie, $MED_{on\ drug}/MED_{baseline}$) for irradiation Conditions 1 and 2.

The percentage change in $MED_{on\ drug}$ at 10 minutes, 1 hour, 24 hours, 48 hours, and 72 hours post-irradiation will be calculated as follows:

- % change = ([$MED_{on\ drug}$ - $MED_{baseline}$]/ $MED_{baseline}$) x 100

Derivation of the PI and percent change in MED at 10 minutes, 1 hour, and 24 hours time points will be performed using precise $MED_{baseline}$ values at the corresponding time point and derivation at 48 hours and 72 hours timepoints will be performed using the precise $MED_{baseline}$ at 24-hour time point.

MED values reported as "> X" on eCRF will be converted to X for the purpose of statistical data analysis, but will be presented as recorded, i.e. as "> X" in the listings.

15.2. PRIMARY ANALYSIS OF PHOTOSENSITIVITY

The objective of this trial is to investigate the photosensitivity under three distinct exposure conditions of BI 730357 following 8 days of administration (i.e. at steady state) on the basis of the primary and secondary endpoints. The trial is designed to allow comparisons between BI 730357 and placebo as well as BI 730357 and a positive control (ciprofloxacin) for each of 2 dose cohorts (400 mg QD and 300 mg BID) separately. These comparisons will be evaluated statistically for each dose cohort separately by use of a mixed model for repeated measures (MMRM). The analysis of primary, secondary and further endpoints will be based on the FAS.

The photosensitivity index (PI) under conditions 1 and 2 is the measurement used for the primary endpoints. It is defined as the ratio of the precise $MED_{baseline}$ to the $MED_{on\text{-}drug}$ at each respective post-irradiation timepoint. Therefore, there will be $MED_{baseline}$ at 10 min, 1h, and 24h that will be used for the respective PI calculations, PI_{10min}, PI_{1h}, and PI_{24h}. For example, the PI_{1h} will be the precise $MED_{baseline}/MED_{on\text{-}drug}$ where each MED was measured at the 1 hour post-irradiation time point. The two primary endpoints are PI at 24 hours under conditions 1 and 2.

For each dose cohort separately, a MMRM (with unstructured [UN] covariance) on PI values will be utilized for the primary analysis. The model will include treatment (BI 730357 and Placebo from the respective dose cohort, Ciprofloxacin), time (10min, 1h, 24h, 48h, and 72h), and treatment-time interaction as fixed effects and subject as a random effect. Adjusted means and differences in PI and 90% CIs for the 2 contrasts of interest (i.e. BI 703357 – placebo at 24h) will be calculated from the model.

The ANOVA model is described by the following equation:

$y_{ijk} = \mu + \tau_i + d_{ij} + \theta_k + (\tau\theta)_{ik} + e_{ijk}$, where

y_{ijk} = PI response measured at time k on subject j receiving treatment i,

μ = the overall mean,

τ_i = the i-th treatment effect, i = 1, 2, 3,

d_{ij} = the random effect associated with the j-th subject receiving treatment i,

θ_k = the k-th time effect, k = 1, 2, 3, 4, 5, and

e_{ijk} = the random error associated with the j-th subject receiving treatment i at time k,

where $d_{ij} \sim MVN(0, \sigma_i^2 I)$ and $e_{ijk} \sim MVN(0, \sigma_2^2 I)$; MVN=multivariate normal.

The SAS code for fitting the above ANOVA model will be similar to:

```
PROC MIXED ;
   CLASS treatment subject time ;
   MODEL PI=treatment time treatment*time/DDFM=KR ;
   REPEATED time / subject(treatment) type=un;
   ESTIMATE statements to obtain point estimates and the corresponding 90%, 95% CIs for contrasts of interest;
RUN ;
```

For each dose cohort, the analysis will be carried out separately for Condition 1 and Condition 2.

15.3. NULL AND ALTERNATIVE HYPOTHESES

15.3.1. 400 MG QD DOSE COHORT

BI 730357 400 mg QD vs Placebo QD

The assessment for absence of photosensitivity will be based upon the differences in mean photosensitivity index (PI) between BI 730357 400 mg QD and placebo QD two-sided 90% confidence intervals (CIs) for the differences in the photosensitivity index between BI 730357 400 mg QD and placebo QD using an acceptance range of -0.4 to 0.4. This method is equivalent to the two-sided t-test procedure, each at the 5% significance level.

The following hypotheses will be tested:

Null hypothesis H_0 (Photosensitive): $\mu_{BI} - \mu_{pbo} \leq -\delta$ or $\mu_{BI} - \mu_{pbo} \geq \delta$

Where μ_{BI} and μ_{pbo} are the means of the endpoint for BI 730357 400 mg QD and placebo QD, respectively, and δ is the limit that defines the acceptance range for photosensitivity equivalence.

Alternative hypothesis H_a (Absence of photsensitivity): $-\delta < \mu_{BI} - \mu_{pbo} < \delta$

In this trial, the equivalence limit δ is 0.4 which is consistent with historical criteria used for positive photosensitivity for a drug [1].

The rejection of the null hypothesis at the a = 0.05 level is equivalent to the inclusion of the 90% confidence interval for $\mu_{BI} - \mu_{pbo}$ in the acceptance range $(-\delta, \delta)$.

Although there are multiple endpoints where the photosensitivity index will be statistically compared, an alpha adjustment is not needed because it is required that all endpoints meet the equivalence criterion as described above simultaneously.

BI 730357 400 mg QD vs ciprofloxacin, Placebo QD vs ciprofloxacin

Comparisons between the mean PI between BI 730357 400 mg QD and ciprofloxacin as well as between placebo QD and ciprofloxacin at the different timepoints under conditions 1 and 2 will be performed.

At each timepoint the null hypothesis will be that there is no difference in the mean PI of BI 730357 400 mg QD compared to ciprofloxacin:

Null hypothesis H_0: $\mu_{BI/pbo} - \mu_{cipro} = 0$

Where $\mu_{BI/pbo}$ and μ_{cipro} are the means of the endpoint for BI 730357 400 mg QD or placebo QD and ciprofloxacin, respectively.

The alternative hypothesis will be that the means are not equal:

Alternative hypothesis H_a: $\mu_{BI/pbo} - \mu_{cipro} \neq 0$

A significant finding of increased photosensitivity of ciprofloxacin compared to BI 730357 400 mg QD and to placebo QD at the $p<0.05$ level will be supportive in concluding that the trial was appropriately designed to test the photosensitivity of BI 730357 400 mg QD.

15.3.2. 300 MG BID DOSE COHORT

For comparisons of BI 730357 300 mg BID vs placebo BID, BI 730357 300 mg BID vs ciprofloxacin, and placebo BID vs ciprofloxacin, null and alternative hypotheses will be identical to the respective null and alternative hypotheses described above for the 400 mg QD dose cohort.

15.4. PRIMARY ENDPOINT ANALYSIS OF PHOTOSENSITIVITY INDEX

400 mg QD Dose Cohort:

The primary analysis will be based on FAS for both conditions 1 and 2 at the 24 hour assessment.

Least squares (LS) mean for the difference between BI 730357 400 mg QD and placebo QD along with the corresponding 2-sided 90% CI will be obtained from the MMRM described in Section 15.2 above.

Absence of photosensitivity between BI 730357 400 mg QD and placebo QD will be concluded if the 2-sided 90% CI is fully contained within the acceptance range (-0.4, 0.4).

A significant finding of increased photosensitivity of ciprofloxacin compared to BI 730357 400 mg QD and to placebo QD at the $p<0.05$ level will be supportive in concluding that the trial was appropriately designed to test the photosensitivity of BI 730357 400 mg QD.

Additionally, descriptive statistics by treatment will be provided for the primary endpoints.

For Conditions 1 and 2, figures of LS mean PI (+/- standard error [SE]) versus time points will be provided.

300 mg BID Dose Cohort:

The primary endpoint analysis of PI for the 300 mg BID dose cohort will be identical to that described above for the 400 mg QD dose cohort. Comparisons of BI 730357 300 mg BID vs placebo BID, BI 730357 300 mg BID vs ciprofloxacin, and placebo BID vs ciprofloxacin will be performed.

15.5. SECONDARY ENDPOINT ANALYSES

400 mg QD Dose Cohort:

The secondary endpoints for differences in PI at 10 minutes and 1 hour under Conditions 1 and 2 will be calculated from the same MMRM model as described for the primary analyses.

Additionally, percent change from baseline in MED at 10 minutes, 1 hour, and 24 hours will be analyzed at each timepoint using the same MMRM model described in the primary analysis.

LS means along with corresponding 95% CIs and p-values for the difference between BI 730357 400 mg QD and placebo QD; between BI 730357 400 mg QD and ciprofloxacin; and between placebo QD and ciprofloxacin will be obtained from the MMRM described in Section 15.2 above.

For Conditions 1 and 2, figures of LS mean % change (+/- SE) versus time points will be provided.

Additionally, descriptive statistics by treatment will be provided for the secondary endpoints.

300 mg BID Dose Cohort:

The secondary endpoint analyses for the 300 mg BID dose cohort will be identical to those described above for the 400 mg QD dose cohort. Comparisons of BI 730357 300 mg BID vs placebo BID, BI 730357 300 mg BID vs ciprofloxacin, and placebo BID vs ciprofloxacin will be performed.

[redacted]

[redacted]

[redacted]

17. SAFETY OUTCOMES

All safety assessments, including AEs, clinical laboratory evaluations, and vital signs will be listed and where appropriate summarized with descriptive statistics by treatment and scheduled visit/time point. Safety summaries will be provided for the following treatment group: Placebo Pooled (pooled from 2 dose groups), BI 730357 400 mg QD, BI 730357 300 mg BID, BI 730357 Pooled (pooled from 2 dose groups) and Ciprofloxacin 500 mg BID. All summaries for safety outcomes will be based on the treated set using the randomized treatment.

No statistical hypothesis testing is planned for safety data, unless otherwise specified with the relevant section.

17.1. ADVERSE EVENTS

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Protocol-specified Adverse Events of Special Interest (AESI) and infection AEs are identified on the eCRF by the investigator.

All adverse events with an onset between start of study medication and 7 days after the last dose study medication (i.e., end of the residual effect period [REP]) will be assigned to the on-treatment period for evaluation and considered as on-treatment AEs. Only on treatment AEs are considered for the summary of adverse events. Adverse Events (AEs) will be coded using MedDRA.

Treatment-emergent adverse events (TEAEs) are defined as AEs occurring between start of study medication and 7 days after the last dose study medication (i.e., end of the REP) inclusive. Adverse events that start before first study medication intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Pretreatment AEs are defined as AEs occurring prior to dosing. These events will be presented in the listings only and are not included in the tabular summary of AEs.

See APPENDIX 2 for handling of partial dates for AEs. In the rare case where it is not possible to assess treatment emergence, the AE will be classified as treatment emergent (i.e. the worst case).

Intensity (Severity)

The AE intensity is classified as mild/moderate/severe. TEAEs starting after the first dose of study medication with a missing severity will be classified as severe for analysis purposes. If a subject reports a TEAE more than once within that system organ class (SOC)/preferred term (PT), the AE with the worst case severity will be used in the corresponding severity summaries.

Causal Relationship to Study Medication

Relationship to study medication, as indicated by the Investigator, is classified as "related" or "not related". TEAEs with a missing relationship to study medication will be regarded as "related" to study medication for analysis purposes. If a subject reports the same AE more than once within that SOC/PT, the AE with the strongest case relationship to study medication will be used in the corresponding relationship summaries.

As an overview incidence summary of TEAEs, number and percentage of subjects with TEAEs, treatment-related TEAEs, mild TEAEs, moderate TEAEs, severe TEAEs, serious TEAEs, treatment-related serious TEAEs, Non-serious TEAEs, AESIs. TEAEs leading to study medication discontinuation, TEAEs leading to death and treatment-related TEAEs leading death will be presented by treatment.

Incidence summaries, including number of events will be presented by SOC and PT for each treatment for the following:

- Overview summary across SOC and PT
- All TEAEs
- TEAEs by causal relationship
- All TEAEs by intensity
- All treatment-related TEAEs by intensity
- Non-serious TEAEs with incidence in preferred terms strictly greater than 5% in at least one of treatment groups.

17.1.1. TEAEs LEADING TO DISCONTINUATION OF STUDY MEDICATION

Treatment-emergent AEs leading to permanent discontinuation of study medication are those TEAEs with response to action taken trial drug due to AE reported as "Drug Withdrawn" on the Adverse Events page of the eCRF.

Treatment-emergent AEs leading to permanent discontinuation of study medication will be listed and summarized using an incidence table by SOC, and PT for each treatment.

17.1.2. SERIOUS ADVERSE EVENTS

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the eCRF, and will be listed. An incidence summary of serious TEAEs by SOC, and PT for each treatment will be prepared.

Non-serious TEAEs with incidence in preferred terms strictly greater than 5% in at least one of treatment groups will be summarized by SOC, and PT for each treatment.

17.1.3. ADVERSE EVENTS OF SPECIAL INTEREST

The following AEs will be recorded as Adverse Events of Special Interest (AESIs) in this trial:

Hepatic Injury

Hepatic injury defined by the following alterations of liver parameters (for subjects with normal liver function at baseline):

- An elevation of aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≥3 times the upper limit of normal (ULN) combined with an elevation of bilirubin ≥2 times ULN measured in the same blood draw sample;

- Aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN.

Severe infections

Opportunistic and mycobacterium tuberculosis infections

These include pneumocystis jirovecii, BK virus disease including PVAN, CMV, posttransplant lymphoproliferative disorder (EBV), progressive multifocal leucoencephalopathy, bartonellosis (disseminated only), blastomycosis, toxoplasmosis, coccidioidomycosis, histoplasmosis, aspergillosis (invasive only), candidiasis (invasive or pharyngeal), cryptococcosis, other invasive fungi (mucormycosis (zygomycosis, rhizopus, mucor, lichtheimia), scedosporium/pseudallescheria boydii, fusarium), legionellosis, listeria monocytogenes (invasive only), tuberculosis, nocardiosis, non-tuberculous mycobacterium, salmonellosis (invasive only), HBV reactivation, herpes simplex (invasive only), herpes zoster, strongyloides (hyperinfection syndrome and disseminated forms only), paracoccidioides, penicillium marneffei, sporothrix schenckii, cryptosporidium species (chronic only), microsporidiosis, leishmaniasis (visceral only), trypanosoma cruzi infection (Chagas' disease) (disseminated only), campylobacteriosis (invasive only), shigellosis (invasive only), vibriosis (invasive due to vibrio vulnificus), HCV progression.

The AESIs are those TEAEs with YES response to the question, "Adverse Event of Special Interest? "on the AE page of the eCRF and will be flagged in listing.

Incidence summaries by SOC and PT will be prepared for each treatment for the following:

- All AEs of hepatic injury
- All AEs of hepatic injury by severity
- All severe infections according to RCTC grading
- All opportunistic and mycobacterium tuberculosis infections
- All opportunistic and mycobacterium tuberculosis infections by severity.

A summary of the number of subjects, percentages, and number of events within will be provided by SOC, PT, and treatment for all treatment-emergent AESI, TEAEs of hepatic injury AESI, infection AESI, serious infection AESI.

17.2. DEATHS

If any subject dies during the study as recorded on the adverse events page of the eCRF, the information will be presented in a data listing.

17.3. LABORATORY EVALUATIONS

Local laboratory results will be included in the reporting of this study for Hematology, Blood Chemistry

and Urinalysis. A list of laboratory assessments to be included in the outputs is included in APPENDIX 3. Presentations will use System International (SI) Units, as provided by the labs.

Protocol-specified clinical laboratory tests will be summarized using descriptive statistics. Clinical laboratory data collected during study conduct, which were not required per protocol, such as for special testing to evaluate an AE, will be listed separately and not summarized.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

All available data will be listed.

The following summaries by treatment will be provided for laboratory data:

- Actual and change from baseline by visit (for quantitative measurements)
- Incidence of as abnormal values according to normal range criteria for urinalysis
- Incidence of Drug-Induced Liver Injury (DILI) findings
- Listing of lab results outside the normal range.

17.3.1. DRUG INDUCED LIVER INJURY (DILI)

- Normal liver function at Baseline is defined as AST, ALT and total bilirubin values measured at baseline are each ≤ the respective ULN
- For post baseline visits:
  - Subjects with normal liver function at baseline and AST and/or ALT ≥3 times ULN combined with total bilirubin ≥2 times ULN measured in the same blood draw sample
  - AST and/or ALT ≥10 times ULN.

17.3.2. LABORATORY REFERENCE RANGES AND ABNORMAL CRITERIA

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges by the lab vendors and categorized as:

- Low: Below the lower limit of the laboratory reference range
- Normal: Within the laboratory reference range (upper and lower limit included)
- High: Above the upper limit of the laboratory reference range.

Clinical laboratory reference/normal ranges will be listed.

17.4. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

- Supine Systolic and Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)
- Body temperature (^{o}C)
- Weight (kg)
- BMI (kg/m^2).

Vital signs will be summarized by treatment using descriptive statistics for baseline, each scheduled visit, and change from baseline to each visit.

Vital signs data will be listed.

17.5. ECG EVALUATIONS

Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as AEs and will be followed up and/or treated as medically appropriate.

17.6. PHYSICAL EXAMINATION

The results of physical examination will be only be included in the source documents available at the site.

18. REFERENCES

[1] Bauer D, Soon RL, Kulmatycki K, Chen Y, Noe A, Chen J, et al
TheDGAT 1inhibitor pradigastat does not induce photosensitivity in healthy human subjects: a randomized controlled trial using three defined sunlight exposure conditions. Photochem Photobiol Sci 15 (9), 1155 - 1162 (2016)

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

OUTPUT CONVENTIONS

TABLE AND LISTING OUTPUT CONVENTIONS

General:

The first row in the body of the table or listing should be blank.

The left-hand column should start in column 1. No indenting or centering of the output should occur.

Rounding should be done with the SAS function ROUND, if no further specification.

Numbers in tables should be rounded, not truncated, if no further specification.

Alphanumeric output should be left aligned.

Numbers should be decimal point aligned.

Whole numbers should be right aligned.

Text values should be left aligned.

The first letter of a text entry should be capitalized

Listings of adverse events, concomitant medications, medical histories, etc. should be sorted in chronological order, with earliest adverse event, medication or history coming first.

The trial drug should appear first in tables with treatments as columns.

In general, only present totals (across treatment groups) at baseline/randomization, and do not present them post randomization.

If possible, include 100% frequencies in the table shell, so that it is clear what the denominator is for percentage calculations.

All listing outputs should be sorted (preferably by Treatment, Site Number and Subject Number).

Do not use superscripts and subscripts.

The width of the entire output should match the linesize option.

Univariate Statistics:

Statistics should be presented in the same order across tables (i.e., n, Mean, SD, Median, IQR, Minimum, Maximum or n, gMean, gCV, Mean, CV, SD, Median, Minimum, Maximum).

Table statistics should line up under the N part of the (N=XXX) in the table header. All decimal points should line up. If the minimum and maximum are output on one line as Minimum, Maximum then the comma should line up with the decimal point.

If the original data has N decimal places, then the summary statistics should have the following decimal places:

- Minimum and maximum: N
- Mean, gMean, median, gCV% and CV%: N + 1
- SD, IQR: N + 2

Frequencies and percentages (n and %):

Percent values should be reported inside parentheses, with one space between the count and the left parenthesis of the percentage. Parentheses should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percentage is less than 100.0. An example is given below:

77 (100.0%)

50 (64.9%)

0 (0.0%)

Percentages will be reported to one decimal place, except percentage <100.0% but >99.9% will be presented as '>99.9%' (e.g., 99.99% is presented as >99.9%); and percentage < 0.1% will be presented as '<0.1%' (e.g., 0.08% is presented as <0.1%). Rounding will be applied after the <0.1% and >99.9% rule.

E.g., (<0.1%)

(6.8%)

(>99.9%)

Percentages may be reported to 0 decimal places as appropriate (for example, where the denominator is relatively small).

Where counts are zero, percentages of 0.0% should appear in the output.

Confidence Intervals:

As a rule, confidence intervals are output to one place more than the raw data, and standard deviations and standard errors to two places more than the raw data.

Confidence intervals should be justified so that parentheses displayed on consecutive lines of a table "line up".

Boundary values of confidence intervals should be separated by a comma.

Boundary values should be padded as necessary to accept negative values and to allow alignment of the decimal place.

An example is given below:

(-0.12, -0.10)

(9.54, 12.91)

P-values:

P-values should be reported to three decimal places, except values <1.000 but >0.999 will be presented as '>0.999' (e.g., 0.9998 is presented as >0.999); and values <0.001 will be presented as '<0.001' (e.g., 0.0009 is presented as <0.001). Rounding will be applied after the <0.001 and >0.999 rule

Ratios:

Ratios should be reported to one more decimal place than the original data.

Spacing:

There must be a minimum of 1 blank space between columns (preferably 2).

Denominators:

If a different count other than the population count is used for a denominator (within the table) to calculate percentages, there should be a row in the table that identifies that number "n".

Alternatively, a footnote should be included in each table with percentages to indicate the denominator for percentages.

Missing values:

A "0" should be used to indicate a zero frequency.

A blank will be used to indicate missing data in an end-of-text table or subject listing.

DATES & TIMES

Depending on data available, dates and times will take the format yyyy-mm-dd; times will take the format hh:mm:ss; combined dates and times will take the format yyyy-mm-ddThh:mm:ss.

SPELLING FORMAT

English US.

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in that order:

Treatment Group	For Tables and Graphs	For Listings
Placebo QD	Placebo QD	Placebo QD
BI 730357 400 mg QD	BI 730357 400 mg QD	BI 730357 400 mg QD
Placebo BID	Placebo BID	Placebo BID
BI 730357 300 mg BID	BI 730357 300 mg BID	BI 730357 300 mg BID
Ciprofloxacin 500 mg BID	Ciprofloxacin 500 mg BID or Cipro 500 mg BID	Ciprofloxacin 500 mg BID or Cipro 500 mg BID

PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order:

Long Name (default)	Short Name
Screening	Scrn
Day -1	
Day x or Day x prodose	Dx or Dx predose
Day x, y hour(s)	Day x, y h
End-of-Treatment	EOT

PRESENTATION OF NOMINAL TIMES

For outputs, nominal times will be represented as follows and in that order:

Long Name (default)	Short Name
x hour(s)	x h

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

Randomized treatment group [in the order Placebo QD, BI 730357 400 mg QD and ciprofloxacin 500 mg

BID for the 400 mg QD dose group first and then, Placebo BID and BI 730357 300 mg BID for the 300 mg BID dose group]

subject ID,

date (where applicable),

For listings where non-randomized subjects are included, these will appear in a category after the randomized treatment groups labelled 'Not Randomized'.

The visit as recorded in the eCRF will be displayed in the listings (and not the remapped visit).

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Partial	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

START DATE	STOP DATE	ACTION
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment

START DATE	STOP DATE	ACTION
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

APPENDIX 3. LABORATORY TESTS

Functional lab group	Test name	A[1]	B[2]	C[3]
Haematology	Haematocrit	X	X	X
	Haemoglobin	X	X	X
	Red blood cells (RBC)	X	X	X
	White blood cells (WBC)	X	X	X
	Platelet count	X	X	X
	MCV	X	X	X
	MCH			
	MCHC			
	RDW			
Automatic WBC differential (relative and absolute)	Neutrophiles total	X	X	X
	Lymphocytes total	X	X	X
	Eosinophiles	X	X	X
	Basophiles	X	X	X
	Monocytes	X	X	X
	Lymphocytes			
Manual differential WBC (if automatic differential WBC is abnormal)	Polymorphnuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes			
Coagulation	Activated partial thromboplastin time (aPTT)	X		
	Prothrombin Time (PT)	X		
	INR	X		
Functional lab group	**Test name**			
Enzymes	Aspartate aminotransferase (AST)	X	X	X
	Alanine aminotransferase (ALT)	X	X	X
	Alkaline phosphatase (AP)	X	X	X
	Gammaglutamyl transferase (GGT)	X	X	X
	Creatine kinase (CK)	X		
	Lipase	X		X
	Amylase	X		X

Substrates	Glucose	X	X	X
	Creatinine	X	X	X
	Urea Nitrogen	X	X	X
	Uric Acid	X	X	X
	Total bilirubin	X	X	X
	Direct bilirubin	X	X	X
	Total protein	X		
	Albumin	X		
	Globulin	X		
	Albumin/Globulin ratio	X		
	C-Reactive Protein (CRP)	X		
	Total cholesterol	X		
Electrolytes	Calcium	X		X
	Sodium	X		X
	Potassium	X		X
	Chloride	X		X
	Phosphate	X		X
Serum Pregnancy test (only for female subjects of childbearing potential) at screening, day -1 and if urine pregnancy test is positive	Human Serum Chorionic Gonadotropin	X	X[4]	
Urinalysis (Stix)	Urine nitrite	X		X
	Urine protein	X		X
	Urine glucose	X		X
	Urine ketone	X		X
	Urine bilirubin	X		X
	Urine Blood	X		X
	Urine leukocyte esterase	X		X
	Urine pH	X		X
	Specific gravity	X		X
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (e.g. presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)			

Urine Pregnancy test (only for female subjects of childbearing potential) at EoT	Human Chorionic Gonadotropin in the urine			X

[1] A: parameters to be determined at screening examination

[2] B: parameters to be determined on Days 1 and 8

[3] C: parameters to be determined at end of trial examination

[4] Day -1 only