STATISTICAL ANALYSIS PLAN

Study protocol code	W00074CI103
Biotrial code	1PF74
Study title	A randomized, single-center, open-label, single dose, two-period, crossover pivotal bioequivalence study comparing binimetinib 3x15 mg and 45 mg tablets in healthy participants
Study investigational medicinal product	binimetinib (MEKTOVI®)
Development phase	Phase I
Sponsor	Pierre Fabre Médicament represented by the Institut de Recherche Pierre Fabre Les Cauquillous 81500 Lavaur FRANCE
Version of the statistical analysis plan	Final Version 1.0
Date of the statistical analysis plan	25AUG2022

SIGNATURE PAGE

TITLE	RESPONSIBILITY	NAME & OFFICE	SIGNATURE/DATE
Biostatistics Project Leader	Author	**Morgane GILLES** BIOTRIAL BIOMETRICS 7-9 rue Jean-Louis Bertrand CS 34246 35042 Rennes Cedex	DocuSigned by: Morgane Gilles Signer Name: Morgane Gilles Signing Reason: I am the author of this document Signing Time: 25-Aug-2022 | 12:24 PM CEST DBB424D211D847DC8F1FB5EE5062B1E5
Pharmaco-kineticist	Approver	**Julien PAGES** BIOTRIAL 7-9 rue Jean-Louis Bertrand CS 34246 35042 Rennes Cedex FRANCE	DocuSigned by: Julien Pages Signer Name: Julien Pages Signing Reason: I approve this document Signing Time: 29-Aug-2022 | 3:19 PM CEST EF9660E1D5F349CF8C9F39DFE7CE4C3F
Sponsor's Head of statistics	Approver	**David JEGOU** Pierre Fabre Médicament represented by the Institut de Recherche Pierre Fabre Les Cauquillous 81500 Lavaur FRANCE	DocuSigned by: David JEGOU Nom du signataire : David JEGOU Motif de la signature : J'approuve ce document Heure de signature : 25-août-2022 | 4:45 PM CEST 3540A39BE287436E8399A578101A44DA
Sponsor's Head of Oncology Innovation Unit	Reviewer	**Eric CHETAILLE** Pierre Fabre Médicament represented by the Institut de Recherche Pierre Fabre Les Cauquillous 81500 Lavaur FRANCE	DocuSigned by: Eric Chetaille Nom du signataire : Eric Chetaille Motif de la signature : J'approuve ce document Heure de signature : 25-août-2022 | 4:38 PM CEST D78024F303A94D729B817924B95EC49F
Sponsor's Pharmaco-kineticist	Reviewer	**Laurence BARTHE** Pierre Fabre Médicament represented by the Institut de Recherche Pierre Fabre Les Cauquillous 81500 Lavaur FRANCE	P.P. DocuSigned by: L Del F Nom du signataire : Laurence Del Frari Motif de la signature : J'ai examiné ce document Heure de signature : 29-août-2022 | 3:23 PM CEST 158FFE47CF7845F4A968FFD6BC4B5002

TITLE	RESPONSIBILITY	NAME & OFFICE	SIGNATURE/DATE
Sponsor's Head of Pharmaco-kinetics	Approver	**Eric DIDIER** Pierre Fabre Médicament represented by the Institut de Recherche Pierre Fabre Les Cauquillous 81500 Lavaur FRANCE	DocuSigned by: Eric Didier Nom du signataire : Eric Didier Motif de la signature : J'approuve ce document Heure de signature : 29-août-2022 | 4:24 PM CEST 4D03DFDAE0834C1A9F22DAA7925C35E8

REVISION HISTORY

Date	Version number	Reason for change	Authored by
30JUN2022	D0.1	Initiation	M.GILLES
28JUL2022	D0.2	Implementation of sponsor's comments	M.GILLES
22AUG2022	D0.3	Implementation of sponsor's comments	M.GILLES
25AUG2022	V1.0	Implementation of sponsor's comments	M.GILLES

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	DEFINITION
ADPP	ADaM Pharmacokinetic Parameters dataset
AE	Adverse Event
ALP	ALkaline Phosphatase
ALT	ALanine aminoTransferase
AST	ASpartate Aminotransferase
ATC	Anatomic Therapeutic Chemical
AUC	Area Under the Curve
AUC_%Extrap_obs	Residual area expressed in percentage
AUC_{last}	Area Under the Curve from time zero to last quantifiable plasma concentration
AUC_{inf}	Area Under the Curve from time zero to infinity
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
CI	Confidence Interval
CK	Creatine Kinase
CL/F	Apparent total body clearance
C_{last}	Last observed quantifiable plasma concentration
C_{max}	Maximum observed plasma concentration
COVID-19	Coronavirus disease 2019
CRF	Case Report Form
CSR	Clinical Study Report
CV	Coefficient of Variation
eCRF	electronic Case Report Form
ECG	ElectroCardioGram
EMA	European Medicines Agency
EOS	End Of Study
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GGT	Gamma Glutamyl Transferase
GMR	Geometric Mean Ratio
HBsAg	Hepatitis B surface Antigen
hCG	human Chorionic Gonadotropin

ABBREVIATION	DEFINITION
HGB	Hemoglobin
HIV	Human Immunodeficiency Virus
i.e.	id est
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product (synonymous with "study drug")
λ_z	First order terminal elimination rate constant
LLN	Lower Limit of Normal range
MedDRA	Medical Dictionary for Regulatory Activities
MR	Metabolic Ratio
MRT	Mean Residence Time
MW	Molecular Weight
NA	Not Applicable
NC	Not Calculated
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
ND	Not Determined
PCR	Polymerase Chain Reaction
PCSA	Potentially Clinically Significant Abnormalities
PK	PharmacoKinetics
PT	Preferred Term
QRS	QRS interval duration
QT	Time interval for ventricular depolarisation and repolarisation
QTc	Corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System®
SD	Standard Deviation
SEM	Standard Error of the Mean
SOC	System Organ Class
SOP	Standard Operating Procedure
$t_{1/2}$	Terminal elimination half-life
T_{last}	Time to reach last observed quantifiable plasma concentration
T_{max}	Time to reach maximum observed plasma concentration

ABBREVIATION	DEFINITION
TEAE	Treatment-Emergent Adverse Event
TOST	Two One-Sided Test
ULN	Upper Limit of Normal range
ULQ	Upper Limit of Quantification
Vz/F	Apparent volume of distribution
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 safety and pharmacokinetics (PK) variables and analysis sets, 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 V1.2 dated 22 June 2022 and will be prepared in accordance with the International Conference on Harmonisation (ICH) E9.

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 first visit of the first participant.

2. Study objectives

2.1. Primary objective

The primary objective is to demonstrate the bioequivalence of binimetinib 1 x 45 mg tablet Test formulation in comparison to 3 x 15 mg tablet Reference formulation in healthy participants under fasted conditions.

2.2. Secondary objectives

The secondary objectives are:

- to measure secondary PK parameters of binimetinib and PK parameters of the metabolite (AR00426032)
- to evaluate the safety and tolerability of binimetinib as a 1 x 45 mg Test tablet in comparison to 3 x 15 mg Reference tablets in healthy participants.

3. Study methodology

3.1. Protocol overview

This will be a randomized, single-center, open-label, two-sequence, two-period, crossover phase I study to demonstrate the bioequivalence of binimetinib 3 x 15 mg and 1 x 45 mg tablets in healthy participants. The Reference (R) formulation will be the currently commercially available tablet containing 15 mg of binimetinib as active substance, administered as three tablets for a total of 45 mg binimetinib. The Test (T) formulation will be the tablet containing 45 mg of binimetinib as active substance in one tablet.

Participants will be randomized to one of 2 treatment sequences (RT or TR) containing 2 treatment periods, with at least a 7-day washout between each dose.

The study will consist of:

- a screening period between 21 and 2 days before the first study treatment administration on Period (P) 1 Day (D) 1,
- 2 treatment periods of 5 days each (including one ambulatory visit at D4 per period),
- a washout of at least 7 days between P1D1 and P2D1,

- an End of Study (EOS) visit to be performed 30 (± 3) days after the last study treatment administration or discontinuation.

Study treatments will be given by the oral route in fasted condition.

In each treatment period, following the 48h post-dose procedures, the participants will be discharged and will return for an ambulatory visit on D4, and then return for the next treatment period or an EOS visit.

The schedule of activities is available in section 15.1.

3.2. Planned analyses

Final analyses will be performed when all participants complete the study and after the database lock.

4. Sample Size

The primary objective of this study is to demonstrate bioequivalence between the Test 1 x 45 mg binimetinib tablet and the Reference 3 x 15 mg binimetinib commercial tablets, based on PK endpoints C_{max}, AUC_{inf} and AUC_{last}.

The null hypothesis is that the true ratio of the geometric mean of the Test treatment to the geometric mean of the Reference treatment, $\mu(T)/\mu(R)$, for the C_{max}, AUC_{inf} and AUC_{last} is either <0.80 or >1.25. The alternate hypothesis is that the true ratio of the geometric mean of the Test treatment to the geometric mean of the Reference treatment for the C_{max}, AUC_{inf} and AUC_{last}, is ≥0.80 and ≤1.25. For each PK parameter designated as a primary endpoint, a two one-sided t-test (TOST) [1] procedure with α=0.05 for each one-sided test will be used to test this set of hypotheses.

Bioequivalence will be declared if the 90% confidence interval (CI) for the true ratio of test to reference geometric means falls entirely within the range of 0.80 to 1.25 for all primary parameters (i.e the null hypothesis must be rejected), in accordance with the European Medicines Agency (EMA) and Food and Drug Administration (FDA) guidelines on the investigation of bioequivalence [2][3].

Based on these criteria, assuming intra participant coefficient of variation (CV_{intra}) of C_{max} to be around 25% as observed on the pilot study [4] and a “Test/Reference” mean ratio of 1.05; thirty-six participants are needed to achieve a power of 90% at an alpha of 0.05.

Up to 40 participants will be included into the study to complete the study with at least 36 evaluable participants.

5. Changes to the planned analysis from protocol

Not applicable.

6. Statistical considerations

Demography and safety data will be analysed using SAS® software version 9.4 or higher (SAS institute Inc. Cary NC USA).

Pharmacokinetic (PK) data will be analysed using Phoenix® WinNonlin® version 8.1 or higher (Certara USA, Inc., Princeton, NJ) and SAS® software version 9.4 or higher (SAS Institute Inc. Cary NC USA).

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

- Quantitative variable: number of participants, 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 CV, and quartiles for PK analyses].
- Qualitative variable: number of participants, absolute and relative frequencies per class.
- Percentages will be provided with one decimal place.

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.

For the values measured outside of the treatment periods, data will be organised overall and, for description at baseline, by sequence:

- Test/Reference
- Reference/Test

With the following footnote: " Reference: binimetinib 3 x 15 mg tablet; Test: binimetinib 1 x 45 mg tablet.".

For the values obtained during the treatment periods, data will be organised by formulation group:

- binimetinib 1 x 45 mg tablet,
- binimetinib 3 x 15 mg tablet.

All safety listings will be sorted by participant, sequence and measurement time if applicable.

All pharmacokinetics listings will be sorted by treatment group, participant and measurement time.

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

- If evaluation precedes first drug administration then:

  (date of evaluation) - (date of first study drug administration)

- Study day -1 will be defined as the day prior to the first administration date.
  - If evaluation is on or after the first drug administration then:
  - (date of evaluation) – (date of first study drug administration) + 1
- Study day 1 will be defined as the day of the first administration date.
- There will be no study day 0.

Handling of missing, retest values and unscheduled visits

No management of missing values or values below/above a limit of detection/quantification will be performed, except for pharmacokinetic values (see section 9.1). In clinical laboratory data, “<LOQ” or “>ULQ” is reported in the qualitative variable. When converting the qualitative variable to the quantitative variable, “<LOQ” or “>ULQ” will be automatically treated as missing.

For all parameters and for participants with retest values, the last non-missing value will be used for the measurement time before the first IMP administration within each period (provided it was measured before IMP administration within each period) and the first non-missing value will be used for the measurement time after the first IMP administration within each period.

Unscheduled visits will not be analysed but presented in listings only.

Handling of incomplete dates

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

Baseline definition

For all parameters, baseline will be defined as the last available assessment prior to the first IMP administration within each period, including additional assessments (where applicable). Assessments that occurred on the same day as first dose, when time of assessment is not available, will be as assumed to be prior to first dose.

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).

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 participants

7.1. Definition of analysis sets

The following analysis sets will be defined:

Enrolled set: all participants who signed the ICF for the study.

Screened set: all enrolled participants having successfully completed the screening period.

Randomized set: all randomized participants.

Safety set: all included participants having taken at least one dose of study treatment, including those who did not complete the study.

Pharmacokinetic set: all of the participants who have taken one dose of study treatment in the two periods without any event (including no vomiting within 4 hours after dosing) and/or important protocol deviation affecting PK evaluation, with complete PK profiles in these two periods, i.e. sufficient PK concentration data to support the calculation of primary PK criteria (see section 9.1).

The analysis sets will be precisely defined and validated during the data review meeting and prior to database lock..

The safety and pharmacokinetic sets will be analysed using participants as treated. The randomized set will be analysed using participants as randomized.

7.2. Participant disposition

A summary table with the description of the number of screened participants, the number of randomized 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 sequence and overall for the participants in the screened set. Corresponding individual listings will be provided.

A summary table with the description of the number and percentage of participants in each analysis set (Randomized set, Safety set and Pharmacokinetic Set) will be prepared by sequence and overall. A specific listing of participants excluded from safety and/or pharmacokinetic analyses will be provided with the reason(s) for exclusion.

A summary table with the number and percentage of participants at each period will be prepared by treatment group and overall on the participants in the randomized set.

Listings with end of study status and study visit dates will also be generated.

In addition, due to possible impact of COVID-19 pandemic on participants' disposition, the following disposition table will be presented for all randomized patients by sequence:

- number (%) of participants infected (i.e. at least one AE related to COVID-19 and/or positive Polymerase Chain Reaction test result).
- number (%) of discontinued participants due to COVID-19 and reasons of discontinuation,
- number (%) of participants impacted (with at least one important protocol deviation due to COVID-19 or for whom the conduct of the study has been impacted (missed visit, remote visit, unscheduled visit, etc.)),
- number (%) of participants with important protocol deviations due to COVID-19.

7.3. Protocol deviations

A summary table by sequence and overall with the number and percentage of participants presenting all protocol deviations judged important during the data review meeting will be prepared for the participants in the randomized set. All important protocol deviations will be listed and important protocol deviations due to COVID-19 will be flagged if applicable.

8. Demographic data and baseline characteristics

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

8.1. Demographic data

The participants' demographic characteristics will be summarised by sequence and overall, and listed:

- age at screening (years) – continuous,
- sex,
- ethnicity,
- height at screening (cm)
- weight at screening (kg)
- Body Mass Index (BMI) recorded at screening (kg/m²)

8.2. Other baseline characteristics

All parameters recorded before dosing (COVID-19 vaccination status, smoking and alcohol history) will be summarised by sequence and overall, and listed.

Positive results as well as all individual data for urine drug screen (benzodiazepines, cocaine, cannabinoids, morphine, amphetamines, methamphetamines and ecstasy), alcohol breath test and urine cotinine test performed at screening and on Day -1 of each period (see section 15.1) will be listed.

Positive results as well as all individual data for serology (Hepatitis B surface antigen, hepatitis C antibody and HIV) will be listed.

For postmenopausal female participants, serum follicle-stimulating hormone (FSH) and estradiol will only be listed.

8.3. Medical and surgical history and procedures

Information on medical and surgical history recorded at the screening visit and procedures will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0.

A table with the number and percentage of participants having at least one previous/ongoing medical history or one surgical history will be generated by sequence and overall, by System Organ Class (SOC) and Preferred Term (PT). Previous/ongoing medical history will be listed as well as prior surgeries and concomitant surgeries.

8.4. Prior and concomitant medications

Information on prior and concomitant medications will be coded according to the WHO Drug Dictionary version of March 2022 (B3 with primary ATC selection).

A prior medication will be defined as a medication stopped prior to the date and time of the first administration of IMP. Prior medications are recorded in the "Concomitant medication" eCRF page and identified by the "Taken prior to treatment start" variable.

A concomitant medication will be defined as a medication that is taken by participants any time during the treatment period (on or after the date and time of first IMP administration for each participant). If the date value does not allow allocation of a medication to the prior or concomitant category (missing or incomplete start or end date), this medication will be considered concomitant.

A table with the number and percentage of participants having taken at least one previous medication and a table with the number and percentage of participants having taken at least one concomitant medication will be generated by sequence and overall (overall and by medication class [2nd level of Anatomical Therapeutic Chemical (ATC)] and medication drug name). Prior 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

Plasma concentrations of binimetinib and corresponding non-compartmental derived PK parameters [AUC from time of administration to last observed plasma concentration (AUC_{last}), AUC_{inf}, C_{max}, T_{max} and AUC Test (T)/Reference (R) ratios] will be used as primary endpoints to evaluate the bioequivalence of binimetinib 1 x 45 mg tablet formulation in comparison to the commercialized 3 x 15 mg tablet formulation in healthy participants under fasted conditions.

The pharmacokinetic statistical analysis will be performed on the PK set.

9.1. Generalities

Reasons for exclusion:

Before concentration data are communicated by the bioanalytical laboratory, the following rules will lead to exclude a participant from the PK set:

- Any participant who discontinued with study treatment (no administration in the second period),
- Any participant having experienced vomiting or diarrhoea within 4 hours after dosing,
- Any participant having taken prohibited concomitant treatment or medication affecting PK throughout the study,
- Any participant for whom a washout of at least 7 days between each dose was not respected,
- Any participant who did not remain fasted for at least 10 hours before dosing,
- The following deviations will be discussed case by case:
  - Any deviation related to PK sample technical handling or storage,
  - Any participant with insufficient PK samples to support the calculation of primary PK criteria.

In the following cases (exceptions), the decision to exclude a participant from the statistical analysis (i.e. participant kept in the PK set but flagged and only listed, concentrations and parameters will not be used for statistical analysis) could be done after concentration data are communicated by the bioanalytical laboratory:

1) Any participant with lack of any measurable concentrations or only very low plasma concentrations for reference formulation (i.e. its AUC is less than 5% of reference formulation geometric mean AUC, calculated without inclusion of data from the outlying participant),
2) Any participant with non-zero baseline concentrations > 5% of C_{max}.

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

Actual sampling times will be used for deriving PK parameters.

- For plasma concentrations and PK parameters:
  - All BLQ values will be substituted according to the rules described in the following table and by type of analysis:

Substitution value if BLQ occurs:			
Type of analysis	Before T_{max}	After T_{max} & between 2 quantifiable concentrations	After T_{max} & NOT between 2 quantifiable concentrations
PK non-compartmental analysis	0	Missing	Missing
Descriptive statistics	0	0	0
Plotting of individual data	0	Missing	Missing
Listing of individual data	BLQ	BLQ	BLQ

- Some conditions for plasma PK parameters have to be fulfilled:

  1) the percentage of the extrapolated AUC (AUC_%Extrap_obs) should not exceed 20% of the AUC_{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 λ_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 (Rsq_{adj}) ≥ 0.8, and a minimum of 3 data points will be used in calculating λ_z excluding C_{max}.

  If these conditions are not fulfilled, the following unreliable PK parameters will be flagged in the listings and will be excluded from the analysis:

  1) if the time interval used for the determination of the elimination rate constant is inferior to 2 x $t_{1/2}$ and/or not with a minimum of 3 data points and/or if the $Rsq_{adj} < 0.8$: λ_z, $t_{1/2}$, AUC_{inf}, CL/F, Vz/F, MRT and MR_{AUC}.

  2) if AUC_%Extrap_obs> 20%: AUC_{inf}, CL/F, Vz/F, MRT and MR_{AUC}.

No graphic representation will be done if all values are BLQ.

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

- If at least 3 of the values are evaluable (either BLQ values replaced by zero or numeric values): statistics will be calculated with the replaced and numeric values.
- If less than 3 values are evaluable: only the minimum and maximum will be presented and the other statistics will be considered as "Not Applicable" (NA).
- If at least one value is BLQ (replaced by 0), the geometric mean and its CV% will be presented as "Not Calculated" (NC).

For **summary statistics for PK parameters**:

- If at least 3 values are analysable and not missing: statistics will be calculated with the available values.

- If less than 3 values are analysable: only the minimum and maximum of the available numeric values will be presented. All other statistics will not be calculated and will be presented as "Not Determined" (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 parameters

Blood samples will be drawn in each treatment period (see section 15.1) at pre-dose and at H0.5, H0.75, H1, H1.25, H1.5, H2, H3, H4, H5, H6, H8, H10, H12, H24, H36, H48 and H72 post-dose of each period.

Relevant plasma pharmacokinetic (PK) parameters of binimetinib and its metabolite AR00426032 will be calculated by standard non-compartmental methods for the participants with sufficient plasma concentration data (a PK profile with at least 3 quantifiable concentrations). The rules defined in the previous section (9.1) will be used.

The different areas under the concentration-time curve (AUC) will be calculated using the linear-log trapezoidal method: the linear trapezoidal method for increasing or equal concentrations and the logarithmic trapezoidal method for decreasing concentrations.

The following plasma pharmacokinetic parameters will be calculated for binimetinib and AR00426032:

Parameters (unit)	Definition
C_{max} (ng/mL)	Maximum observed plasma concentration
T_{max} (h)	Time to reach maximum observed plasma concentration
T_{last} (h)	Time to reach last observed quantifiable plasma concentration
AUC_{last} (ng/mL.h)	Area under the plasma concentration-time curve from time zero to the last quantifiable plasma concentration
AUC_{inf} (ng/mL.h)	Area under the plasma concentration-time curve from time zero to infinity, calculated as follows: $AUC_{inf} = AUC_{last} + \frac{C_{last}}{\lambda_z}$, where C_{last} is the last observed quantifiable concentration
λ_z (/h)	First order terminal elimination rate constant
$t_{1/2}$ (h)	Terminal elimination half-life, calculated as follows: $t_{1/2} = \ln(2)/\lambda_z$
MRT (h)	Mean Residence Time, calculated as follows: $MRT = \frac{AUMC_{inf}}{AUC_{inf}}$ where $AUMC_{inf}$ is the area under the first moment curve from zero to infinity.

The following plasma pharmacokinetic parameters will be calculated only for binimetinib:

Parameters (unit)	Definition
AUC_%Extrap_obs (%)	Residual area expressed in percentage

Parameters (unit)	Definition
CL/F (L/h)	Apparent total body clearance, calculated as follows: $CL/F = Dose / AUC_{inf}$
Vz/F (L)	Apparent volume of distribution, calculated as follows: $Vz/F = CL/F / \lambda_z$
MR_{AUC}	Metabolite-parent ratio based on AUC_{inf} accounting for differences in molecular weights (MW), calculated as follows: $MR_{AUC} = \frac{AUC_{inf\ AR00426032} / MW_{AR00426032}}{AUC_{inf\ binimetinib} / MW_{binimetinib}}$

9.2.2. Plasma pharmacokinetic analysis

Listings with plasma concentrations (including PK blood sampling dates, times and elapsed times) and PK parameters will be provided by formulation group and participant. These listings will be generated for all participants with an available PK profile (complete or incomplete), including those who are excluded from the pharmacokinetic set. Participants excluded will be flagged.

Plasma concentrations and PK parameters of binimetinib and AR00426032 including descriptive statistics will be presented in tables separately for each formulation group.

Individual plasma concentration versus time profiles of binimetinib and AR00426032 will be presented graphically on linear and log/linear coordinates for each participant with all formulations received by the participant on the same graph.

The graph of arithmetic mean ± SD over time will be provided for plasma concentration of binimetinib and AR00426032 on linear and log/linear coordinates with all formulation groups on the same graph as well as for each formulation group with both analytes on the same graph. Individual plasma concentration-time profiles (spaghetti plots) of binimetinib and AR00426032 will also be presented for each formulation group on linear and log/linear coordinates.

<u>For binimetinib only:</u>

Scatter plots will be generated for the comparison of the C_{max}, AUC_{last} and AUC_{inf} (if applicable) parameters of binimetinib between the formulation groups.

Box whisker plots will be generated for the comparison of C_{max}, AUC_{last} and AUC_{inf} (if applicable) parameters of binimetinib between the formulation groups.

To demonstrate the bioequivalence between the two formulations, primary PK parameters (C_{max}, AUC_{last} and AUC_{inf}) will be analyzed separately using linear mixed effects model with log-transformed PK parameter (variable PARAMCD) as the dependent variable, sequence (TRTSEQPN), period (APERIOD) and formulation (TRTAN) as fixed effects and participant within sequence (USUBJID(TRTSEQPN)) as random effect. Point estimates and 90% CIs will be provided for the ratio of Test to Reference (3 x 15 mg formulation as Reference and 1 x 45 mg formulation as Test). In accordance with EMA and FDA guidelines, bioequivalence will be declared if the 90% CI for the ratio of Test to Reference geometric means is within the range of 80.00% to 125.00% (0.80 to 1.25) for all primary endpoints.

Estimated geometric mean ratios (GMRs) and 90% CIs will also be displayed in a figure.

The following SAS code will be used:

```
proc mixed data=ADPP method=REML;
    by PARAMCD;
```

```
        class TRTSEQPN APERIOD TRTAN USUBJID;
        model ln(AVAL) = TRTSEQPN APERIOD TRTAN / solution ddfm=kr;
        random USUBJID(TRTSEQPN);
        lsmeans TRTAN / cl alpha=0.10;
        estimate 'Test versus Reference' TRTAN -1 1 / cl alpha=0.10 e;
run;
```

The Wilcoxon signed-rank test will be used to test for the difference in T_{max} of binimetinib between the 2 formulations.

Differences in T_{max} of binimetinib between the 2 formulations will be explored by computing the Hodges-Lehmann shift estimate and the corresponding 90% CI. The difference between the 2 formulations [di=(xi, yi)] for each participant and for binimetinib is calculated and sorted, then the average value of the difference of each ordered pair (dj,di) with i≤j is computed and the median difference is estimated, then the confidence interval for the mean difference is estimated based on the Wilcoxon signed-rank distribution.

10. Pharmacodynamics data

Not applicable.

11. Safety data

The safety analyses will be performed on the safety set.

11.1. Adverse events

Adverse events, including pre-treatment events, will be recorded from the time of consent through until the EOS visit.

A treatment-emergent adverse event (TEAE) is an adverse event that starts or worsens during the on-treatment period. All analyses described in section 11.1 will be based on TEAEs if not otherwise specified.

The following treatment periods will then be considered:

Period	**Start date/time**	**End date/time**
Before any treatment	Date/time of inform consent	Date/time of first IMP administration of period 1 - 1 minute
Treatment 1	Date/time of first IMP administration of period 1	Date/time of first IMP administration of period 2 - 1 minute
Treatment 2	Date/time of first IMP administration of period 2	Date of end of study

Adverse events will be summarized by worst grade according to the National Cancer Institute - Common Terminology Criteria for Adverse Events version 5.0 (NCI-CTCAE V5.0 [5]) per participant and coded using MedDRA Version 24.0.

A summary table will present the number and percentage of participants with a TEAE overall and by formulation, including:

- TEAEs;
- TEAEs, grade >=3;
- Related TEAEs;
- Related TEAEs, grade >=3;
- TEAEs leading to any dose reduction;
- Related TEAEs leading to any dose reduction;
- TEAEs leading to permanent treatment discontinuation;
- Related TEAEs leading to permanent treatment discontinuation;
- Serious TEAEs;
- Related serious TEAEs;
- TEAEs leading to death;
- Related TEAEs leading to death.

Treatment-emergent adverse events will be summarised in tables as follows [overall and by SOC and PT]:

- Number and percentage of participants with at least one TEAE and number of occurrences of a TEAE by formulation and overall,
- By worst NCI-CTCAE grade, with the number and percentage of participants with at least one TEAE and number of occurrences of a TEAE by formulation and overall,
- By causality to study treatment, with the number and percentage of participants with at least one TEAE and number of occurrences of a TEAE by formulation and overall.

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

Additionally, AEs related to COVID-19 will be summarised by formulation and overall and listed separately. If there are only a few adverse events related to COVID-19 (≤10), only a listing will be generated.

All adverse events reported in the electronic Case Report Form (eCRF) 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 TEAEs leading to death and other serious and significant TEAEs (SAEs or TEAEs leading to study withdrawal). If more than 10 of these TEAEs are observed, a summary table with the number and percentage of participants with at least one TEAE and number of occurrences of a TEAE by formulation and overall will be provided, as well as three distinct listings (for TEAEs leading to death, TEAEs leading to study withdrawal and SAE).

Note:

i. The occurrence of an adverse event is defined by the appearance of a new single event, the reappearance of a previously recovered event or the worsening of a continuous event in severity or seriousness (relative to its previous status).
ii. In the descriptive tables, the number of participants with at least one adverse event/TEAE for a given PT will also correspond to the number of adverse events/TEAEs whatever the number of occurrences during the studied period.
iii. In case of a change of severity or causality for an event during the same treatment period, the severity will be the highest recorded intensity and the causality will be the highest likelihood recorded.
iv. SOCs will be sorted by descending order of frequency for the overall, PTs will be sorted by descending order of frequency for the overall within each SOC.

11.2. Clinical laboratory data

The following clinical laboratory parameters will be measured (see section 15.1):

- at screening,
- on Day -1 of each period;
- at H24 and H48 post-dose of each period;
- at EOS.

Haematology parameters will be listed and grouped as follows:

- Red blood cells: erythrocytes (10^12/L), ery. mean corpuscular hemoglobin (pg), ery. mean corpuscular volume (MCV) (fL), hematocrit (ratio), hemoglobin (HGB) (g/L) and reticulocytes/erythrocytes (%).
- White blood cells: leukocytes (10^9/L), basophils (10^9/L), basophils/leukocytes (%), eosinophils (10^9/L), eosinophils/leukocytes (%), 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).

Blood chemistry parameters will be listed and grouped as follows:

- Liver function: alanine aminotransferase (ALT) (IU/L), alkaline phosphatase (ALP) (IU/L), aspartate aminotransferase (AST) (IU/L), bilirubin (µmol/L), gamma glutamyl transferase (GGT) (IU/L) and indirect bilirubin (µmol/L).
- Renal chemistry: creatinine (µmol/L) and urea (mmol/L).
- Electrolytes: bicarbonate (mmol/L), calcium (mmol/L), chloride (mmol/L), magnesium (mmol/L), potassium (mmol/L) and sodium (mmol/L).
- Metabolism parameters: glucose (mmol/L), cholesterol (mmol/L) and urate (µmol/L).
- Other proteins: albumin (g/L), creatine kinase (CK) (IU/L), lactate dehydrogenase (IU/L) and protein (g/L).
- Digestive enzymes: amylase (IU/L) and lipase (IU/L).

Coagulation parameters will be listed and grouped as follows:

- Coagulation parameters: activated partial thromboplastin time (sec) and prothrombin time (sec).

Urinalysis parameters will be listed and grouped as follows:

- Planned urinalysis parameters: dipstick determination of pH, erythrocytes, glucose, ketones, leukocytes and protein.
- Direct microscopy (in case of abnormal urinalysis parameters and in the listing only).

For haematology, blood chemistry and coagulation, raw data and changes from baseline will be described by formulation group at baseline and for each post-baseline measurement.

For urinalysis, raw data (planned parameters) will be described by summary statistics or frequency tables by formulation group at baseline and for each post-baseline measurement.

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

For haematology, blood chemistry and coagulation, for laboratory tests covered by the NCI-CTCAE [5] laboratory data will be graded accordingly. Grade 0 will be assigned for all non-

missing values not graded as 1 or higher. Grade 5 (death) will not be used. The parameters to be analyzed according to NCI-CTCAE criteria are the following:

- Haematology:
  - Red blood cells: HGB;
  - White blood cells: leukocytes, eosinophils, lymphocytes and neutrophils;
  - Other parameters: platelets.
- Blood chemistry:
  - Liver function: ALT, ALP, AST, bilirubin and GGT.
  - Renal chemistry: creatinine;
  - Electrolytes: bicarbonate, calcium*, magnesium, potassium and sodium;
  - Metabolism parameters: glucose and cholesterol;
  - Other proteins: albumin, CK and lactate dehydrogenase;
  - Digestive enzymes: amylase and lipase.
- Coagulation: activated partial thromboplastin time.

* For calcium, NCI-CTCAE grading is based on corrected calcium, calculated from albumin and calcium as follows based on International System of Units (SI): corrected calcium (mmol/L) = measured total calcium (mmol/L) + 0.02 x (40 - serum albumin (g/L)).

Shift tables with the number of participants having values in each NCI-CTCAE grade according to the baseline position will be prepared by formulation group for each post-baseline measurement. A similar table will be provided with low/normal/high classification for laboratory tests not covered by the NCI-CTCAE, which are the following:

- Haematology:
  - Red blood cells: erythrocytes, ery. mean corpuscular HGB, ery. MCV, haematocrit and reticulocytes/erythrocytes;
  - White blood cells: basophils and monocytes;
- Blood chemistry:
  - Liver function: indirect bilirubin;
  - Renal chemistry: urea;
  - Electrolytes: calcium and chloride;
  - Metabolism parameters: urate;
  - Other proteins: protein;

Values (raw data and changes from baseline at each measurement time) will be listed and data out of normal ranges will be flagged with clinical significance information.

Urinalysis values will be listed, including direct microscopy, if any.

11.3. Other safety parameters

11.3.1. Vital signs data

Supine and standing systolic and diastolic blood pressure (mmHg), pulse rate (beats/min) and body temperature (C°) be measured (see section 15.1):

- at screening,
- on Day -1 of each period,
- at Day 1 pre-dose, H24 and H72 post-dose of each period,
- at EOS.

The presence of orthostatic hypotension and the presence of abnormal HR increase will be derived as follows for a pair of values (supine and standing) corresponding to the same examination:

- Orthostatic hypotension: standing SBP - supine SBP $\leq$ -20 mmHg or
  standing DBP - supine DBP $\leq$ -10 mmHg,
- Abnormal PR increase: standing PR - supine PR $\geq$ 30 beats/min.

Raw data and changes from baseline (for supine position only) will be described by treatment group at baseline and for each post-baseline measurement. Missing data will define a separate category.

A summary table with the number and percentage of participants with PCSA values (defined in section 15.2) will be generated by formulation and measurement time.

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

The number and percentage of participants with at least one orthostatic hypotension will be presented by formulation and measurement time.

The number and percentage of participants with at least one abnormal HR increase will be presented by formulation and measurement time.

Values (raw data and changes from baseline (for supine position only) at each measurement time) will be listed and PCSA values will be flagged with clinical significance information.

A listing of participants having at least one orthostatic hypotension or at least one abnormal HR increase will be provided.

11.3.2. Electrocardiogram data

Standard 12-lead ECG parameters (including heart rate (beats/min), PR interval (msec), QRS duration (msec), QRS axis (deg), QT interval (msec) and Fridericia QTc interval (msec)) and ECG abnormalities will be recorded in triplicate (see section 15.1):

- at screening,
- on Day -1 of each period,
- at Day 1 pre-dose and H24 post-dose of each period,
- at EOS.

The mean of the triplicate ECGs will serve as analysable data.

Only interpretable ECGs will be analysed.

Raw data and changes from baseline (except for QRS axis in degrees and ECG abnormalities) will be described by formulation at baseline and for the each post-baseline measurement.

Shift tables with the number of participants having values lower than the lower PCSA limit (Low), normal and higher than the upper PCSA limit (High) (defined in section 15.2) according to the baseline position will be prepared by formulation group for each post-baseline measurement.

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

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

11.3.3. Physical examination

A complete physical examination, including at minima assessments of the cardiovascular, respiratory, gastrointestinal, dermatological and neurological, musculoskeletal in addition to head, eyes, ears, nose, throat, neck and lymph nodes systems will be performed (see section 15.1):

- at screening,
- on Day -1 of each period,
- at H24 post-dose of each period,
- at EOS.

Height will be measured at screening and weight at screening, on Day -1 and at EOS (see section 15.1). BMI will be calculated from the participants' height and weight according to the following formula: weight (kg)/(height(m))^2.

For weight and BMI, raw data will be described overall and by measurement time.

Abnormal results as well as all individual data will be listed.

11.3.4. Visual and ophthalmologic examinations

11.3.4.1. Visual assessment

A general inspection of the eyes, examination of motility and alignment, any visual disturbances such as blurred vision or loss of vision will be performed (see section 15.1):

- at screening,
- on Day -1 of each period,
- at H24 and H72 post-dose of each period,
- at EOS.

Abnormal results as well as all individual data will be listed.

11.3.4.2. Ophthalmologic examination

Best corrected visual acuity for distance testing, optical coherence tomography and/or fluorescein angiography, slit lamp examination, IOP and dilated fundoscopy with attention to retinal abnormalities will be performed (see section 15.1):

- at screening,
- at EOS.

Abnormal results as well as all individual data will be listed.

11.3.5. Substance use and physical activity

Tobacco, xanthine, alcohol, grapefruit and recreational drugs consumption as well as physical activity are recorded on Day -1 and Day 4 of each period (see section 15.1).

Substance use and activity as well as all individual data will be listed.

11.3.6. COVID-19 tests

COVID-19 antigenic test will be performed (see section 15.1):

- at screening,
- on Day -1 of each period,
- at EOS.

COVID-19 polymerase chain reaction (PCR) test is to be performed on Day -1 of each period if required.

Positive results as well as all individual data will be listed.

11.3.7. Pregnancy test

For all female participants, a blood pregnancy test (hCG) will be performed (see section 15.1):

- at screening,
- on Day -1 of each period,
- at EOS.

Positive results as well as all individual data will be listed.

12. Procedures and data formats

Biotrial standard operating procedures (SOP) will be followed, and in particular on SOP GL-6.3.6: Programming of the statistical analysis, results editing and quality control.

Derived data produced for the generation of TFLs will follow CDISC ADaM standard (ADaM Model v. 2.1 / ADaM IG v. 1.1 or later version).

13. Reporting conventions

All tables, figures and listings to be developed, as well as the shells for each TFL, are described in a separate document. 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).

	Orientation=Portrait	Orientation=Landscape
Page margins	Top=2.5 cm; Bottom=4.3 cm; Left=2.8 cm; Right=1.5 cm	Top=2.8 cm; Bottom=1.5 cm; Inside=2.8 cm; Outside=2 cm
Gutter	0 cm, left	0 cm
Header	1.5 cm	1.5 cm
Footer	3.3 cm	1.5 cm

Table and Figure Page Set Up Requirements:

- Font Type = Time New Roman
- Font Size = 10 pt (at a maximum, can be reduced to 9 or 8)

- Paper Size = A4 (21 cm x 29.7 cm)
- Graphs: Portable Network Graphics (PNG) format

Listings Page Set Up Requirements:

- Font Type = Courier New
- Font Size = 6 pt (at a minimum)
- Paper Size = A4 (21 cm x 29.7 cm)

Summary statistics will be presented as follows.

Parameter (Unit)	**Statistics / Category**	**Group X (N=xx)**
Quantitative Variable (unit)	n	xx
	Geometric Mean[&]	xx.x
	Mean[+] ± SD	xx.x ± xx.xx
	SEM[&]	xx.xx
	CV%[&]	xx.x
	Geometric CV%[&]	xx.x
	Median	xx.x
	Q1 ; Q3[&]	xx.x ; xx.x
	Min ; Max	xx ; xx
Qualitative Variable	Class 1	xx (xx.x %)
	Class 2	xx (xx.x %)
	…	…

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

[&] For PK parameters only.

14. References

1. Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. J Pharmacokinet Biopharm. 1987 Dec;15(6):657-80. doi: 10.1007/BF01068419. PMID: 3450848.

2. EMA. Guideline on the Investigation of Bioequivalence. CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **. 20 Jan 2010.

3. Guidance for Industry; Statistical Approaches to Establishing Bioequivalence; U.S. Department of Health and Human Services; Food and Drug Administration Center for Drug Evaluation and Research (CDER); January 2001.

4. W00074CI101. A randomized, single-center, open-label, single dose, two-period, crossover study to investigate the relative bioavailability of binimetinib 3 x15 mg and 45 mg tablets in healthy participants. Pierre Fabre Médicament. 2022.

5. National Cancer Institute, Common Terminology Criteria for Adverse Events (CTCAE version 5.0), November 2017. Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

15. Appendices

15.1. Appendix 1 - Schedule of activities of the study

		Treatment Phase																				
Epoch	**Screening**	**Treatment Period 1**										**Washout**	**Treatment Period 2**									**Follow-up**
Procedure/Assessment	**Screening**	**Run-in**	**Period 1**									**Washout period[a]**	**Run-in**	**Period 2**								**End of Study[b]**
	D-21 to D-2	**D-1**	**D1**					**D2**		**D3**	**D4**	**At least 7 days**	**D-1**	**D1**					**D2**		**D3**	**D4**	**30 (±3) days after last dosing**
Relative time (h)	**Screening**		**Pre-dose**	**Dosing t0h**	**t3h**	**t4h**	**t12h**	**t24h**	**t36h**	**t48h**	**t72h**			**Pre-dose**	**Dosing t0h**	**t3h**	**t4h**	**t12h**	**t24h**	**t36h**	**t48h**	**t72h**	
Ambulatory visits	X										X											X	X
Stay in center		<----------									>			<----------								>	
Discharge										X											X		
Informed consent	X																						
Sequence randomization			X																				
Inclusion and exclusion criteria	X	X											X [c]										
Demography[d]	X																						
Medical history	X																						
Alcohol history	X																						
Smoking history	X																						
Drug / alcohol / tobacco / substance usage[e]	X	X											X										
Prior medications / therapies / procedures	X	X																					
COVID-19 vaccination status	X																						
Height	X																						

		Treatment Phase																				
Epoch	**Screening**	**Treatment Period 1**										**Washout**	**Treatment Period 2**									**Follow-up**
Procedure/Assessment	**Screening**	**Run-in**	**Period 1**									**Washout period[a]**	**Run-in**	**Period 2**								**End of Study[b]**
	D-21 to D-2	**D-1**	**D1**					**D2**		**D3**	**D4**	**At least 7 days**	**D-1**	**D1**					**D2**		**D3**	**D4**	**30 (±3) days after last dosing**
Relative time (h)	**Screening**		**Pre-dose**	**Dosing t0h**	**t3h**	**t4h**	**t12h**	**t24h**	**t36h**	**t48h**	**t72h**			**Pre-dose**	**Dosing t0h**	**t3h**	**t4h**	**t12h**	**t24h**	**t36h**	**t48h**	**t72h**	
Weight	X	X											X										X
Complete physical examination	X	X						X					X						X				X
Vital signs[f]	X	X	X					X			X		X	X					X			X	X
Visual examination[g]	X	X						X			X		X						X			X	X
Ophthalmologic examination[h]	X																						X
Standard 12-Lead ECG[i]	X	X	X					X					X	X					X				X
Standard cardiac echocardiography[j]	X																						
Hepatitis B surface antigen, hepatitis C antibody and HIV	X																						
COVID-19 test[k]	X	X											X										X
FSH and estradiol[l]	X																						
Pregnancy test[m]	X	X											X										X
Hematology[n]	X	X						X		X			X						X		X		X
Clinical chemistry[o]	X	X						X		X			X						X		X		X
Coagulation[p]	X	X						X		X			X						X		X		X
Urinalysis[q]	X	X						X		X			X						X		X		X
PK blood samples[r]			<----------								---------->			<----------									---------->	
Concomitant medications/therapies	X	Assess continuously																					

		Treatment Phase																				
Epoch	**Screening**	**Treatment Period 1**										**Washout**	**Treatment Period 2**									**Follow-up**
Procedure/Assessment	**Screening**	**Run-in**	**Period 1**									**Washout period[a]**	**Run-in**	**Period 2**								**End of Study[b]**
	D-21 to D-2	**D-1**	**D1**					**D2**		**D3**	**D4**	**At least 7 days**	**D-1**	**D1**				**D2**		**D3**	**D4**	**30 (±3) days after last dosing**
Relative time (h)	**Screening**		**Pre-dose**	**Dosing t0h**	**t3h**	**t4h**	**t12h**	**t24h**	**t36h**	**t48h**	**t72h**			**Pre-dose**	**Dosing t0h**	**t3h**	**t4h**	**t12h**	**t24h**	**t36h**	**t48h**	**t72h**	
Adverse events[s]	X	Assess continuously																				
Study treatment administration				X											X							
Meals: B=Breakfast, Lu=Lunch, Di=Dinner[t]		Lu, Di				Lu	Di	B	Di	B			Lu, Di				Lu	Di	B	Di	B		

At least 7 days between P1D1 and P2D1.
The end-of-study (EOS) visit [30 (± 3 days) after the last study treatment administration or discontinuation] must be done for all the included participants, except participants who did not receive any dose of study treatment, for whom the EOS visit is not required.
For P2D-1: exclusion criteria and only inclusion criteria 7 (vital sign) and 8 (safety lab) will be checked. Clinical relevance of abnormal value could be discussed for the participant's participation in the second period of the trial. However, and among the exclusion criteria PR interval >220ms is acceptable, if not clinically significant (NCS).
Sex, age at screening, year of birth and ethnicity.
Urine drug screen, alcohol breath test and urine cotinine test.
Supine and standing systolic and diastolic BP and PR (after at least 5 minutes at rest in the supine position and after standing for 5 minutes), and body temperature.
Visual assessment (general inspection of the eyes, examination of motility and alignment, any visual disturbances such as blurred vision or loss of vision) to be performed on site by the Investigator.
Full ophthalmologic examination by ophthalmologist to be performed at screening (within 1 week before randomization: D-9 to D-2) and EOS (within 1 week before EOS) and in case of emergency, including best corrected visual acuity for distance testing, optical coherence tomography and/or fluorescein angiography, slit lamp examination, intraocular pressure and fundoscopy with attention to retinal abnormalities.
ECGs are to be performed in triplicate (conducted within approximately 5 to 10 minutes total time). ECGs should be performed before blood collection at equivalent nominal time points.
Within 1 week before randomization (D-9 to D-2).
COVID-19 antigenic test is to be performed at screening and D-1 of each treatment period and at the EOS visit. COVID-19 polymerase chain reaction (PCR) test is to be performed on P1D-1, if required.
For postmenopausal female participants, serum FSH and estradiol to be performed at screening to confirm postmenopausal status (except if the participant is treated with HRT).
For all female participants, serum pregnancy tests are to be performed at screening, D-1 of each period and at the EOS visit.
Erythrocytes (red blood cells, RBC), hematocrit, hemoglobin, platelets; leukocyte count with differential: basophils, eosinophils, lymphocytes, monocytes, neutrophils/absolute neutrophil count; RBC indices: mean corpuscular hemoglobin, mean corpuscular volume, reticulocytes/erythrocytes.

ALT, albumin, ALP, AST, GGT, bicarbonate, bilirubin (total and indirect), urea, calcium, chloride, CK, creatinine, amylase, lipase, total cholesterol, glucose, lactate dehydrogenase, magnesium, potassium, sodium, total protein, uric acid.
aPTT and prothrombin ratio.
Urinalysis (dipstick: pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrites and leukocyte esterase) will be performed. In case of positive results for white blood cells, red blood cells and/or nitrites, urine will be sent to the laboratory for microscopy and culture. If there is an explanation for the positive dipstick results (e.g., menses), this will have to be discussed with the Sponsor and should be recorded, and there might be no need to perform microscopy and culture)
Serial PK blood samples will be collected at pre-dose within 15 min before treatment administration (0h), and t+0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12h post-dose, as well as at 24, 36, 48 and 72h post-dose. 1 min, 3 min and 5 min time windows will be authorized up to 0.75 h, up to 1.5 h and up to 12 h, respectively. 15 min, 30 min and 120 min time windows will be authorized at 24h, 36h and 48h-72h, respectively.
All AEs are collected from when the participant first provides informed consent until the EOS visit [30 (± 3) days after the last study treatment administration or discontinuation].
In addition, a snack will be provided in the afternoon of D1 and lunch will be provided on D2.

15.2. Appendix 2 - Criteria for Potentially Clinically Significant Abnormalities (PCSA)

PARAMETER	LOWER PCSA VALUE	UPPER PCSA VALUE
Vital signs		
Supine HR	≤ 45 beats/min and change from baseline ≤ -20 beats/min	≥ 100 beats/min and change from baseline ≥ 20 beats/min
Supine SBP	≤ 90 mmHg and change from baseline ≤ -20 mmHg	≥ 140 mmHg and change from baseline ≥ 20 mmHg
Supine DBP	≤ 50 mmHg and change from baseline ≤ -10 mmHg	≥ 90 mmHg and change from baseline ≥ 10 mmHg
Standard 12-lead ECG parameters		
HR	≤ 45 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) > 500 msec (High+) change from baseline > 30 msec and change from baseline ≤ 60 msec (High) change from baseline > 60 msec (High+)

DocuSign

Certificate Of Completion

Envelope Id: BB21C0C18759442BA254E544100C11FB
Status: Completed
Subject: Please DocuSign: W00074CI103_SAP_V1.0_25AUG2022.pdf
Source Envelope:
Document Pages: 32
Signatures: 6
Envelope Originator:
Certificate Pages: 6
Initials: 0
Morgane Gilles
AutoNav: Enabled
morgane.gilles@biotrial.com
EnvelopeId Stamping: Disabled
IP Address: 194.250.122.241
Time Zone: (UTC+01:00) Brussels, Copenhagen, Madrid, Paris

Record Tracking

Status: Original
8/25/2022 12:18:09 PM
Holder: Morgane Gilles
morgane.gilles@biotrial.com
Location: DocuSign

Signer Events	Signature	Timestamp
David JEGOU david.jegou@pierre-fabre.com Pierre Fabre Security Level: Email, Account Authentication (Required)	David JEGOU Signature Adoption: Pre-selected Style Signature ID: 3540A39B-E287-436E-8399-A578101A44DA Using IP Address: 213.190.76.192 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): J'approuve ce document	Sent: 8/25/2022 12:24:09 PM Viewed: 8/25/2022 4:44:13 PM Signed: 8/25/2022 4:45:29 PM
Electronic Record and Signature Disclosure: Accepted: 8/31/2021 5:43:36 PM ID: e0125ab9-c308-414f-865c-785d6fab2462		
Eric Chetaille eric.chetaille@pierre-fabre.com Directeur de l'Unité d'Innovation en Oncologie Security Level: Email, Account Authentication (Required)	Eric Chetaille Signature Adoption: Pre-selected Style Signature ID: D78024F3-03A9-4D72-9B81-7924B95EC49F Using IP Address: 90.3.51.171 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): J'approuve ce document	Sent: 8/25/2022 12:24:09 PM Viewed: 8/25/2022 1:18:11 PM Signed: 8/25/2022 4:38:13 PM
Electronic Record and Signature Disclosure: Accepted: 6/8/2021 3:59:00 PM ID: fefcc40e-d4ba-46cf-8119-7f13f74841ee		

Signer Events	Signature	Timestamp
Eric Didier eric.didier@pierre-fabre.com Directeur du Département Pharmacocinétique Pierre Fabre Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 4D03DFDA-E083-4C1A-9F22-DAA7925C35E8 Using IP Address: 213.190.76.192 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): J'approuve ce document	Sent: 8/25/2022 12:24:11 PM Resent: 8/29/2022 3:20:27 PM Viewed: 8/29/2022 4:23:47 PM Signed: 8/29/2022 4:24:24 PM
Electronic Record and Signature Disclosure: Accepted: 9/1/2021 9:34:18 AM ID: d8b03761-30df-4845-b2e6-c1c1b0bf93d5		
Julien Pages julien.pages@biotrial.com Pharmacokineticist Security Level: Email, Account Authentication (Required)	Julien Pages Signature Adoption: Pre-selected Style Signature ID: EF9660E1-D5F3-49CF-8C9F-39DFE7CE4C3F Using IP Address: 92.162.196.108 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 8/25/2022 12:24:10 PM Viewed: 8/29/2022 3:19:02 PM Signed: 8/29/2022 3:19:49 PM
Electronic Record and Signature Disclosure: Accepted: 1/10/2022 5:19:35 PM ID: d1599a58-53f1-4cb7-a342-fc2ee263b3ee		
Laurence Del Frari laurence.del.frari@pierre-fabre.com Pierre Fabre Security Level: Email, Account Authentication (Required)	 Signature Adoption: Uploaded Signature Image Signature ID: 158FFE47-CF78-45F4-A968-FFD6BC4B5002 Using IP Address: 213.190.76.192 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): J'ai examiné ce document	Sent: 8/25/2022 12:24:10 PM Resent: 8/29/2022 3:20:27 PM Viewed: 8/29/2022 3:21:42 PM Signed: 8/29/2022 3:23:47 PM
Electronic Record and Signature Disclosure: Accepted: 8/25/2022 5:11:20 PM ID: a0deec80-b042-472c-b993-fc3429db1e87		

Signer Events	Signature	Timestamp
Morgane Gilles morgane.gilles@biotrial.com Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: DBB424D2-11D8-47DC-8F1F-B5EE5062B1E5 Using IP Address: 194.250.122.241 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 8/25/2022 12:24:10 PM Viewed: 8/25/2022 12:24:25 PM Signed: 8/25/2022 12:24:47 PM
Electronic Record and Signature Disclosure: Accepted: 2/26/2021 11:21:38 AM ID: bb8d561f-f71b-4aa7-b92c-fc21a2ddb193		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	8/25/2022 12:24:11 PM
Certified Delivered	Security Checked	8/25/2022 12:24:25 PM
Signing Complete	Security Checked	8/25/2022 12:24:47 PM
Completed	Security Checked	8/29/2022 4:24:24 PM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, Biotrial Research (CFR Part 11 account) (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact Biotrial Research (CFR Part 11 account):

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: gavin.lewis@biotrial.com

To advise Biotrial Research (CFR Part 11 account) of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at gavin.lewis@biotrial.com and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from Biotrial Research (CFR Part 11 account)

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to gavin.lewis@biotrial.com and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with Biotrial Research (CFR Part 11 account)

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to gavin.lewis@biotrial.com and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify Biotrial Research (CFR Part 11 account) as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by Biotrial Research (CFR Part 11 account) during the course of your relationship with Biotrial Research (CFR Part 11 account).