
# STATISTICAL ANALYSIS PLAN

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|---|---|
| Study protocol code | Clin_IrCPI_101 |
| Biotrial code | 2BIOXO1 |
| ATC study code | M2154 |
| Study title | A Phase I, Double Blind, Placebo Controlled, Single Ascending Dose Study of Intravenously Administered Ir-CPI to Evaluate Pharmacokinetics, Pharmacodynamics, Safety and Tolerability in Healthy Male Volunteers. |
| Study investigational medicinal product | Ixodes ricinus-Contact Phase Inhibitor (Ir-CPI) |
| Development phase | Phase I |
| Sponsor | BIOXODES SA<br>Parc d'activités économiques du Wex<br>Rue de la Plaine, 11<br>6900 Marche-en-Famene<br>BELGIUM |
| Version of the statistical analysis plan | Final version 1.0 |
| Date of the statistical analysis plan | 09 July 2020 |

# SIGNATURE PAGE

| RESPONSIBILITY | NAME & OFFICE | SIGNATURE | DATE |
|---|---|---|---|
| Biostatistics Project Leader | Corinne MAUDET<br>BIOTRIAL BIOMETRICS<br>7-9 rue Jean-Louis Bertrand<br>CS 34246<br>35042 Rennes Cedex<br>FRANCE | | 09JUL2020 |
| Pharmacokineticist/ Pharmacodynamics expert | Séverine PICHOT<br>BIOTRIAL<br>7-9 rue Jean-Louis Bertrand<br>CS 34246<br>35042 Rennes Cedex<br>FRANCE | | 10 JUL 2020 |
| Sponsor's Senior Project Manager | Joël TASSIGNON<br>BIOXODES SA<br>Parc d'activités économiques du Wex<br>Rue de la Plaine, 11<br>6900 Marche-en-Famene<br>BELGIUM | 09 JULY 2020 | Joël Tassignon (Authentication)<br>Signature numérique de Joël Tassignon (Authentication)<br>Date : 2020.07.09 19:44:52 +02'00' |
| Sponsor's Clinical Project Manager | Malika ACHOUR<br>BIOXODES SA<br>Parc d'activités économiques du Wex<br>Rue de la Plaine, 11<br>6900 Marche-en-Famene<br>BELGIUM | | 09 JUL 2020 |
| Sponsor's Medical Monitor | Steven RAMAEL<br>BIOXODES SA<br>Parc d'activités économiques du Wex<br>Rue de la Plaine, 11<br>6900 Marche-en-Famene<br>BELGIUM | | 10. JUL 2020 |

# REVISION HISTORY

| Date | Version number | Reason for change | Authored by |
|---|---|---|---|
| 12JUN2020 | Draft 0.1 | Initial version | C. MAUDET |
| 26JUN2020 | Draft 0.2 | Integration of BIOXODES comments | C. MAUDET |
| 09JUL2020 | Final version 1.0 | . Integration of BIOXODES comments<br>. Addition of QTcB formula<br>. Addition of Steven RAMAEL in the signatory list | C. MAUDET |

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| ABBREVIATION | DEFINITION |
|---|---|
| ADA | Anti-Drug Antibodies |
| ADPP | ADaM Pharmacokinetic Parameters |
| AE | Adverse Event |
| AESI | Adverse Event of Specific Interest |
| ALT | Alanine aminotransferase |
| ANOVA | Analysis of Variance |
| aPTT | activated Partial Thromboplastin Time |
| AST | Aspartate aminotransferase |
| ATC | Anatomic Therapeutic Chemical |
| AUC | Area Under the Curve |
| $AUC_{0\text{-}6h}$ | Area Under the Curve from time zero to 6h |
| $AUC_{0\text{-}last}$ | Area Under the Curve from time zero to last measurable plasma concentration |
| $AUC_{0\text{-}inf}$ | Area Under the Curve from time zero to infinity |
| BLQ | Below the Limit of Quantification |
| BMI | Body Mass Index |
| $C_{last}$ | Last measurable plasma concentration |
| $C_{max}$ | Maximum observed plasma concentration |
| CI | Confidence Interval |
| CL | Total body clearance |
| CysC | Cystatin C |
| CRF | Case Report Form |
| CV | Coefficient of Variation |
| DBP | Diastolic Blood Pressure |
| ECG | ElectroCardioGram |
| FDA | Food and Drug Administration – U.S. authority |
| FIH | First-In-Human |
| FXI | Factor XI |
| FXII | Factor XII |
| GGT | Gamma Glutamyl Transferase |
| hsCRP | high sensitivity C-Reactive Protein |
| HBsAg | Hepatitis B surface Antigen |
| HCV | Hepatitis C Virus |

| ABBREVIATION | DEFINITION |
|---|---|
| HIV | Human Immunodeficiency Virus |
| i.e. | id est |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| IMP | Investigational Medicinal Product (synonymous with "study drug") |
| Ir-CPI | Ixodes ricinus-Contact Phase Inhibitor |
| IS | Included Set |
| $\lambda_z$ | Terminal elimination rate constant |
| KIM | Kidney Injury Molecule |
| LDH | Lactate Dehydrogenase |
| LLN | Lower Limit of Normal range |
| LLOQ | Lower Limit of quantification |
| MedDRA | Medical Dictionary for Regulatory Activities |
| ND | Not Determined |
| NGAL | Neutrophil Gelatinase-Associated Lipocalin |
| NOAEL | No Observed Adverse Effect Level |
| PCSA | Potentially Clinically Significant Abnormalities |
| PD | PharmacoDynamics |
| PDS | PharmacoDynamics Set |
| PK | PharmacoKinetics |
| PKS | PharmacoKinetic Set |
| PT | Preferred Term |
| QRS | QRS interval duration |
| QT | Time interval for ventricular depolarisation and repolarisation |
| QTc | Corrected QT interval |
| QTcB | QT interval corrected using Bazett's formula |
| QTcF | QT interval corrected using Fridericia's formula |
| RS | Randomised Set |
| SAD | Single Ascending Dose |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAS® | Statistical Analysis System® |
| SBP | Systolic Blood Pressure |
| SD | Standard Deviation |

| ABBREVIATION | DEFINITION |
|---|---|
| SEM | Standard Error of the Mean |
| SOC | System Organ Class |
| SpO2 | Peripheral Capillary Oxygen Saturation |
| SRC | Safety Review Committee |
| SS | Safety Set |
| SVT | SupraVentricular Tachycardia |
| $t_{1/2}$ | Terminal elimination half-life |
| $t_{max}$ | time to reach maximum observed plasma concentration |
| TEAE | Treatment-Emergent Adverse Event |
| TNF | Tumor Necrosis Factor |
| ULN | Upper Limit of Normal range |
| Vdz | Volume of distribution |
| VT | Ventricular Tachycardia |
| WHO | World Health Organisation |

# *1. Introduction*

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analysing study data and outlines the statistical programming specifications, tables, figures and listings. It describes the pharmacokinetics, pharmacodynamics, safety and tolerability variables and populations, anticipated data transformations and manipulations, and other details of the analyses not provided in the study protocol.

The analyses described are based upon the final clinical study protocol V4.0 dated 06 December 2019 and minutes of Safety Review Committee (SRC) meetings, and are prepared in accordance with the International Conference on Harmonisation (ICH) E9 Step 4 version dated 05 February 1998 [1].

The statistical analyses will be performed by the Biostatistics unit of BIOTRIAL BIOMETRICS in agreement with the Sponsor.

The SAP will be validated and signed before the study database is locked.

# *2. Study objectives*

## 2.1. Primary objectives

The primary objectives are:

- Part 1: To assess the safety and tolerability of Ir-CPI following a single ascending 6-hour intravenous infusion in healthy male participants.
- Part 2: To assess the safety and tolerability of Ir-CPI following a combination of rapid (30 minutes) and slow (5.5 hours) intravenous infusion over a total of 6 hours in healthy male participants (see Note at the end of this section).

## 2.2. Secondary objectives

Secondary objectives are:

- Part 1: To assess the pharmacokinetics (PK) of Ir-CPI following single ascending 6-hour intravenous infusion in healthy male participants.
- Part 2: To assess the PK of Ir-CPI following a combination of rapid (30 minutes) and slow (5.5 hours) intravenous infusion over a total of 6 hours in healthy male participants (see Note at the end of this section).
- Investigate the preliminary pharmacodynamics (PD) of Ir-CPI in healthy male participants using a validated method according to the Food and Drug Administration (FDA) guidelines 2018 for activated Partial Thromboplastin Time (aPTT). Inhibition of Factor XI (FXI) and Factor XII (FXII) procoagulant activities will also be assessed to support the aPTT dynamics.

## 2.3. Exploratory objectives

Exploratory objectives are:

- Investigate the potential of Ir-CPI to induce the formation of anti-drug antibodies (ADA), including their capability to neutralize drug activity.
- Investigate the effect of Ir-CPI on markers related to the coagulation system.
- Investigate the effect of Ir-CPI on biomarkers of renal injury.
- Investigate the effect of Ir-CPI on inflammatory markers.

- Assess the PK of Ir-CPI in urine.
- PK PD relationship (graphical analyses).

**Note:** Only the Part 1 was performed with 4 cohorts (A, B, C and D) (instead of Part 1 with 5 cohorts and Part 2 with 3 cohorts) and with the following doses discussed during SRC meetings:

- Cohort A: Ir-CPI 1.5 mg/kg;
- Cohort B: Ir-CPI 3 mg/kg;
- Cohort C: Ir-CPI 6 mg/kg;
- Cohort D: Ir-CPI 9 mg/kg.

Consequently, in all the following descriptions, only the Part 1 will be detailed in this SAP.

# *3. Study methodology*

## 3.1. Study design

This study is a First-In-Human (FIH) Phase 1, double-blind, placebo controlled, single dose escalation study of Ir-CPI in healthy male participants.

The study will consist of:

- Part 1: an Ir-CPI or matching placebo single ascending dose administration in healthy male participants using a continuous 6-hour intravenous infusion.

The flowchart of this study is detailed in section 16.1.

In all the following descriptions, the term *postdose* is defined as « after start of infusion ».

The terms *panel* and *cohort* can be used interchangeably.

## 3.2. Randomisation

For this double blind, placebo-controlled, ascending dose trial of single dose infusions of Ir-CPI/Placebo, the participants will be randomised taking into account the specific requirements for the sentinel groups.

Four (4) panels (A to D), each consisting of eight (8) healthy male participants will be randomised to receive either Ir-CPI or matching placebo: first, 2 sentinel participants (1:1 active / placebo) then for the rest of the group, a 5:1 ratio (active / placebo). The four (4) panels will be administered Ir-CPI/Placebo in a sequential group design.

## 3.3. Treatment(s) received

An Ir-CPI or matching placebo single ascending dose will be administered to the participants using a continuous 6-hour intravenous infusion.

Each of the four (4) panels will receive:

- Cohort A: Ir-CPI 1.5 mg/kg;
- Cohort B: Ir-CPI 3 mg/kg;
- Cohort C: Ir-CPI 6 mg/kg;
- Cohort D: Ir-CPI 9 mg/kg.

### 3.4. Visits

For cohorts from A to D, the study will include the following visits (see section 16.1.1):

| | Cohorts A, B and C | Cohort D |
|---|---|---|
| **Screening** | from Day-28 to Day -2 (Visit V1) | |
| **Randomisation** | Day 1 (pre-dose, Visit V3) | |
| **Treatment period** | from Day -1 (Visit V2) to Day 5 (Visit V7) | from Day -1 (Visit V2) to Day 7 (Visit V8) |
| **Discharge visit** | Day 10 (± 2 days) (Visit V8) | Day 10 (± 2 days) (Visit V9) |
| **Extra ambulatory visits for ADA analysis** | Day 30 (± 3 days) (1 month, Visit V9)<br>Day 90 (± 7 days) (3 months, Visit V10)<br>Day 180 (± 7 days) (6 months, Visit V11) | Day 30 (± 3 days) (1 month, Visit V10)<br>Day 90 (± 7 days) (3 months, Visit V11)<br>Day 180 (± 7 days) (6 months, Visit V12) |

All participants will receive a single intravenous dose of Ir-CPI/Placebo at Day 1, given as a 6-hour infusion.

## 4. *Sample Size*

The number of participants is not based on statistical power considerations. A sample size of 8 participants per panel (i.e., 6 active and 2 placebo) was chosen based on the design of similar SAD studies and is considered adequate to provide an initial assessment of the safety and tolerability profile of Ir-CPI.

## *5. Changes to the planned analysis from protocol*

The following changes are added compared to the planned analysis detailed in the study protocol:

- Addition of the Screened set (defined as all of the subjects having signed an informed consent form) (see section 7.1).
- Orthostatic hypotension and abnormal HR will not be derived because there are not standing vital signs measured during the study.
- Only the Part 1 was performed with 4 cohorts (A, B, C and D) (instead of Part 1 with 5 cohorts and Part 2 with 3 cohorts) and with the following dose modifications discussed during SRC meetings (see minutes of these meetings):
  - Cohort A: Ir-CPI 1.5 mg/kg;
  - Cohort B: Ir-CPI 3 mg/kg;
  - Cohort C: Ir-CPI 6 mg/kg;
  - Cohort D: Ir-CPI 9 mg/kg.
- In exploratory objectives, the investigation of the ADA capability to neutralize drug activity was not performed, and the assessment of the PK of Ir-CPI in urine was also not done.
- Addition of statistical analysis of $AUC_{0\text{-}96h}$ and $AUC_{0\text{-}last}$ (see section 9.2.2).

# *6. Statistical considerations*

## *6.1. Software environment*

Statistical analyses (demography, pharmacodynamics, safety and tolerability data) will be performed using SAS® software version 9.4 (SAS institute Inc. Cary NC USA).

PK parameters will be calculated using Phoenix® WinNonlin® version 8.1 (Certara USA, Inc., Princeton, NJ) and will be analysed using SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA).

## *6.2. Descriptive statistics and data listings*

Descriptive statistics will be supplied according to the nature of the criteria:

- Quantitative variable: sample size, arithmetic mean, standard deviation (SD), standard error of the mean (SEM), minimum, median and maximum, and [quartiles if necessary with geometric mean, arithmetic and geometric coefficients of variation (CV), and quartiles for PK parameters].
- Qualitative variable: sample size, absolute and relative frequencies per class. Percentages will be provided with one decimal place.

If the sample size of one treatment group is less than or equal to 2, only the number of observed values, the minimum and the maximum will be presented for quantitative variables and the percentage of subjects will not be presented for qualitative variables.

Unless specified otherwise, the calculation of percentages will be based on the number of observed values. Therefore, counts of missing values will be included in the denominator and displayed as a separate category if any.

Data will be organised by treatment group:

- Pooled Placebo;
- Ir-CPI 1.5 mg/kg;
- Ir-CPI 3 mg/kg;
- Ir-CPI 6 mg/kg;
- Ir-CPI 9 mg/kg.

All demographic, pharmacokinetics, pharmacodynamics, safety and tolerability listings will be sorted by treatment group, subject and measurement time if applicable.

All listings containing an evaluation date will display the study day defined as the day relative to the administration of study drug:

- Study day 1 will be defined as the day of the study product administration date;
- Study day -1 will be defined as the day prior to the study product administration date;
- There will be no study day 0.

## *6.3. Handling of missing and retest values*

No management of missing values or values below/above a limit of detection/quantification will be performed, except for pharmacokinetic values (see section 0).

For all parameters and for subjects with retest values, the last reliable value will be used for the measurement time before the study drug administration (provided it was measured before

the study drug administration) and the first reliable value will be used for the measurement time after the study drug administration.

### *6.4. Handling of incomplete dates*

No management of incomplete dates will be performed. The incomplete dates will be labelled as such in the listings.

If the start date of a medication or an adverse event is missing or incomplete and the end date is missing, on or after the study drug administration, it will be considered as concomitant/treatment emergent.

### *6.5. Baseline definition*

For all parameters, baseline will be defined as the last available measurement prior to the IMP administration.

### *6.6. Duration*

Duration (in days, hh:mm) will be calculated by the difference between the start and stop date and time (e.g. duration of AE [days, hh:mm] = end of AE date and time – AE onset date and time).

Duration (in days) will be calculated by the difference between the start and stop date + 1 (e.g. duration of a medication [days] = end of medication date – onset of medication date + 1).

### *6.7. Type I error rate*

Unless stated otherwise, statistical tests will be two-sided and will be carried out at the 5 % level of significance.

## *7. Description of study subjects*

### *7.1. Definition of analysis sets*

The following analysis sets will be defined:

- Screened set: all of the subjects having signed an informed consent form (ICF).
- Included set (IS): all the included participants who have signed an ICF.
- Randomised set (RS): all the randomised participants.
- Safety set (SS): all the included participants who have received at least a partial dose of IMP (Ir-CPI or placebo).
- Pharmacodynamic set (PDS): all the included participants who have completed the study without any protocol deviation affecting PD evaluation and with at least one available post-baseline PD data.
- Pharmacokinetic set (PKS): all of the included participants who have been administered a complete infusion of IMP without major protocol deviation affecting PK evaluation. The inclusion of the subjects with incomplete PK profile(s) or incomplete infusion will be discussed before the PK concentration dataset is locked.

The analysis sets will be precisely defined and validated during the blind review meeting.

The safety and pharmacokinetic sets will be analysed using subjects as treated. The randomised and pharmacodynamic sets will be analysed using subjects as randomised.

### *7.2. Subject disposition*

Subject disposition will be described.

A summary table with the description of the number of screened participants, the number of included participants, the number of randomised participants, the number of participants who completed the study and the number of participants who discontinued the study, classified by main reason of withdrawal, will be prepared by treatment group and overall for the subjects in the IS. Corresponding individual listings will be provided.

A summary table with the description of the number and percentage of subjects in each analysis set (IS, RS, SS, PDS and PKS) will be prepared by treatment group and overall. A specific listing of subjects excluded from analysis sets will be provided with the reason(s) for exclusion.

A summary table with the number and percentage of subjects at each visit will be prepared by treatment group and overall on the subjects in the RS. A specific listing with discontinued participants will be prepared. Listings with analysis sets, end of study status and visit dates will also be generated.

### *7.3. Protocol deviations*

A summary table by treatment group and overall with the number and percentage of subjects presenting deviations relating to inclusion/exclusion criteria will be prepared for the subjects in the RS. A summary table by treatment group and overall with the number and percentage of subjects presenting other protocol deviations (all deviations judged relevant during the blind review meeting) will also be prepared by status of the deviations (minor/major). The corresponding listings will be provided with the status of the deviations.

## *8. Demographic data and baseline characteristics*

The analyses of the demographic and baseline characteristics will be performed on the Randomised set.

### *8.1. Demographic data*

The participants' demographic characteristics (age, sex, ethnicity, race, height, weight and BMI recorded at screening) will be summarised by treatment group and overall, and listed.

### *8.2. Other baseline characteristics*

All parameters recorded before dosing (subjects' habits like tobacco, alcohol and caffeine consumption, diet) will be summarised by treatment group and overall, and listed.

Abnormal or positive results as well as all individual data for serology (presence of HIV antibodies, hepatitis B surface antigen (HBsAg), and hepatitis C virus (HCV) antibodies), urine drug screen (amphetamines, benzodiazepine, cocaine, opiates, barbiturate and cannabinoids) and alcohol breath test will be listed.

Birth control method will also be listed.

### *8.3. Medical and surgical history and procedures*

Information on medical and surgical history (including blood donation) recorded at the screening visit and procedures will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0.

A table with the number and percentage of subjects having at least one previous/ongoing medical history or one surgical history will be generated by treatment group and overall. Previous/ongoing medical history will be listed as well as prior surgeries and concomitant surgeries.

### *8.4. Previous and concomitant medications*

Information on previous and concomitant medications will be coded according to the WHO drug Dictionary version of March 2019.

A previous medication will be defined as a relevant treatment received by the participant within 2 weeks before the study product administration. A concomitant medication will be defined as a medication the participant takes during the study and until the last extra ambulatory V11 visit only if related to a reported AE, other than the study drugs, including any prescription or over-the counter drug (including vitamins, herbal and mineral supplements). If the date value does not allow allocation of a medication to the previous or concomitant category (missing or incomplete start or end date), this medication will be considered concomitant.

A table with the number and percentage of subjects having taken at least one previous medication and a table with the number and percentage of subjects having taken at least one concomitant medication will be generated by treatment group and overall (overall and by medication class [2$^{nd}$ level of Anatomical Therapeutic Chemical (ATC)] and medication drug name). Previous and concomitant medications will be listed separately.

### *8.5. Compliance*

A listing with IMP administration dates and times will be generated. Time of meals intake will also be listed.

## *9. Pharmacokinetic data*

The pharmacokinetic analysis will be performed on the PKS.

### *9.1. Generalities*

The following rules for **PK parameter calculation** will be used:

- Actual sampling times will be used for deriving PK parameters.
- If an entire concentration-time profile is below the limit of quantification (BLQ), BLQ values will not be replaced and the profile will be excluded from the PK analysis.
- For plasma concentrations, all BLQ values occurring prior to the first detectable concentration and negative values will be replaced by “0”.
- Embedded BLQ values (BLQ values between two measurable concentrations) will be treated as missing.
- All BLQ values occurring after the first detectable plasma concentration at the end of infusion: if there are several consecutives ones, the first one will be replaced by the lower limit of quantification (LLOQ) divided by 2 (“LLOQ/2”) and the following ones by missing.
- If the pre-dose concentration is ≤ 5 % of the $C_{max}$ value for a particular subject, that subject’s data, without any adjustments, may be included in all pharmacokinetic and

statistical analysis. If the pre-dose value is > 5 % of $C_{max}$, two analyses will be performed: one with the pre-dose value and the other one with the pre-dose value replaced by 0.

- If there are late positive concentration values following 2 BLQ concentration values in the terminal phase, these values will be evaluated. If these values are considered to be anomalous, they will be set to missing.
- Some conditions for PK parameters have to be fulfilled:
  1) the percentage of the extrapolated AUC should not exceed 20 % of the $AUC_{0\text{-}inf}$ of each individual profile,
  2) the elimination rate constant should be determined over a time interval equal to at least 2 x $t_{1/2}$,
  3) the determination of $\lambda_z$ should use only those data points judged to describe the terminal log-linear decline resulting in an adjusted coefficient of determination value $R^2 > 0.7$, and a minimum of 3 data points will be used in calculating $\lambda_z$ excluding $C_{max}$.

  If these conditions are not fulfilled, the following unreliable PK parameters will not be calculated, will be considered not determined (ND) in the listings and will be excluded from the analysis:
  1) if extrapolated AUC > 20 %: $AUC_{ext}$, $AUC_{0\text{-}inf}$, CL and $Vd_z$;
  2) if the time interval used for the determination of the elimination rate constant is inferior to 2 x $t_{1/2}$ or if the adjusted $R^2 < 0.7$: $\lambda_z$, $t_{1/2}$, $AUC_{0\text{-}inf}$, $R^2$, CL and $Vd_z$.

The following rules for **plasma concentration versus time graphic representation** will be used:

- No graphic representation will be done if all values are BLQ.
- BLQ values occurring prior to the first detectable concentration will be replaced by “0”.
- Embedded BLQ values (BLQ values between two measurable concentrations) will be treated as missing.
- All BLQ values occurring after the first detectable plasma concentration at the end of infusion: if there are several consecutives ones, the first one will be replaced by the lower limit of quantification (LLOQ) divided by 2 (“LLOQ/2”) and the following ones by missing.

The following rules for **mean plasma concentration calculation** will be used:

For BLQ concentrations <u>before</u> the first detectable concentration:

- If more than (or equal to) half of the values are either BLQ values replaceable by zero and/or numeric values: statistics will be calculated with the replaceable and numeric values.
- If more than half of the values are BLQ values not replaceable by zero (i.e., subjects for whom all values are BLQ): only the maximum will be presented and the other statistics will be considered BLQ.

For BLQ concentrations <u>after</u> the first detectable concentration:

- If more than (or equal to) half of the values are not BLQ: statistics will be calculated with missing and replaced BLQ values.

- If more than half of the values are BLQ: only the maximum will be presented and the other statistics will be considered BLQ.

For **summary statistics for PK parameters**:

- If more than (or equal to) half of the values are **not ND and not missing**: statistics will be calculated with the available values.
- If more than half of the values are **ND or missing**: only the minimum, median and maximum of the available numeric values will be presented. All other statistics will not be calculated and will be presented as ND.

All BLQ concentrations and missing data will be labelled as such in the concentration data listings.

### *9.2. Plasma concentrations and pharmacokinetic parameters*

#### 9.2.1. Plasma PK parameters

Blood samples will be drawn (see section 16.1):

- For cohorts A, B and C:
  - on Day 1 at pre-dose then post-dose (after start of infusion) at H0.5, H1, H1.5, H2, H4, H6, H6.5, H7, H7.5, H8, H10, H12, H16, then at D2 (H24), D3 (H48), D4 (H72) and D5 (H96).
    In case of infusion less than 6 hours, blood sample for Ir-CPI pharmacokinetics will be done at the end of infusion then H0.5, H1, H1.5, H2, H4, H6, H10, H18, H42, H66 and H90 after the end of infusion.

- For cohort D:
  - on Day 1 at pre-dose then post-dose (after start of infusion) at H0.5, H1, H1.5, H2, H4, H6, H6.5, H7, H7.5, H8, H10, H12, H16, then at D2 (H24), D3 (H48), D4 (H72), D5 (H96) and D7 (H144).
    In case of infusion less than 6 hours, blood sample for Ir-CPI pharmacokinetics will be done at the end of infusion then H0.5, H1, H1.5, H2, H4, H6, H10, H18, H42, H66, H90 and H138 after the end of infusion.

Relevant plasma pharmacokinetic (PK) parameters will be calculated for Ir-CPI by non-compartmental methods, as appropriate for those participants with sufficient plasma concentration data. The rules defined in the previous section (0) will be used.

The different areas under the concentration-time curve (AUC) will be calculated using the linear trapezoidal summation (both the ascending phase and the descending phase).

The following plasma pharmacokinetic parameters will be calculated for Ir-CPI:

| Parameters (unit) | Definition |
|---|---|
| $C_{max}$ (ng.mL) | Maximum observed plasma concentration |
| $t_{max}$ (h) | Time to reach maximum observed plasma concentration |
| $AUC_{0\text{-}6h}$ (ng/mL.h) | Area under the plasma concentration-time curve from time zero to 6 hours |
| $AUC_{0\text{-}last}$ (ng/mL.h) | Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration |

| Parameters (unit) | Definition |
|---|---|
| $AUC_{0\text{-}96h}$ (ng/mL.h) | Area under the plasma concentration-time curve from time zero to 96 hours (in order to be comparable between all the 4 cohorts) |
| $AUC_{0\text{-}144h}$ (ng/mL.h) | Area under the plasma concentration-time curve from time zero to 144 hours (only for Cohort D) |
| $AUC_{0\text{-}inf}$ (ng/mL.h) | Area under the plasma concentration-time curve from time zero to infinity, calculated as follows: $AUC_{0\text{-}inf} = AUC_{0\text{-}last} + C_{last}/\lambda_z$, where $C_{last}$ is the last quantifiable concentration |
| $t_{1/2}$ (h) | Terminal elimination half-life, calculated as follows: $t_{1/2} = Ln(2)/\lambda_z$ |
| $\lambda_z$ ($h^{-1}$) | Terminal elimination rate constant |
| CL (L/h) | Total body clearance, calculated as follows: $CL = Dose / AUC_{0\text{-}inf}$ |
| $Vd_z$ (L) | Volume of distribution, calculated as follows: $Vd_z = CL / \lambda_z$ |

### 9.2.2. Plasma pharmacokinetic analysis

The plasma pharmacokinetic analysis will be performed on the PKS set.

Subjects receiving placebo will not be included in the summary and analysis of PK parameters. Listings with plasma concentrations (including dates and times of PK blood sampling) and PK parameters will be provided by treatment group and subject. These listings will be generated for all subjects with an available PK profile (complete or incomplete), including those who are excluded from the PKS.

Plasma concentrations and PK parameters of Ir-CPI including descriptive statistics will be presented in tables separately for each treatment group.

Individual plasma concentration versus time profiles of Ir-CPI will be presented graphically on linear and log/linear coordinates for each subject.

The graph of arithmetic mean ± SEM over time will be provided for plasma concentration of Ir-CPI on linear and log/linear coordinates with all treatment groups (cohorts A, B, C and D) on the same graph. A reference line corresponding to the lowest $C_{max}$ values at the NOAEL (No Observed Adverse Effect Level), i.e. 53.7µg/mL will be added on the graph of mean and individual concentration-time profiles on log/linear coordinated only.

A graph of arithmetic mean ± SEM with min-max curves over time will be provided for plasma concentration of Ir-CPI for each treatment group on linear coordinates.

Individual plasma concentration-time profiles (spaghetti plots) of Ir-CPI will also be presented for each treatment group on linear coordinates.

Box whisker plots will be generated for the comparison of $C_{max}$, $AUC_{0\text{-}6h}$ , $AUC_{0\text{-}96h}$, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$.

The linear dose-proportionality of the maximum concentration ($C_{max}$) and the areas under the concentration-time curve ($AUC_{0\text{-}6h}$, $AUC_{0\text{-}96h}$, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$) will be assessed for Ir-CPI using an exponential regression model ("power model") that measures the degree of non-linear proportionality [2]. The PK parameter and dose values will be logarithmically

transformed prior to analysis and evaluated using a 1-factor analysis of variance (ANOVA) including log (dose) as fixed effect and subject as random effect.

Linear dose-proportionality will be concluded if the two-sided 90 % confidence interval (CI) for the slope value of the log-transformed dose is within the critical [(1+ln(LL)/ln(r)) ; (1+ln(UL)/ln(r))] region, where r = Dose Maximum/Dose Minimum, LL = 0.8 and UL = 1.25 [2].

The following SAS® code will be used:

```
proc mixed data=ADPP method=REML;
        by PARAMCD;
        class USUBJID;
        model ln(AVAL) = ln(dose) / solution cl alpha=0.10 ddfm=kr;
        random USUBJID;
run;
```

## *10. Pharmacodynamics data*

The pharmacodynamic analysis will be performed on the PDS set.

PD aPTT, Factor XI and Factor XII inhibition will be measured by the change from baseline (central lab). PD aPTT and FXI/FXII parameters will be measured (see section 16.1):

- For cohorts A, B and C:
  - on D1, pre-dose then at 30min, 60min, 90min, 2h, 4h, 6h, 6h30, 7h, 7h30, 8h, 10h, 12h, 16h post-dose, then on D2 (24h), D3 (48h), D4 (72h), D5 (96h) and discharge visit (D10 ± 2 days) (see section 16.1).
    In case of infusion less than 6 hours and besides assessment at pre-dose, 30 min, 60 min, 90 min, 2h and 4h after start of infusion, parameters should be measured at the end of infusion, then 30min, 60 min, 90min, 2h, 4h, 6h, 10h, then 18h, 42h, 66h and 90h after the end of infusion and then at the discharge visit.

- For cohort D:
  - on D1, pre-dose then at 30min, 60min, 90min, 2h, 4h, 6h, 6h30, 7h, 7h30, 8h, 10h, 12h, 16h post-dose, then on D2 (24h), D3 (48h), D4 (72h), D5 (96h), D7 (144h) and discharge visit (D10 ± 2 days) (see section 16.1).
    In case of infusion less than 6 hours and besides assessment at pre-dose, 30 min, 60 min, 90 min, 2h and 4h after start of infusion, parameters should be measured at the end of infusion, then 30min, 60min, 90min, 2h, 4h, 6h, 10h, then 18h, 42h, 66h, 90h and 138h after the end of infusion and then at the discharge visit.

For each time point, including the baseline time point, an aPTT ratio will be calculated by dividing the aPTT value (in sec) of the specific time point (aPTT*) by the baseline aPTT value (in sec) (aPTT°) of the same volunteer (aPTT ratio = aPTT*/aPTT°). The baseline time-point is considered as having an aPTT ratio of 1. A graphical representation of aPTT ratio in function of the time will be done per volunteer. The mean ± SEM, min and max curves will be also represented for each cohort on separate graphs. The mean ± SEM curves of all cohorts (A, B, C, D) will be also represented on one graph.

Concerning FXI and FXII PD parameters, a graphical representation of individual data of FXI activity in each cohort, in function of the time, will be done. Another graphical representation of FXII activity in each cohort, in function of the time, will be done. In these graphs, the normal lower ranges of FXI and FXII activities will be indicated as horizontal lines.

Moreover, FXI or FXII inhibition, expressed in percentages, for each time point (including the baseline time point), has to be calculated for each volunteer. To do so, the calculation is the following:

- Percentage of FXI inhibition= (100-((FXI*/FXI°)*100)
- Percentage of FXII inhibition= (100-((FXII*/FXII°)*100)

FXI* or FXII*: FXI or FXII percentage of inhibition of a specific time point

FXI° or FXII°: FXI or FXII percentage of inhibition of the baseline time point

The baseline time point is considered as 0 % of FXI or FXII inhibition. A graphical representation of FXI or FXII inhibition, expressed as percentages, in function of the time will be done per volunteer. The mean ± SEM, min and max curves will be also represented for each cohort on separate graphs. The mean ± SEM curves of all cohorts (A, B, C, D) will be also represented on a same graph.

Descriptive statistics of changes from baseline will be provided by treatment group and each measurement time for changes from baseline of aPTT ratio and absolute values.

Descriptive statistics will be provided by treatment group on each measurement time for aPTT values (absolute values and changes from baseline), aPTT ratio (ratio values and changes from baseline of ratios) and percentage of FXI or FXII inhibition (calculated percentages and changes from baseline of percentages).

All pharmacodynamics parameters will be listed.

## *11. Exploratory Pharmacokinetic / Pharmacodynamic analysis*

Evaluation of the relationship between concentrations of Ir-CPI and the PD parameters: the change from baseline in coagulation parameters (i.e. aPTT ratio) defined above, FXI and FXII inhibition will be graphically investigated and displayed. The analysis will be performed on the PDS.

## *12. Exploratory Biomarkers Evaluation*

The exploratory biomarkers evaluation will be performed on the PDS.

The following exploratory outcome measurements are defined:

- In blood: D-dimers, fibrinogen, prothrombin time PT (expressed in seconds and as INR), TNFα, hsCRP, cystatin C (CysC), ADA.
- In urine: Urinary microalbumin, Kidney Injury Molecule (KIM-1), Urinary Neutrophil Gelatinase-Associated Lopocalin (NGAL).

Samples for D-dimers, fibrinogen, PT, hsCRP and TNFα will be collected at pre-dose on D1 and then 2h, 4h, 6h, 8h, 12h post-dose, at 24h (D2), at 48h (D3), at 72h (D4) discharge visit (D10 ± 2 days) (see section 16.1).

CysC samples will be collected at screening, then from D1 to D4: pre-dose (D1), 24h (D2), 72h postdose (D4), and then at the discharge visit (D10±2 days) (see section 16.1).

ADA analysis samples will be collected at pre-dose on the day of infusion, at the discharge visit (D10 ± 2 days), on D30 and on D90. If ADAs are detected in D90 samples, ADA analysis samples will be collected also at D180 (see section 16.1).

Urine collections will be done at these intervals pre-dose, [0-6h[, [6-12h[ and [12-24h[ after start of infusion. Urinary NGAL, microalbuminuria and KIM-1 will be assessed (see section 16.1).

For each parameter, descriptive statistics will be provided by treatment group on absolute values and changes from baseline for each measurement time. Graph over time by treatment group will be also produced.

Presence of ADA (and their titration for ADA+ samples) and sub-classes determination (isotype) will be described by treatment group and measurement time.

All exploratory parameters will be listed.

# *13. Safety data*

The safety analyses will be performed on the SS.

## *13.1. Adverse events*

Adverse events, including pre-treatment events, will be recorded from the time of consent through the end of the study.

Adverse events will be coded according to MedDRA Version 22.0.

A treatment-emergent adverse event (TEAE) is an adverse event that occurs after IMP dosing or that was present prior to dosing but was exacerbated between dosing during a treatment period and the end of the study.

Adverse events (including AESIs) will be summarised in tables as follows [overall and by System Organ Class (SOC) and Preferred Term (PT)]:

- Number and percentage of subjects with at least one adverse event and number of occurrences of an adverse event by treatment group and overall,
- Number and percentage of subjects with at least one TEAE and number of occurrences of a TEAE by treatment group and overall,
- By intensity, with the number and percentage of subjects with at least one TEAE and number of occurrences of a TEAE by treatment group and overall,
- By causality, with the number and percentage of subjects with at least one TEAE and number of occurrences of a TEAE by treatment group and overall.

If there are only a few adverse events (≤ 10), only a listing will be generated.

All adverse events reported in the Case Report Form (CRF) will be listed with the SOC, the PT and the Investigator's verbatim. All TEAEs will also be listed with the SOC and the PT. An additional listing will be provided for AEs leading to death and other serious and significant AEs (SAEs or AEs leading to study withdrawal).

*Note: In case of a change of intensity or causality for an event during the treatment period, the intensity will be the highest recorded intensity and the causality will be the highest likelihood recorded.*

### *13.2. Clinical laboratory data*

The following clinical laboratory parameters will be measured at screening, then from D1 to D4: pre-dose (D1), 24h (D2), 72h post-dose (D4), and then at the discharge visit (D10 ± 2 days) (see section 16.1).

**Haematology** parameters will be listed and grouped as follows:

- Red blood cells: erythrocytes (10^12/L), haematocrit (ratio), hemoglobin (g/L);

- White blood cells: basophils (10^9/L), basophils/leukocytes (%), eosinophils (10^9/L), eosinophils/leukocytes (%), leukocytes (10^9/L), lymphocytes (10^9/L), lymphocytes/leukocytes (%), monocytes (10^9/L), monocytes/leukocytes (%), neutrophils (10^9/L) and neutrophils/leukocytes (%);

- Other parameters: platelets (10^9/L).

**Coagulation** parameters will be listed and grouped as follows:

- Coagulation parameters: activated Partial Thromboplastin Time (sec) and aPTT ratio (see calculation in section 10).

**Blood chemistry parameters** will be listed and grouped as follows:

- Liver function: alanine aminotransferase (ALT) (IU/L), alkaline phosphatase (IU/L), aspartate aminotransferase (AST) (IU/L), total bilirubin (fraction of direct bilirubin in case > 1.25 x ULN) (µmol/L) and gamma glutamyl transferase (GGT) (IU/L), lactate dehydrogenase (LDH) (IU/L);

- Renal chemistry: creatinine (µmol/L) and urea (mmol/L);

- Electrolytes: bicarbonate, calcium, chloride, phosphorus, potassium and sodium (all electrolytes expressed in mmol/L);

- Metabolism parameters: fasting glucose (mmol/L);

- Other proteins: albumin (g/L), creatine kinase (and fraction of CK-MB if > 1.5 x ULN) (IU/L) and total protein (g/L).

**Urinalysis** parameters will be listed and grouped as follows:

- Planned urinalysis parameters: cylinders, erythrocytes and leucocytes.

For haematology, blood chemistry and coagulation, absolute values and changes from baseline will be described by treatment group (and overall) and measurement time.

For urinalysis, absolute values will be described by summary statistics or frequency tables by treatment group and measurement time.

For haematology, blood chemistry, coagulation and urinalysis, values higher or lower than the laboratory reference range (H, L) will be listed.

For haematology and blood chemistry, a summary table with the number and percentage of subjects with potentially clinically significant abnormal (PCSA) values (defined in section 16.2) will be generated by treatment group (and overall) and measurement time.

For haematology and blood chemistry, shift tables with the number of subjects having values lower than the lower PCSA limit (Low), normal and higher than the upper PCSA limit (High)

(defined in section 16.2) according to the baseline position will be prepared by treatment group and measurement time.

A specific listing of subjects with PCSA values will be generated.

Values (absolute values and changes from baseline) will be listed and data out of normal/PCSA ranges will be flagged with clinical significance information.

Urinalysis values will be listed.

### *13.3. Other safety parameters*

#### 13.3.1. Vital signs data

Supine systolic and diastolic blood pressure (mmHg), heart rate (beats/min) and body temperature (C°) will be measured at screening, then from D1 to D4 (pre-dose, 60min, 2h, 4h, 6h, 8h, 10h, 12h, 24h, 48h, 72h post-dose), and the discharge visit (D10 ± 2 days) (see section 16.1).

Weight will be measured at screening and the discharge visit (D10 ± 2 days).

Absolute values and changes from baseline will be described by treatment group (and overall) and measurement time.

Graphs of median ± SEM over time will be provided for changes from baseline with all treatment groups on the same graph. The median of all treatment groups will be also represented.

A summary table with the number and percentage of subjects with PCSA values (defined in section 16.2) will be generated by treatment group and measurement time.

A specific listing of subjects with PCSA values will be generated.

Values (absolute values and changes from baseline) will be listed and PCSA values will be flagged with clinical significance information.

#### 13.3.2. Electrocardiogram data

Supine 12-lead ECG parameters [including heart rate (beats/min), PR interval (msec), QRS duration (msec), QRS axis (deg), QTc interval (msec), Bazett QTc interval (QTcB) (msec) and Fridericia QTc interval (QTcF) (msec)] and ECG abnormalities will be recorded at screening, then on D1 (pre-dose, 2h, 4h, 6h, 8h, 12h), 24h (D2), 48h (D3), 72h (D4) post-dose and at the discharge visit (D10 ± 2 days) (see section 16.1).

Only interpretable ECGs will be analysed.

QTcB will be derived using the following formula:

$$QTcB\,(ms) = QT\,(ms) \times \sqrt{\frac{HR\,(bpm)}{60}}$$

Absolute values and changes from baseline (except for QRS axis in degrees and ECG abnormalities) will be described by treatment group (and overall) and measurement time.

Graphs of median ± SEM over time will be provided for changes from baseline with all treatment groups on the same graph. The median of all treatment groups will be also represented.

A summary table with the number and percentage of subjects with PCSA values (defined in section 16.2) will be generated by treatment group and measurement time.

Shift tables with the number of subjects having values lower than the lower PCSA limit (Low), normal and higher than the upper PCSA limit (High) (defined in section 16.2) according to the baseline position will be prepared by treatment group and measurement time.

A specific listing of subjects with PCSA values will be generated.

Values [absolute values/ECG abnormalities and changes from baseline (except for QRS axis in degrees)] will be listed and data out of the PCSA ranges will be flagged with clinical significance information.

### 13.3.3. Physical examination

Physical examination will be performed at screening, D-1, D2, D3 (only for cohort D) and the discharge visit (D10 ± 2 days) (see section 16.1).

Physical examination includes basic neurological testing for isocoria, light reflexes, gait and balance).

Abnormal results for physical examination will be listed with clinical significance information. All individual data for physical examination will be listed and abnormalities will be flagged.

### 13.3.4. Telemetry monitoring (including SpO2)

Cardiac monitoring using telemetry (3-lead minimum and including SpO2) will be performed at Day 1 from 1h pre-dose up to 12h post-dose (see section 16.1).

SpO2, non-artifact events [arrhythmias, bradycardia, tachycardia, pause, ventricular tachycardia (VT), supraventricular tachycardia (SVT)] will be described by treatment group (and overall) and measurement time.

Abnormal results will be listed with clinical significance information. All individual data will be listed and abnormalities will be flagged.

### 13.3.5. Occult blood in faeces

Hemoccult® testing will be performed to investigate any presence of occult blood in faeces at screening and from D2 to D4 (see section 16.1).

Absence/presence of occult blood in faeces will be described by treatment group (and overall) and measurement time.

Abnormal results will be listed with clinical significance information. All individual data will be listed and abnormalities will be flagged.

### 13.3.6. Exposure to tick bites

Any absence/presence of exposure to tick bites at D1 pre-dose, the discharge visit (D10 ± 2 days), and the extra ambulatory visits for ADA analysis (D30 ± 3 days, D90 ± 7 days and D180 ± 7 days) (see section 16.1) will be collected.

An extra serology sample will be also collected at baseline for anti-Borrelia IgG and IgM assays for archiving only. Consequently, no statistical description will be performed.

Absence/presence of exposure to tick bites will be described by treatment group (and overall) and measurement time.

## *14. Reporting conventions*

All tables, figures and listings are detailed in section 16.4. They will be prepared using SAS® software as rtf files and the rtf files will be compiled as PDF files (one PDF file by main section).

The footers will be presented as follows: --- STUDY Clin_IrCPI_101 / <name of the program>.SAS / <name of the output>.RTF / DDMMMYY HH:MM ---.

Table and Listing Page Set Up Requirements:

- Font Type = Courier New
- Font Size = 8 pt (at a minimum)
- Page Margins: Top=2 cm; Bottom=2 cm; Left=2 cm; Right=2 cm
- Paper Size = A4 (21 cm x 29.7 cm)
- Page Orientation: Landscape
- Graphs: Portable Network Graphics (PNG) format

Summary statistics will be presented as follows.

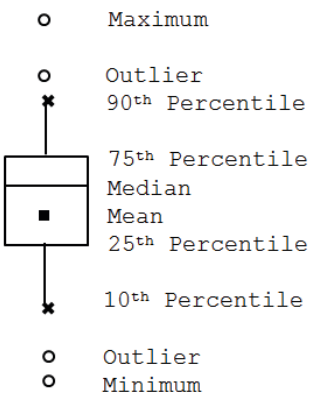
| **Parameter (unit)** | **Statistics / Category** | **Group X (N=xx)** |
|---|---|---|
| Quantitative variable (unit)* | n | xx |
| | Mean+ | xx.xx |
| | SD | xx.xx |
| | SEM | xx.xx |
| | Geometric Mean& | xx.xx |
| | CV% Geometric mean& | xx.xxx |
| | Median | xx.xx |
| | Q1 ; Q3& | xx.x ; xx.x |
| | Min ; Max | xx.x ; xx.x |
| Qualitative variable | Class 1 n (%) | xx (xx.x) |
| | Class 2 n (%) | xx (xx.x) |
| | … | … |

***** All statistics, except the minimum and the maximum, will be provided with an additional decimal place compared to the variable itself. PK parameter coefficients of variation will be provided with one decimal place.

+ For PK parameters only, “Arithmetic Mean” term will be specified in order to distinguish with the geometric mean.

& To provide for PK parameters only.

Box plots will be built as follows:




## *15. References*

[1] International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use. ICH Harmonised tripartite guideline. Statistical Principles for Clinical Trials E9 – Current step 4 dated 5 February 1998.

[2] Brian P. Smith, et al. Confidence interval criteria for assessment of dose proportionality. Pharmaceutical research. 2000 Oct;17(10):1278-1283.

# *16. Appendices*

## *16.1. Appendix 1 - Flow chart/Schedule of assessments of the study*

### 16.1.1. Part 1: Single 6-hour infusion for Cohorts A, B and C

| Assessments | Screening visit [1] | Treatment Period | | | | | | Discharge Visit | Extra ambulatory visits for ADA analysis |
|---|---|---|---|---|---|---|---|---|---|
| | Visit 1 (V1)<br>D-28 to D-2 | V2<br>D-1 | V3<br>D1<br>[2] | V4<br>D2 | V5<br>D3 | V6<br>D4 | V7<br>D5 | V8<br>D10 ± 2d | V9: D30 (±3d),<br>V10: D90 (±7d)<br>V11: D180 (±7d) [22] |
| *Screening / Administrative / Other Assessments* | | | | | | | | | |
| Informed consent | X | | | | | | | | |
| Demography [3] | X | | | | | | | | |
| Inclusion / exclusion criteria | X | X | | | | | | | |
| Medical and medication history | X | | | | | | | | |
| Life restriction monitoring | | X | | | X | X | X | X | |
| Drug / alcohol screen[4] | X | X | | | | | | | |
| Serology[5] | X | | | | | | | | |
| Randomisation to treatment | | | X | | | | | | |
| In-patient period | | ◄ | ——— | ► | | | | | |
| *Safety Assessments* | | | | | | | | | |
| Physical exam [6] | X | X | | X | | | | X | |
| Brief physical exam [7] | | | X | | | | | | |
| Vital signs [8] | X | | X | X | X | X | | X | |
| Telemetry (including $SpO_2$)[9] | | | ◄ | ► | | | | | |
| Height and BMI | X | | | | | | | | |
| Weight | X | | | | | | | X | |
| Faeces collection (Hemoccult® test) | X | | | ◄ | ——— | ——— | ► | | |
| Supine 12-lead ECG [10] | X | | X | X | X | X | | X | |
| Serum chemistry[11] | X | | X | X | | X | | X | |
| Haematology [11] | X | | X | X | | X | | X | |
| Exposure to tick bites [12] | | | X | | | | | X | X |
| Anti-Borrelia immunity (IgG/IgM) [13] | | | X | | | | | | |
| Safety aPTT [14] | X | | X | X | X | X | | X | |
| Urinalysis [15] | X | | X | X | | X | | X | |

| Assessments | Screening visit [1] | Treatment Period | | | | | | Discharge Visit | Extra ambulatory visits for ADA analysis |
|---|---|---|---|---|---|---|---|---|---|
| | Visit 1 (V1)<br>D-28 to D-2 | V2<br>D-1 | V3<br>D1<br>[2] | V4<br>D2 | V5<br>D3 | V6<br>D4 | V7<br>D5 | V8<br>D10 ± 2d | V9: D30 (±3d),<br>V10: D90 (±7d)<br>V11: D180 (±7d) [22] |
| Adverse event monitoring | ← | — | — | — | — | — | — | — | → |
| Concomitant medication monitoring | ← | — | — | — | — | — | — | — | Only if related to the reported AE |
| *Study drug Administration / Pharmacokinetic / Pharmacodynamic Assessments* | | | | | | | | | |
| Study drug administration [16] | | | X | | | | | | |
| PD samples cluster A: PD aPTT (central lab) and FXI/FXII activities [17] | | | X | X | X | X | X | X | |
| PD samples cluster B [18] | | | X | X | X | X | | X | |
| CysC samples [19] | X | | X | X | | X | | X | |
| Blood PK samples [20] | | | X | X | X | X | X | | |
| Immunogenicity Testing (ADA) [21] | | | X | | | | | X | X [22] |
| Urine collection [23] | | | ← | → | | | | | |

NOTE: postdose is defined as « after start of infusion"

1. Screening procedures must occur within 28 days up to 2 days before study drug administration.
2. The results of the analysis of the D1 predose samples are collected to establish baseline references and are not needed before administration.
3. Demography includes: year of birth, age, sex, ethnicity and race.
4. See laboratory safety parameter assessments (section 9.7.6) for list of tests to be run.
5. See laboratory safety parameter assessments (section 9.7.6) for list of tests to be run.
6. Physical Examination (including basic neurological testing for isocoria, light reflexes, gait and balance) should be performed at screening, on D-1, then 24h postdose (D2) and at the discharge visit.
7. An abbreviated physical exam should be performed at 8h postdose on D1.
8. Supine vital signs should be measured after 5 minutes of rest in a supine position and include body temperature, resting pulse rate, and blood pressure: at screening, then from D1 to D4, vital signs should be done predose, 60min, 2h, 4h, 6h, 8h, 10h, 12h, 24h, 48h, 72h postdose, and then at the discharge visit (D10+/-2d).
9. Cardiac monitoring using telemetry (3-lead minimum and including $SpO_2$) is to be performed from 1h predose up to 12h postdose.
10. ECG should be done at screening, then on D1 (predose, 2h, 4h, 6h, 8h, 12h), 24h (D2), 48h (D3), 72h (D4) postdose and at the discharge visit. Timing can be adjusted based on emerging PK data.

11. See laboratory safety parameter assessments for list of tests to be run (section 9.7.6): screening, then from D1 to D4: Predose (D1), 24h (D2), 72h postdose (D4), and then at the discharge visit.
12. Participants will be asked at baseline if they have been previously exposed to tick bites. At the discharge and extra-ambulatory visits performed for ADA analysis, the participants will be asked if they have been exposed to tick bite since the previous visit (response recorded as yes/no/unknown). If the answer is yes, then the participant will be asked to provide information on treatment (e.g. antibiotics) and on presence of erythema migrans and other signs or symptoms.
13. The baseline chemistry (predose sample) will also contain an extra archive serum sample for anti-Borrelia serology testing (IgG and IgM) as backup to test for anti-Borrelia antibodies due to previous exposure via potential tick bites.
14. Safety aPTT (local lab) at screening, then on D1, predose, then 2h, 4h, 6h, 8h, 12h, D2 (24h), D3 (48h) and D4 (72h) postdose and at the discharge visit.
15. Urinalysis at screening, then predose (D1), 24h (D2), 72h postdose (D4) and at the discharge visit. See laboratory safety parameter assessments for list of tests to be run (section 9.7.6).
16. All participants will receive a single intravenous dose of Ir-CPI/Placebo given as a 6-hour infusion. Post dose is measured after the beginning of infusion. A light breakfast (2 slices of bread with ham or cheese and jam, glass of water) can be given between 2h and 1h before start of infusion. Lunch will be served after completion of the infusion.
17. Cluster A (central lab): the effect of Ir-CPI on PD aPTT (central lab) (not to be confused with safety aPTT) and on FXI/FXII activities will be measured on D1: pre-dose, then at 30min, 60min, 90min, 2h, 4h, 6h, 6h30, 7h, 7h30, 8h, 10h, 12h, 16h post-dose, then on D2 (24h), D3 (48h), D4 (72h), D5 (96h) and discharge visit. In case of infusion less than 6 hours and besides assessment at predose, 30 min, 60 min, 90 min, 2h and 4h after start of infusion, Cluster A (central lab) parameters should be measured at the end of infusion, then 30 min, 60 min, 90 min, 2h, 4h, 6h, 10h, then 18h, 42h, 66h and 90h after the end of infusion and then at the discharge visit.
18. Cluster B (local lab) the effect of Ir-CPI on PT (sec and INR), D-dimers, fibrinogen, hsCRP and TNFα will be measured on D1, predose then at 2h, 4h, 6h, 8h, 12h post-dose, on D2 (24h post-dose), D3 (48h) and D4 (72h) and discharge visit. In case of infusion less than 6 hours and besides assessment on D1 at predose and at 2h and 4h after start of infusion, Cluster B (local lab) parameters will be measured at the end of infusion, then 2h, 6h, 18h, 42h and 66h after the end of infusion and then at the discharge visit.
19. CysC (central lab) will be collected at screening, then from D1 to D4: Predose (D1), 24h (D2), 72h postdose (D4), and then at the discharge visit.
20. Blood samples for Ir-CPI PK will be done on D1, pre-dose and at 30min, 60min, 90min, 2h, 4h, 6h, 6h30, 7h, 7h30, 8h, 10h, 12h, 16h, then D2 (24h), D3 (48h), D4 (72h) and D5 (96h) post-dose (after start of infusion). In case of infusion less than 6 hours, blood sample for Ir-CPI pharmacokinetics will be done at the end of infusion then 30min, 60min, 90min, 2h, 4h, 6h, 10h, 18h, 42h, 66h and 90h after end of infusion.
21. ADA analysis sample: pre-dose on the day of infusion, at the discharge visit, on D30 and on D90.
22. D180 only if ADAs are detected in the D90 samples.
23. Urine collections for PK assay are to be done at these intervals predose, [0-6h[, [6-12h[ and [12-24h] after start of infusion. Urinary NGAL, microalbuminuria and KIM-1 will be assessed.

### 16.1.2. Part 1: Single 6-hour infusion for Cohort D

| Assessments | Screening visit [1] | Treatment Period | | | | | | | Discharge Visit | Extra ambulatory visits for ADA analysis |
|---|---|---|---|---|---|---|---|---|---|---|
| | Visit 1 (V1) D-28 to D-2 | V2 D-1 | V3 D1 [2] | V4 D2 [6] | V5 D3 [6] | V6 D4 | V7 D5 | V8 D7 | V9 D10 ± 2d | V10: D30 (±3d), V11: D90 (±7d) V12: D180 (±7d) [23] |
| *Screening / Administrative / Other Assessments* | | | | | | | | | | |
| Informed consent | X | | | | | | | | | |
| Demography [3] | X | | | | | | | | | |
| Inclusion / exclusion criteria | X | X | | | | | | | | |
| Medical and medication history | X | | | | | | | | | |
| Life restriction monitoring | | X | | | X | X | X | X | X | |
| Drug / alcohol screen[4] | X | X | | | | | | | | |
| Serology[5] | X | | | | | | | | | |
| Randomisation to treatment | | | X | | | | | | | |
| In-patient period [6] | | ◄ | ——— | ► | ····· | ► | | | | |
| *Safety Assessments* | | | | | | | | | | |
| Physical exam[7] | X | X | | X[7] | X[7] | | | | X | |
| Brief physical exam[8] | | | X | | | | | | | |
| Vital signs[9] | X | | X | X | X | X | | | X | |
| Telemetry (including $SpO_2$)[10] | | | ◄——► | | | | | | | |
| Height and BMI | X | | | | | | | | | |
| Weight | X | | | | | | | | X | |
| Faeces collection (Hemoccult® test) | X | | | ◄——— | ——— | ——► | | | | |
| Supine 12-lead ECG[11] | X | | X | X | X | X | | | X | |
| Serum chemistry[12] | X | | X | X | | X | | | X | |
| Haematology [12] | X | | X | X | | X | | | X | |
| Exposure to tick bites [13] | | | X | | | | | | X | X |
| Anti-Borrelia immunity (IgG/IgM) [14] | | | X | | | | | | | |
| Safety aPTT[15] | X | | X | X | X | X | X | X | X | |
| Urinalysis[16] | X | | X | X | | X | | | X | |
| Adverse event monitoring | ◄ | ——— | ——— | ——— | ——— | ——— | ——— | ——— | ——► | |
| Concomitant medication monitoring | ◄ | ——— | ——— | ——— | ——— | ——— | ——— | ——► | | Only if related to the reported AE |

| Assessments | Screening visit [1] | Treatment Period | | | | | | | Discharge Visit | Extra ambulatory visits for ADA analysis |
|---|---|---|---|---|---|---|---|---|---|---|
| | Visit 1 (V1) D-28 to D-2 | V2 D-1 | V3 D1 [2] | V4 D2 [6] | V5 D3 [6] | V6 D4 | V7 D5 | V8 D7 | V9 D10 ± 2d | V10: D30 (±3d), V11: D90 (±7d) V12: D180 (±7d) [23] |
| *Study Drug Administration / Pharmacokinetic / Pharmacodynamic Assessments* | | | | | | | | | | |
| Study drug administration[17] | | | X | | | | | | | |
| PD samples cluster A: PD aPTT (central lab) and FXI/FXII activities [18] | | | X | X | X | X | X | X | X | |
| PD samples cluster B[19] | | | X | X | X | X | | | X | |
| CysC samples [20] | X | | X | X | | X | | | X | |
| Blood PK samples[21] | | | X | X | X | X | X | X | | |
| Immunogenicity Testing (ADA) [22] | | | X | | | | | | X | X[23] |
| Urine collection [24] | | | ◄ | ——— | ► | | | | | |

NOTE: postdose is defined as « after start of infusion"

1. Screening procedures must occur within 28 days up to 2 days before study drug administration.
2. The results of the analysis of the D1 predose samples are collected to establish baseline references and are not needed before administration.
3. Demography includes: year of birth, age, sex, ethnicity and race.
4. See laboratory safety parameter assessments (section 9.7.6) for list of tests to be run.
5. See laboratory safety parameter assessments (section 9.7.6) for list of tests to be run.
6. A safety aPTT sample is drawn on D2, 24h after D1 administration. All participants will remain hospitalised until the investigator is able to review the 24h aPTT assay results. If, for each participant, the results are less than or equal to 2X aPTT level at baseline (i.e. D1 predose), then the participants may leave the clinic. They will return for the ambulatory visits on D3 (48h post infusion start), D4 (72h), D5 (96h) and D7 (144h). If the 24h safety aPTT assay of one participant is above 2X the participant's baseline aPTT, then all participants will remain hospitalised until the completion of the D3 (48h) assessments and an additional aPTT sample will be drawn at 36h. If the 36h aPTT assay result of a participant is more than 2X baseline aPTT of this participant, the investigator will decide the most appropriate procedures for the follow-up of this participant. Participants will return for the ambulatory visits on D4 (72h), D5 (96h) and D7 (144h).
7. A full physical examination (including basic neurological testing for isocoria, light reflexes, gait and balance) should be performed at screening, on D-1, then, at 24h postdose (D2), also at 48h (D3) if hospitalisation is extended (see footnote 6), and at the discharge visit.
8. An abbreviated physical examination will be performed at 8h postdose on D1.
9. Supine vital signs should be measured after 5 minutes of rest in a supine position and include body temperature, resting pulse rate, and blood pressure: at screening, then from D1 to D4, vital signs should be done predose, 60min, 2h, 4h, 6h, 8h, 10h, 12h, 24h, 48h, 72h postdose, and then at the discharge visit (D10+/-2d).
10. Cardiac monitoring using telemetry (3-lead minimum and including $SpO_2$) is to be performed from 1h predose up to 12h postdose.

11. ECG should be done at screening, then on D1 (predose, 2h, 4h, 6h, 8h, 12h), 24h (D2), 48h (D3), 72h (D4) postdose and at the discharge visit. Timing can be adjusted based on emerging PK data.
12. See laboratory safety parameter assessments for list of tests to be run (section 9.7.6): screening, then from D1 to D4: Predose (D1), 24h (D2), 72h postdose (D4), and then at the discharge visit.
13. Participants will be asked at baseline if they have been previously exposed to tick bites. At the discharge and extra-ambulatory visits performed for ADA analysis, the participants will be asked if they have been exposed to tick bite since the previous visit (response recorded as yes/no/unknown). If the answer is yes, then the participant will be asked to provide information on treatment (e.g. antibiotics) and on presence of erythema migrans and other signs or symptoms.
14. The baseline chemistry (predose sample) will also contain an extra archive serum sample for anti-Borrelia serology testing (IgG and IgM) as backup to test for anti-Borrelia antibodies due to previous exposure via potential tick bites.
15. Safety aPTT (local lab) at screening, then on D1, predose, then 2h, 4h, 6h, 8h, 12h, 24h (D2), 36h (D2, optional sample only drawn if hospitalisation is extended at least until 36h postdose, see footnote 6), D3 (48h), D4 (72h), D5 (96h), D7 (144h) postdose and at the discharge visit.
16. Urinalysis at screening, then predose (D1), 24h (D2), 72h postdose (D4) and at the discharge visit. See laboratory safety parameter assessments for list of tests to be run (section 9.7.6).
17. All participants will receive a single intravenous dose of Ir-CPI/Placebo given as a 6-hour infusion. Post dose is measured after the beginning of infusion. A light breakfast (2 slices of bread with ham or cheese and jam, glass of water) can be given between 2h and 1h before start of infusion. Lunch will be served after completion of the infusion.
18. Cluster A (central lab): the effect of Ir-CPI on PD aPTT (central lab) (not to be confused with safety aPTT) and on FXI/FXII activities will be measured on D1: pre-dose, then at 30min, 60min, 90min, 2h, 4h, 6h, 6h30, 7h, 7h30, 8h, 10h, 12h, 16h post-dose, then on D2 (24h), D3 (48h), D4 (72h), D5 (96h), D7 (144h) and discharge visit. In case of infusion less than 6 hours and besides assessment at predose, 30 min, 60 min, 90 min, 2h and 4h after start of infusion, Cluster A (central lab) parameters should be measured at the end of infusion, then 30 min, 60 min, 90 min, 2h, 4h, 6h, 10h, then 18h, 42h, 66h, 90h and 138h after the end of infusion and then at the discharge visit.
19. Cluster B (local lab) the effect of Ir-CPI on PT (sec and INR), D-dimers, fibrinogen, hsCRP and TNFα will be measured on D1, predose then at 2h, 4h, 6h, 8h, 12h post-dose, on D2 (24h post-dose), D3 (48h) and D4 (72h) and discharge visit. In case of infusion less than 6 hours and besides assessment on D1 at predose and at 2h and 4h after start of infusion, Cluster B (local lab) parameters will be measured at the end of infusion, then 2h, 6h, 18h, 42h and 66h after the end of infusion and then at the discharge visit.
20. CysC (central lab) will be collected at screening, then from D1 to D4: Predose (D1), 24h (D2), 72h postdose (D4), and then at the discharge visit.
21. Blood samples for Ir-CPI PK will be done on D1, pre-dose and at 30min, 60min, 90min, 2h, 4h, 6h, 6h30, 7h, 7h30, 8h, 10h, 12h, 16h, then D2 (24h), D3 (48h), D4 (72h), D5 (96h) and D7 (144h) post-dose (after start of infusion). In case of infusion less than 6 hours, blood sample for Ir-CPI pharmacokinetics will be done at the end of infusion then 30min, 60min, 90min, 2h, 4h, 6h, 10h, 18h, 42h, 66h, 90h and 138h after end of infusion.
22. ADA analysis sample: pre-dose on the day of infusion, at the discharge visit, on D30 and on D90.
23. D180 only if ADAs are detected in the D90 samples.
24. Urine collections for PK assay are to be done at these intervals predose, [0-6h[, [6-12h[ and [12-24h] after start of infusion. Urinary NGAL, microalbuminuria and KIM-1 will be assessed.

## *16.2. Appendix 2 - Criteria for Potentially Clinically Significant Abnormalities (PCSA)*

| PARAMETER | LOWER PCSA VALUE | UPPER PCSA VALUE |
|---|---|---|
| **Laboratory parameters** | | |
| AST | | ≥ 3 ULN and < 5 ULN (High)<br>≥ 5 ULN and < 10 ULN (High+)<br>≥ 10 ULN and < 20 ULN (High++)<br>≥ 20 ULN (High+++) |
| ALT | | ≥ 3 ULN and < 5 ULN (High)<br>≥ 5 ULN and < 10 ULN (High+)<br>≥ 10 ULN and < 20 ULN (High++)<br>≥ 20 ULN (High+++) |
| Gamma GT | | ≥ 3 ULN |
| Alkaline phosphatase | | ≥ 2 ULN |
| Total bilirubin | | ≥ 2 ULN |
| Creatinine | | ≥ 150 µmol/L |
| Sodium | ≤ 129 mmol/L | ≥ 160 mmol/L |
| Potassium | < 3 mmol/L | ≥ 5.5 mmol/L |
| Glucose | ≤ 3.9 mmol/L and < LLN | ≥ 7 mmol/L |
| Hemoglobin | ≤ 100 g/L | |
| Platelets | < 100 10^9/L | |
| Leukocytes | < 3 10^9/L (< 2 10^9/L for Black or African American) | |
| Neutrophils | < 1.5 10^9/L (< 1 10^9/L for Black or African American) | |
| Eosinophils | | > 0.5 10^9/L or > ULN if ULN > 0.5 10^9/L |
| aPTT value | | > 180 sec |
| aPTT ratio | | > 3 |
| **Vital signs** | | |
| Supine HR | ≤ 40 beats/min and change from baseline ≤ -20 beats/min | ≥ 100 beats/min and change from baseline ≥ 20 beats/min |
| Supine SBP | ≤ 95 mmHg and change from baseline ≤ -20 mmHg | ≥ 140 mmHg and change from baseline ≥ 20 mmHg |
| Supine DBP | ≤ 45 mmHg and change from baseline ≤ -10 mmHg | ≥ 90 mmHg and change from baseline ≥ 10 mmHg |
| **ECG parameters** | | |
| HR | ≤ 40 beats/min and change from baseline ≤ -20 beats/min | ≥ 100 beats/min and change from baseline ≥ 20 beats/min |
| PR | | ≥ 220 msec |
| QRS | | ≥ 120 msec |
| QTc | | > 450 msec and ≤ 500 msec (High)<br>> 500 msec (High+)<br>change from baseline > 30 msec and change from baseline ≤ 60 msec (High)<br>change from baseline > 60 msec (High+) |

## *16.3. Appendix 3 – Normal ranges for vital signs and ECG parameters*

| **Vital signs** | |
|---|---|
| Supine SBP | 90 ≤ SBP ≤ 150 mmHg |
| Supine DBP | 50 ≤ DBP ≤ 90 mmHg |
| Heart rate | 40 ≤ HR ≤ 100 |
| Tympanic temperature | 36.0 ≤ T ≤ 37.5 |
| **ECG parameters** | |
| HR | 40 bpm ≤ HR ≤ 100 bpm |
| PR | 110 ms ≤ PR ≤ 220 ms |
| QRS | QRS ≤ 120 ms |
| QTcF | QTc ≤ 450 ms |

### *16.4. Appendix 4 - List of tables, listings and figures included in the clinical study report*

| NUMBER | TITLE |
|---|---|
| **14** | **TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT** |
| **14.1** | **Demographic data** |
| **14.1.1** | **Description of study subjects** |
| 14.1.1.1 | Subject disposition – Included set |
| 14.1.1.2 | Analysis sets – Included set |
| 14.1.1.3 | Study visits – Randomised set |
| **14.1.2** | **Protocol deviations** |
| 14.1.2.1 | Deviations relating to inclusion/exclusion criteria – Randomised set |
| 14.1.2.2 | Other deviations – Randomised set |
| **14.1.3** | **Demographic data and baseline characteristics** |
| *14.1.3.1* | *Demographic data – Randomised set* |
| *14.1.3.2* | *Other baseline characteristics* |
| 14.1.3.2.1 | Subjects' habits – Randomised set |
| 14.1.3.2.2 | Listing of positive serology results – Randomised set |
| 14.1.3.2.3 | Listing of positive urine drug screen results – Randomised set |
| 14.1.3.2.4 | Listing of positive alcohol breath tests – Randomised set |
| *14.1.3.3* | *Medical and surgical history – Randomised set* |
| **14.1.4** | **Previous and concomitant medications** |
| 14.1.4.1 | Previous medications – Randomised set |
| 14.1.4.2 | Concomitant medications – Randomised set |
| **14.2** | **Pharmacokinetic and Pharmacodynamics data** |
| **14.2.1** | **Pharmacokinetic data** |
| **14.2.1.1** | **Plasma concentrations** |
| 14.2.1.1.1 | Plasma concentrations for Ir-CPI – Pharmacokinetic set |
| 14.2.1.1.2 | Graphs of plasma concentration means (±SEM), min-max curves over time by treatment groups for Ir-CPI – Pharmacokinetic set |
| 14.2.1.1.3 | Graphs of plasma concentration means (±SEM) over time for Ir-CPI – Pharmacokinetic set |
| 14.2.1.1.4 | Individual plasma concentration-time profiles (spaghetti plots) for Ir-CPI – Pharmacokinetic set |
| **14.2.1.2** | **PK parameters in plasma** |
| 14.2.1.2.1 | PK parameters in plasma for Ir-CPI – Pharmacokinetic set |
| 14.2.1.2.2 | Analysis of dose-proportionality for $C_{max}$, $AUC_{0\text{-}6h}$, $AUC_{0\text{-}96h}$ and $AUC_{0\text{-}inf}$ for Ir-CPI – Pharmacokinetic set |
| 14.2.1.2.3 | Box whisker plots of $C_{max}$, $AUC_{0\text{-}6h}$, $AUC_{0\text{-}96h}$ and $AUC_{0\text{-}inf}$ for Ir-CPI – Pharmacokinetic set |
| **14.2.2** | **Pharmacodynamics data** |

| NUMBER | TITLE |
|---|---|
| 14.2.2.1 | Pharmacodynamic parameters for Ir-CPI – Pharmacodynamic set |
| 14.2.2.2 | Graphs of aPTT ratio means (± SEM), min and max curves over time by treatment groups – Pharmacodynamic set |
| 14.2.2.3 | Graphs of aPTT ratio means (± SEM) over time – Pharmacodynamic set |
| 14.2.2.4 | Graph of FXI and FXII inhibition means (± SEM), min and max values over time by treatment groups – Pharmacodynamic set |
| 14.2.2.5 | Graph FXI and FXII inhibition means (± SEM) values over time – Pharmacodynamic set |
| 14.2.2.6 | Individual aPTT ratio, FXI and FXII activities, FXI and FXII inhibition profiles (spaghetti plots) over time by treatment groups – Pharmacodynamic set |
| **14.2.3** | **Exploratory analysis** |
| **14.2.3.1** | **Exploratory analysis Pharmacokinetic / Pharmacodynamic analysis** |
| 14.2.3.1.1 | Graph of the relationship between treatment groups and concentrations of Ir-CPI and the change from baseline in coagulation parameters – Pharmacodynamic set |
| **14.2.3.2** | **Exploratory Biomarker's Evaluation** |
| 14.2.3.2.1 | Biomarker parameters for Ir-CPI – Pharmacodynamic set |
| 14.2.3.2.2 | Graphs of biomarker means (±SEM) over time for Ir-CPI by treatment group – Pharmacodynamic set |
| 14.2.3.2.3 | Presence of ADA and their titration for ADA+ samples – Pharmacodynamic set |
| 14.2.3.2.4 | Sub-classes determination – Pharmacodynamic set |
| **14.3** | **Safety data** |
| **14.3.1** | **Adverse events** |
| 14.3.1.1 | Adverse events – Safety set |
| 14.3.1.2 | Treatment-emergent adverse events |
| 14.3.1.2.1 | Treatment-emergent adverse events – Safety set |
| 14.3.1.2.2 | Treatment-emergent adverse events by intensity – Safety set |
| 14.3.1.2.3 | Treatment-emergent adverse events by causality – Safety set |
| 14.3.1.3 | Adverse events of special interest – Safety set |
| **14.3.2** | **Listing of deaths, other serious and significant adverse events – Safety set** |
| **14.3.3** | **Clinical laboratory data** |
| **14.3.3.1** | **Haematology** |
| 14.3.3.1.1 | Summary statistics – Safety set |
| 14.3.3.1.2 | Listing of subjects presenting abnormal values – Safety set |
| 14.3.3.1.3 | Number and percentage of subjects with PCSA values – Safety set |
| 14.3.3.1.4 | Shift tables (PCSA values) – Safety set |

| NUMBER | TITLE |
|---|---|
| 14.3.3.1.5 | Listing of subjects presenting PCSA values – Safety set |
| **14.3.3.2** | **Blood chemistry** |
| 14.3.3.2.1 | Summary statistics – Safety set |
| 14.3.3.2.2 | Listing of subjects presenting abnormal values – Safety set |
| 14.3.3.2.3 | Number and percentage of subjects with PCSA values – Safety set |
| 14.3.3.2.4 | Shift tables (PCSA values) – Safety set |
| 14.3.3.2.5 | Listing of subjects presenting PCSA values – Safety set |
| **14.3.3.3** | **Coagulation** |
| 14.3.3.3.1 | Summary statistics – Safety set |
| 14.3.3.3.2 | Listing of subjects presenting abnormal values – Safety set |
| **14.3.3.4** | **Urinalysis** |
| 14.3.3.4.1 | Summary statistics – Safety set |
| 14.3.3.4.2 | Listing of subjects presenting abnormal values – Safety set |
| **14.3.4** | **Other safety parameters** |
| **14.3.4.1** | **Vital signs data** |
| 14.3.4.1.1 | Summary statistics – Safety set |
| 14.3.4.1.2 | Graphs of vital signs (median ± SEM) over time (changes from baseline) – Safety set |
| 14.3.4.1.3 | Number and percentage of subjects with PCSA values – Safety set |
| 14.3.4.1.4 | Listing of subjects presenting PCSA values – Safety set |
| **14.3.4.2** | **Electrocardiogram data – Standard 12-lead ECG parameters** |
| 14.3.4.2.1 | Summary statistics – Safety set |
| 14.3.4.2.2 | Graphs of ECG parameters (median ± SEM) over time (changes from baseline) – Safety set |
| 14.3.4.2.3 | Number and percentage of subjects with PCSA values – Safety set |
| 14.3.4.2.4 | Shift tables (PCSA values) – Safety set |
| 14.3.4.2.5 | Listing of subjects presenting PCSA values – Safety set |
| **14.3.4.3** | **Physical examination** |
| 14.3.4.3.1 | Listing of subjects presenting abnormal results – Safety set |
| **14.3.4.4** | **Telemetry monitoring** |
| 14.3.4.4.1 | Summary statistics – Safety set |
| 14.3.4.4.2 | Listing of subjects presenting abnormal results – Safety set |
| **14.3.4.5** | **Occult blood in faeces** |
| 14.3.4.5.1 | Summary statistics – Safety set |
| 14.3.4.5.2 | Listing of subjects presenting abnormal results – Safety set |

| NUMBER | TITLE |
|---|---|
| **14.3.4.6** | **Exposure to tick bites – Safety set** |
| **16.1** | **STUDY INFORMATION** |
| **16.1.7** | **Randomisation scheme and codes (subject identification and treatment assigned) – Randomised set** |
| **16.1.9** | **Documentation of statistical methods** |
| *16.1.9.1* | *Statistical analysis plan (integrated by the medical writer during the creation of the appendices of the clinical study report)* |
| 16.1.9.2. | ANOVA: Analysis of dose-proportionality for $C_{max}$, $AUC_{0-6h}$, $AUC_{0-96h}$ and $AUC_{0-inf}$ for Ir-CPI – Pharmacokinetic set |
| **16.2** | **SUBJECT DATA LISTINGS** |
| **16.2.1** | **Subject disposition** |
| 16.2.1.1 | Discontinued subjects – Included set |
| 16.2.1.2 | Subject disposition and analysis sets – Included set |
| 16.2.1.3 | End of study status – Included set |
| 16.2.1.4 | Subject visit dates – Included set |
| 16.2.1.5 | Screen failures – Screened set |
| **16.2.2** | **Protocol deviations** |
| 16.2.2.1 | Deviations relating to inclusion/exclusion criteria – Randomised set |
| 16.2.2.2 | Other deviations – Randomised set |
| **16.2.3** | **Subjects excluded from analysis sets – Randomised set** |
| **16.2.4** | **Demographic data and baseline characteristics** |
| **16.2.4.1** | **Demographic data – Randomised set** |
| **16.2.4.2** | **Other baseline characteristics** |
| 16.2.4.2.1 | Subjects' habits – Randomised set |
| 16.2.4.2.2 | Serology – Randomised set |
| 16.2.4.2.3 | Urine drug screen – Randomised set |
| 16.2.4.2.4 | Alcohol breath test – Randomised set |
| 16.2.4.2.5 | Birth control method – Randomised set |
| **16.2.4.3** | **Medical and surgical history and procedures** |
| 16.2.4.3.1 | Medical history – Randomised set |
| 16.2.4.3.2 | Surgical history – Randomised set |
| 16.2.4.3.3 | Concomitant procedures – Randomised set |
| **16.2.4.4** | **Previous and concomitant medications** |
| 16.2.4.4.1 | Previous medications – Randomised set |
| 16.2.4.4.2 | Concomitant medications – Randomised set |

| NUMBER | TITLE |
|---|---|
| **16.2.5** | **Compliance and/or drug concentration data** |
| **16.2.5.1** | **Compliance and dosing data** |
| 16.2.5.1.1 | IMP administration – Randomised set |
| 16.2.5.1.2 | Meals intake – Randomised set |
| **16.2.5.2** | **Pharmacokinetic data** |
| **16.2.5.2.1** | **Plasma concentrations and pharmacokinetic parameters** |
| 16.2.5.2.1.1 | Plasma concentrations – Randomised set |
| 16.2.5.2.1.2 | Individual plasma concentration-time curves – Pharmacokinetic set |
| 16.2.5.2.1.3 | PK parameters in plasma – Randomised set |
| **16.2.6** | **Pharmacodynamics data** |
| 16.2.6.1 | Pharmacodynamic parameters – Pharmacodynamic set |
| 16.2.6.2 | Exploratory biomarker parameters – Pharmacodynamic set |
| **16.2.7** | **Adverse event listings** |
| 16.2.7.1 | Treatment-emergent adverse events – Randomised set |
| 16.2.7.2 | Adverse events for special interest – Randomised set |
| 16.2.7.3 | All adverse events – Randomised set |
| **16.2.8** | **Clinical laboratory data** |
| **16.2.8.1** | **Haematology** |
| 16.2.8.1.1 | Normal ranges for SI units and local units |
| 16.2.8.1.2 | PCSA ranges |
| 16.2.8.1.3 | All haematology values (SI unit) – Randomised set |
| **16.2.8.2** | **Blood chemistry** |
| 16.2.8.2.1 | Normal ranges for SI units and local units |
| 16.2.8.2.2 | PCSA ranges |
| 16.2.8.2.3 | All blood chemistry values (SI unit) – Randomised set |
| **16.2.8.3** | **Coagulation** |
| 16.2.8.3.1 | Normal ranges for SI units and local units |
| 16.2.8.3.2 | PCSA ranges |
| 16.2.8.3.3 | All coagulation values (SI unit) – Randomised set |
| **16.2.8.4** | **Urinalysis – Randomised set** |
| **16.2.9** | **Other safety parameters** |
| **16.2.9.1** | **Vital signs data – Randomised set** |
| **16.2.9.2** | **Electrocardiogram data - Standard 12-lead ECG parameters – Randomised set** |

| NUMBER | TITLE |
|---|---|
| **16.2.9.3** | **Physical examination – Randomised set** |
| **16.2.9.4** | **Telemetry monitoring – Randomised set** |
| **16.2.9.5** | **Occult blood in faeces – Randomised set** |
| **16.2.9.6** | **Exposure to tick bites– Randomised set** |

BIOTRIAL
DRUG EVALUATION AND PHARMACOLOGY RESEARCH

**Protocol Number: Clin_IrCPI_101**

**Version and date: 4.0 – 06DEC2019**

# TITLE: Appendix to the final Statistical Analysis Plan for compartmental pharmacokinetic analysis of Ir-CPI plasma concentrations, Pharmacokinetic-Pharmacodynamic analysis and Anti-Drug Antibodies analysis
# Date: 13AUG2020 - Version: Final version 1.0

## *1. Introduction*

This appendix covers the details of the post-hoc analyses on Pharmacokinetics (PK), pharmacokinetics/pharmacodynamics (PK/PD) and Anti-Drug Antibodies (ADA) data from Clin_IrCPI_101 study as well as anticipated data transformations and manipulations. It completes the final Statistical Analysis Plan (SAP) (version V1.0 dated 09 July 2020) and it is based on Sponsor requests.

This SAP will support additional post-hoc analyses on:

- PK data and PK/PD endpoints performed by the Pharmacokineticist of BIOTRIAL in agreement with the Sponsor.
- ADA data (presence, titration, sub-classes and the capability to neutralize drug activity) performed by the Biostatistics unit of BIOTRIAL BIOMETRICS in agreement with the Sponsor.

PK and PK/PD parameters will be calculated using Phoenix® WinNonlin® version 8.1 Certara USA, Inc., Princeton, NJ) and ADA analysis will be performed using SAS® software version 9.4 (SAS institute Inc. Cary NC USA).

In accordance with the Sponsor, negative values, identified after the calculation of Factor XI and Factor XII inhibition in the main analysis, will be replaced by 0.

## *2. Compartmental pharmacokinetic analysis*

The rules defined in the section **Erreur ! Source du renvoi introuvable.** of the final SAP will be used.
The actual blood sampling time and infusion duration will be used. The theoretical dose (mg/kg) will be used.

### *2.1. Plasma PK endpoints*

Blood samples will be drawn:

- For cohorts A, B and C:
  - on Day 1 at pre-dose then post-dose (after start of infusion) at H0.5, H1, H1.5, H2, H4, H6, H6.5, H7, H7.5, H8, H10, H12, H16, then at D2 (H24), D3 (H48), D4 (H72) and D5 (H96).
    In case of infusion less than 6 hours, blood sample for Ir-CPI pharmacokinetics will be done at the end of infusion then H0.5, H1, H1.5, H2, H4, H6, H10, H18, H42, H66 and H90 after the end of infusion.
- For cohort D:
  - on Day 1 at pre-dose then post-dose (after start of infusion) at H0.5, H1, H1.5, H2, H4, H6, H6.5, H7, H7.5, H8, H10, H12, H16, then at D2 (H24), D3 (H48), D4 (H72), D5 (H96) and D7 (H144).
    In case of infusion less than 6 hours, blood sample for Ir-CPI pharmacokinetics will be done at the end of infusion then H0.5, H1, H1.5, H2, H4, H6, H10, H18, H42, H66, H90 and H138 after the end of infusion.

### *2.2. Plasma pharmacokinetic analysis*

The compartmental pharmacokinetic analysis will be performed on the Pharmacokinetic set (PKS) defined in the final SAP as all of the included participants who have been administered a complete infusion of IMP without major protocol deviation affecting PK evaluation.

Subjects receiving placebo will not be included in the summary and analysis of PK parameters.

Graphical exploration of plasma concentrations versus time profiles will be performed by subject and by group.

For the description of individual plasma concentration-time profiles, one-, two- and three compartment models will be investigated using non-linear regression from models of the Phoenix WinNonlin library.

To assess how the compartmental model explains the individual concentration data:

- The evaluation of the goodness of fit and the estimated parameters will be based, but not only, on the Akaike information criterion, the Schwarz Bayesian Criterion (SBC), the coefficient of variability (CV) of the parameter estimates, the random distribution of residuals (weighted or not) between measured and predicted concentrations with respect to time, correlation between independent model parameters (<0.95) will be checked to select the model that best fits the observed data.
- Individual plots of observed and predicted concentrations, residual versus (vs.) predicted concentrations and residual vs. time profiles of Ir-CPI will be presented graphically on linear and log/linear coordinates with the PK model selected to best fits the observed data.
- Relevant plasma PK parameters will be calculated for Ir-CPI by compartmental methods, as appropriate for those participants with sufficient plasma concentration data. PK parameters obtained by compartmental analysis including descriptive statistics will be presented in tables separately for each treatment group.

# *3. Pharmacokinetic-Pharmacodynamic analysis*

The evaluation of the relationship between plasma concentrations of Ir-CPI and the PD parameters, i.e. the change from baseline in coagulation parameters (i.e. aPTT ratio), FXI and FXII inhibition are graphically investigated and displayed according to the final SAP.

## *3.1. Plasma PD endpoints*

Effect of Ir-CPI on PD aPTT, Factor XI and Factor XII inhibition will be measured by the change from baseline (central lab). PD aPTT and FXI/FXII parameters will be measured:

- For cohorts A, B and C:
  - on D1, pre-dose then at 30min, 60min, 90min, 2h, 4h, 6h, 6h30, 7h, 7h30, 8h, 10h, 12h, 16h post-dose, then on D2 (24h), D3 (48h), D4 (72h), D5 (96h) and discharge visit (D10 ± 2 days).
    In case of infusion less than 6 hours and besides assessment at pre-dose, 30 min, 60 min, 90 min, 2h and 4h after start of infusion, parameters should be measured at the end of infusion, then 30min, 60 min, 90min, 2h, 4h, 6h, 10h, then 18h, 42h, 66h and 90h after the end of infusion and then at the discharge visit.

- For cohort D:
  - on D1, pre-dose then at 30min, 60min, 90min, 2h, 4h, 6h, 6h30, 7h, 7h30, 8h, 10h, 12h, 16h post-dose, then on D2 (24h), D3 (48h), D4 (72h), D5 (96h), D7 (144h) and discharge visit (D10 ± 2 days).
    In case of infusion less than 6 hours and besides assessment at pre-dose, 30 min, 60 min, 90 min, 2h and 4h after start of infusion, parameters should be measured at the end of infusion, then 30min, 60min, 90min, 2h, 4h, 6h, 10h, then 18h, 42h, 66h, 90h and 138h after the end of infusion and then at the discharge visit.

For each time point, including the baseline time point, an aPTT ratio was calculated by dividing the aPTT value (in sec) of the specific time point (aPTT*) by the baseline aPTT value (in sec) (aPTT°) of the same volunteer (aPTT ratio = aPTT*/aPTT°). This ratio in function of the time will be used. The baseline time-point is considered as having an aPTT ratio of 1.

Concerning FXI and FXII PD parameters, individual data of FXI activity and FXII activity in function of the time will be used. Moreover, FXI or FXII inhibition, expressed in percentages, for each time point (including the baseline time point), were calculated for each volunteer according to the main SAP:

- Percentage of FXI inhibition= 100-[(FXI*/FXI°)*100]
- Percentage of FXII inhibition= 100-[(FXII*/FXII°)*100]

In case of negative values, these values will be replaced by 0 (for the main and post-hoc analyses).

*FXI* or FXII*: FXI or FXII percentage of inhibition of a specific time point*
*FXI° or FXII°: FXI or FXII percentage of inhibition of the baseline time point*
*The baseline time point is considered as 0 % of FXI or FXII inhibition.*

### *3.2. PK-PD analysis*

The pharmacokinetic-pharmacodynamic analysis will be performed on the Pharmacodynamic set (PDS) defined in the final SAP as all the included participants who have completed the study without any protocol deviation affecting PD evaluation and with at least one available post-baseline data.

Subjects receiving placebo will be included in the summary and analysis of PK-PD relationship.

The rationale for PK/PD analysis is to link pharmacokinetics and pharmacodynamics in order to establish and evaluate dose-concentration-response relationships and subsequently describe and predict the effect-time courses resulting from a drug dose. PK-PD relationship will be investigated mainly to assess potential correlation between Ir-CPI exposure and the aPTT ratio.

The pharmacokinetic-pharmacodynamic analysis dedicated to FXI and FXII responses will be investigated (or not if considered not appropriate) based on exploratory analysis of the main SAP.

The preliminary graphical exploration will be performed in order to assess the effect of Ir-CPI on aPTT ratio with the dose, the pattern of the relationship for the previous PD model, the linearity assumption and the potential hysteresis between concentrations and response.

The model development will be based on the evaluation of the relation between effect and concentration using non-linear regression from model of the Phoenix WinNonlin library. A direct effect relationship was assumed for aPTT according to the safety aPTT data from interim analysis.

To compare structural models, the evaluation of the goodness of fit and the estimated parameters will be based, but not only, on the Akaike information criterion, the coefficient of variability (CV) of the parameter estimates, the random distribution of residuals between measured and predicted concentrations with respect to time, correlation between independent model parameters (<0.95) will be checked.

Plots of concentration-effect relationship between concentrations versus the corresponding aPTT ratio after Ir-CPI administration will be presented graphically with the PK-PD model selected to best fits the observed data (observed and fitted data).

Relevant PK-PD parameters estimated from the selected model will be described.

## *4. ADA analysis*

ADA analysis samples will be collected at pre-dose on the day of infusion, at the discharge visit (D10 ± 2 days), on D30 and on D90. If ADAs are detected in D90 samples, ADA analysis samples will be collected also at D180.

Samples are determined as ADA-positive or -negative according to the results of the screening and/or confirmatory ADA assays. Only samples confirmed as positive by the confirmatory assay were considered for titration and sub-classes assays.

Titers of anti-Ir-CPI antibodies in study samples (titration assay) are determined as the last dilution factor with a result above the Floating Cut Point (FCP) determined for ADA assay.

The results are expressed in $Dil^{-1}$ and reported for each ADA-positive volunteer at each time point.

In addition, for each ADA-positive volunteers, the presence or absence of the 3 ADA sub-classes (i.e. IgG, IgM and IgE) are determined. The results are expressed as Negative, Positive or NA (Not applicable, ADA negative sample not analyzed for Ig sub-classes).

As specified in the final SAP, presence of ADA, their titration and sub-classes determination (isotype) for ADA+ sampleswill be described by treatment group and measurement time. All data will be listed.

Within each treatment group, pairwise comparisons (predose *vs* each ADA+ timepoint) will be performed using Dunnett's adjustment due to multiple testing.

Ability of ADA to neutralize the activity of Ir-CPI will be determined in a coagulation assay. Baseline plasma samples and ADA-positive samples of the same volunteer will be spiked with known concentration of Ir-CPI increasing the coagulation time. Coagulation time of spiked baseline and ADA-positive plasma will be compared in order to define if the ADAs interfere with the activity of Ir-CPI. A titration will be performed to define the proportion of ADAs in the samples having neutralizing abilities.

ADA neutralizing drug activity will be described by treatment group.

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BIOTRIAL
DRUG EVALUATION AND PHARMACOLOGY RESEARCH

**Protocol Number: Clin_IrCPI_101**

**Version and date: 5.0 – 15OCT2020**

# TITLE: Appendix n°2 to the final Statistical Analysis Plan for Descriptive analysis of Pharmacokinetic-Pharmacodynamic and safety parameters by ADA group
# Date: 12NOV2020 - Version: Final version 1.0

## *1. Introduction*

This appendix covers the details of the post-hoc analysis n°2 on pharmacokinetics, pharmacodynamics and safety endpoints from the Clin_IrCPI_101 study. It completes the final Statistical Analysis Plan (SAP) (version V1.0 dated 09 July 2020) and it is based on Sponsor requests.

This SAP will support the post-hoc analysis on PK (based on compartmental PK analysis) and safety endpoints by Anti-Drug Antibodies (ADA) group.

This additional analysis will be performed using SAS® software version 9.4 (SAS institute Inc. Cary NC USA).

## *2. Statistical analysis*

The ADA group will be defined using data on the presence of ADA (defined as screening + confirmatory positive results) whatever the study day. If a subject is positive for the presence of ADA at a specific day, he will be included in the ADA+ group.

Additional analyses will be performed on the following PK and safety endpoints:

- PK parameters: Alpha_HL, Beta_HL, total body clearance (CL), volume of distribution at steady-state ($V_{ss}$) and AUC (Area under the concentration versus time curve);

*Note: AUC will be normalized by theoretical Ir-CPI dose (1.5, 3, 6 or 9 mg/kg) using the following formula:* $nAUC_{0-x} = AUC_{0-x}$ */ theoretical Ir-CPI dose.*

- PD and safety aPTT ratio at the following selected timepoints: 2h, 4h, 6h, 8h, 12h, 24h, 48h and 72h.

Descriptive statistics will be generated on all aforementioned endpoints, by ADA group (ADA+ and ADA-) and treatment group (Ir-CPI 1.5 mg/kg, Ir-CPI 3 mg/kg, Ir-CPI 6 mg/kg and Ir-CPI 9 mg/kg).

The following descriptive statistics will be supplied: sample size, arithmetic mean, standard deviation (SD), standard error of the mean (SEM), minimum, median and maximum, and [quartiles if necessary with geometric mean, arithmetic and geometric coefficients of variation (CV), and quartiles for PK parameters]. If the sample size of one treatment group is less than or equal to 2, only the number of observed values, the minimum and the maximum will be presented.

No inferential analysis will be performed due to the small sample size in each treatment group/ADA+.

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