PIERRE FABRE MEDICAMENT

Les Cauquillous
81500 Lavaur FRANCE
Represented by: Institut de Recherche Pierre Fabre

EudraCT N°: 2022-000610-34

Clinical Study Protocol N° W00074CI103

Biotrial Code: 1PF74

A randomized, single-center, open-label, single dose, two-period, crossover pivotal bioequivalence study comparing binimetinib 3 x 15 mg and 45 mg tablets in healthy participants
Short title: Bioequivalence binimetinib 3 x 15 mg and 45 mg formulations

Investigational Medicinal Product Code:	Binimetinib
Development Phase:	I
Principal Investigator:	**Sponsor:**
Marina Klein, MD	Pierre Fabre Médicament
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Version 2.0	Date: 26 OCT 2022

Protocol Approval Form

The protocol entitled "A randomized, single-center, open-label, single dose, two-period, crossover pivotal bioequivalence study comparing binimetinib 3 x15 mg and 45 mg tablets in healthy participants", version 2.0 dated 26 / OCT / 2022 has been approved for submission to the French Ethics Committee and regulatory authorities (CPP and ANSM) by:

Sponsor's Representative:

Date:
26-oct.-2022 | 2:29 PM CEST

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Eric Chetaille
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Eric Chetaille, MD

Principal Investigator's Approval

I, the undersigned, have examined this protocol and agree to conduct this trial according to this protocol, to comply with its requirements, subject to ethical and safety considerations, as set out in this protocol, the Declaration of Helsinki 1964 (latest revision Fortaleza 2013) and all other laws and regulations on the use of investigational medicinal products.

Principal Investigator:

Date:
26-oct.-2022 | 2:28 PM CEST

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Marina Klein, MD

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1. SYNOPSIS

Name of Company: PIERRE FABRE MEDICAMENT Les Cauquillous 81500 Lavaur France Represented by: Institut de Recherche Pierre Fabre
Name of Finished Product: binimetinib (MEKTOVI®)
Name of active ingredient: binimetinib
Title of Study: A randomized, single-center, open-label, single dose, two-period, crossover pivotal bioequivalence study comparing binimetinib 3 x15 mg and 45 mg tablets in healthy participants.
Short title: Bioequivalence binimetinib 3 x 15 mg and 45 mg formulations.
Principal Investigator: Marina Klein, MD
Study center: Biotrial, 7-9 rue Jean-Louis Bertrand, CS 34246, 35042 Rennes Cedex, France.
Publication (reference): NA
Clinical Phase: Phase I
Rationale: The currently commercially available MEKTOVI® (binimetinib) 15 mg tablets are provided as immediate release film-coated tablets for oral administration. For the treatment of adult patients with unresectable or metastatic melanoma with virus-induced rapidly accelerated fibrosarcoma murine sarcoma viral oncogene homolog B (BRAF) V600 mutation, the recommended dosing regimen is 45 mg twice daily (*bis in die*, BID). No food effect with the commercial formulation of 15 mg was demonstrated. In order to reduce the patient's burden, a new strength tablet containing 45 mg of binimetinib as active ingredient is being developed. As a result, the number of binimetinib tablets to be taken by the patients will be reduced from 6 tablets (6 x 15 mg) to 2 tablets (2 x 45 mg) per day. Binimetinib is a Class 4 compound in the Biopharmaceutics Classification System, therefore changes in the formulation require a bioequivalence (BE) study in case of post-approval changes. Given that binimetinib did not reveal any relevant signal of genotoxic or mutagenic risk in preclinical studies (binimetinib Investigator's Brochure latest version), with an acceptable safety profile following single oral dose administration up to 45 mg, this study will be performed in healthy participants, a population in which extrinsic factors influencing the pharmacokinetics (PK) are expected to be minimal.

Objectives and associated endpoints/estimands:

	Objectives	Endpoints
Primary	To demonstrate the bioequivalence of binimetinib 45 mg tablet Test formulation in comparison to 3 x 15 mg tablet Reference formulation in healthy participants under fasted conditions.	Plasma concentrations of binimetinib and corresponding non-compartmental derived PK parameters [area under the plasma concentration-time curve (AUC) from time of administration to last observed plasma concentration (AUC_{last}), AUC from time of administration to infinity (AUC_{inf}), maximum observed plasma concentration (C_{max}), AUC Test (T)/Reference (R) ratios].
Secondary	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.	• Secondary PK parameters of binimetinib: Time to reach Cmax (Tmax) and terminal half-life ($t_{1/2,}$ λ_z), residual area (AUC_%Extrap_obs), mean residence time (MRT). • PK parameters of AR00426032: $AUC_{last,}$ AUC_{inf}, C_{max}, T_{max}, $t_{1/2,}$ λ_z, mean residence time (MRT). • Incidence, nature and severity of treatment-emergent adverse events (TEAEs). • TEAEs leading to dose interruption or discontinuation. • Treatment-emergent serious adverse events (treatment-emergent SAEs). • Changes in clinical laboratory parameters, vital signs, electrocardiograms (ECGs), ophthalmologic examinations.

Estimands:

The primary estimands are to demonstrate the bioequivalence of binimetinib 45 mg-tablet in comparison to the currently commercialized 3 x 15 mg tablets in healthy participants under fasted conditions.

Forty (40) healthy participants will be enrolled to obtain a minimum of 36 evaluable healthy participants, who will receive within a crossover design the 2 formulations under fasted conditions.

To demonstrate the bioequivalence between the two formulations, primary PK parameters (AUC_{last}, AUC_{inf} and C_{max}) will be analyzed separately using a linear mixed effects model with the log-transformed PK parameter as the dependent variable. Point estimates and 90% confidence intervals (CIs) will be provided for the ratio of Test to Reference (45 mg formulation as Test and 3 x 15 mg formulation as Reference). Two one-sided t-tests will be used to test the ratio of Test to Reference. Bioequivalence will be declared if the 90% CI for the ratio of Test to Reference geometric means is within the range of 0.80 to 1.25 for all primary endpoints. T_{max} will be analyzed using non-parametric methods for paired data.

Design:

This will be a randomized, single-center, open-label, 2-sequence, 2-period crossover Phase I study in healthy participants. Participants will receive each treatment after a washout period.

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, administered as one tablet.

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

Thus, 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 oral route in fasted conditions.

Details of the timing of each clinical visit and the assessments to be performed at each visit are summarized in the schedule of activities (SoA).

Number of participants:

A total of 40 healthy participants will be included in the study to allow for the completion of 36 participants evaluable for PK.

Rationale for Number of Participants:

The primary objective of this study is to demonstrate bioequivalence between the test **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, μ(Test)/ μ(Reference), for the C_{max}, AUC_{last}, and AUC_{inf} 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 either ≥0.80 or ≤1.25.
For each PK parameter designated as a primary endpoint, a two one-sided t-test (TOST) [Schuirmann et.al., 1987] 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% 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 EMA guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **. 20 Jan 2010).
Based on these criteria, assuming intra participant CV (CVintra) of C_{max} to be around 25% as observed on the pilot study (W00074CI101) and a "Test/Reference" geometric mean ratio of 1.05; thirty-six healthy 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.

Duration of participation:

The duration of study participation by participant will be approximately 2 months and this will include a screening evaluation up to 21 days before the first administration, 2 treatment periods of 5 days each (including one ambulatory visit on D4 per period) with at least a 7-day wash-out period between P1D1 and P2D1, and an EOS visit 30 (±3) days after the last study treatment administration or discontinuation of the last participant.

End-of-study definition:

The study will be completed when all participants have undergone the EOS visit [i.e., 30 (± 3) days after the last study treatment administration or discontinuation].

Study products, dose and mode of administration:

Study treatment will be administered orally on D1 in the morning under fasted conditions.

Dosing: participants will fast from 10 hours before dosing until 4 hours after dosing where they will be served lunch. Dinner will be served approximately 12 hours after dosing.

Study treatment / Pharmaceutical form / Dose Strength	Dose	Mode of administration
Test (T) formulation		
Binimetinib, oral film-coated tablet, 45 mg	45 mg (1 tablet)	Oral, in fasted conditions
Reference (R) formulation		
Binimetinib, oral film-coated tablet, 15 mg	45 mg (3 tablets)	Oral, in fasted conditions

Participants will receive 2 single oral administrations of 45 mg binimetinib, separated by a washout of at least 7 days between 2 study treatment intakes.

Criteria for inclusion / exclusion:

Inclusion:

All the following inclusion criteria must be met for a participant to be eligible to be included in this study:

1. Provide a signed and dated informed consent form.
2. Healthy participant.

   Note: defined as an absence of clinically significant abnormalities and any active medical conditions, as identified by a detailed medical history, complete physical examination, vital signs, clinical laboratory tests, cardiac and ophthalmologic evaluation as assessed by the Investigator.
3. Male and female between ≥ 18 and ≤ 65 years of age (at the day of consent signature).
4. Female participants must be postmenopausal or sterilized.

   Note: due to preclinical data of teratogenicity and lack of data on human pregnancies with binimetinib, women of childbearing potential are excluded from this study.

   Women are considered postmenopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum follicle stimulating hormone (FSH) levels > 40 mIU/mL and estradiol < 20 pg/mL [except if treated with hormone replacement therapy (HRT)] or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks prior to dosing. In case of doubt on the menopausal status, the participant will not be included. In the case of oophorectomy alone, the reproductive status of the woman should be confirmed by a follow-up hormone level assessment to consider her of non-childbearing potential.
5. Men with a female partner of childbearing potential will be required to use an effective method of birth control or practice abstinence for the entire study duration, and for up to 30 days following the last dose of the study treatment.

   Note: the following birth control is recommended: condom for the male participant and an intrauterine device with spermicide or oral or implanted hormonal contraception for the female partner.
6. Body mass index (BMI) of ≥ 18.5 to < 30 kg/m^2, with body weight ≥ 50 kg and < 100 kg.
7. Vital signs within the following ranges or if out of normal ranges, considered as not clinically significant by the Investigator except for high diastolic blood pressure (BP):

   (After at least 5 minutes rest in the supine position)

   a. Supine systolic BP ≥ 90 mmHg and ≤ 140 mmHg
   b. Supine diastolic BP ≥ 50 mmHg and ≤ 90 mmHg.
   c. Supine pulse rate (PR): ≥ 45 to ≤ 100 beats per minute (bpm).
   d. Body temperature between ≥ 35.0°C and ≤ 37.5°C.
   e. Orthostatic hypotension has to be ruled out based on the following criteria after standing for 5 minutes:
      i. More than a 20 mmHg decrease in systolic BP or 10 mmHg decrease in diastolic BP.
      ii. Clinical signs/symptoms of postural hypotension (dizziness, syncope, etc.), regardless of vital signs.
8. Participants must have safety laboratory values within the normal ranges or if out of normal ranges considered as not clinically significant by the Investigator except for the following parameters:
   a. Total bilirubin ≤ upper limit of normal (ULN).
   b. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT) ≤ ULN and alkaline phosphatase (ALP) ≤1.1 X ULN.
   c. Serum creatinine within normal range, except on PID-1 and P2D-1 (≤ 1.1 X ULN).
   d. Serum amylase and lipase ≤ ULN.
   e. Fasting glucose, coagulation panel (prothrombin ratio) within normal range and activated partial thromboplastin time (aPTT) ≤ 1.1 X ULN.

      NB: It should be noted that for the parameters acceptable at ≤ 1.1 X ULN, if more than one parameter exceeds ULN, the subject will be excluded.

Criteria for inclusion / exclusion:

Inclusion (continued):

9. Able to communicate well with the Investigator and comply with the requirements of the study.
10. Participants must be willing to comply with dietary and fluid restrictions (from D-7 to 72 hours after the last study treatment administration).
11. Willing to remain in the clinical research unit as required by the protocol.
12. Covered by a health insurance system where applicable, and/or in compliance with the recommendations of the national laws in force relating to biomedical research.

Exclusion:

Participants meeting any of the following criteria will not be eligible to be included in this study:

1. Concurrent severe and/or uncontrolled medical conditions (e.g., uncontrolled diabetes, active or uncontrolled infection) that could cause unacceptable safety risks or compromise compliance with protocol.
2. Pregnant or currently breastfeeding women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.
3. A past medical history of clinically significant ECG abnormalities or a family history (grandparents, parents, and siblings) of prolonged QT interval syndrome.
4. Impaired cardiovascular function.

   Note: including any one of the following:

   a. Left ventricular ejection fraction (LVEF) < 50% or below the institutional lower limit of the normal range (whichever was higher), as determined by standard cardiac echocardiography.
   b. Inability to determine the QT interval on ECG.
   c. Complete left bundle branch block.
   d. Use of a ventricular-paced pacemaker.
   e. Congenital long QT syndrome.
   f. History of or presence of clinically significant ventricular or atrial tachyarrhythmia.
   g. Clinically significant resting bradycardia (< 45 bpm).
   h. History of clinically documented myocardial infarction.
   i. History of angina pectoris.
   j. History of known structural abnormalities (i.e., cardiomyopathy).
   k. Other clinically significant cardiovascular disease (e.g., congestive heart failure, atherosclerosis, labile hypertension or uncontrolled hypertension).
   l. Abnormal ECG defined as:
      i. PR interval > 220 msec, QRS complex > 110 msec, QT interval corrected using Fridericia's method (QTcF) > 450 msec (male) and > 470 msec (female).
      ii. Any ST/T wave abnormalities.
      iii. Any atrial or ventricular arrhythmias, which are of clinical significance and may have had an impact on the safety of the participant or the study as determined by the Investigator.
      iv. Any cardiac conduction abnormalities.

Criteria for inclusion / exclusion:

Exclusion (continued):

5. History of fainting spells or orthostatic hypotension episodes.
6. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism or excretion of drugs or which may jeopardize the participant in case of participation in the study.

   Note: The Investigator should be guided by evidence of any of the following:

   a. History of inflammatory bowel syndrome, gastritis, ulcers, gastrointestinal or rectal bleeding.
   b. History of major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, cholecystectomy or bowel resection.
   c. History of, or clinical evidence of, pancreatic injury or pancreatitis.
   d. Clinical evidence of liver disease or liver injury as indicated by abnormal liver function tests such as ALT, AST, GGT, ALP, or serum bilirubin.
   e. Malabsorption syndrome.
   f. History of impaired renal function or elevated creatinine values indicating impaired renal function.
   g. Evidence of urinary tract obstruction or difficulty in voiding at screening.
7. History of autonomic dysfunction or Gilbert syndrome.
8. History of immunocompromised status, including a positive human immunodeficiency virus (HIV) infection (detected by enzyme-linked immunosorbent assay and western blot) test result.
9. A positive test for hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab), positive coronavirus disease 2019 (COVID-19) test result or other clinically relevant viral infections.
10. Significant illness within the 2 weeks prior to dosing.
11. History of clinically significant drug allergy.
12. History of atopic allergy (asthma, urticaria, and eczematous dermatitis).
13. Use of any prescription drugs or over-the-counter (OTC) medications (except acetaminophen, i.e., paracetamol) and vitamins, supplements, and herbal remedies within 2 weeks prior to dosing.
14. Participants taking acetaminophen (i.e., paracetamol) on a daily basis for more than 2 consecutive days within 1 week prior to dosing should not be enrolled.
15. History or current evidence of central serous retinopathy (CSR), retinal vein occlusion (RVO) or ophthalmopathy, as assessed by ophthalmologic examination at baseline that would be considered a risk factor for CSR/RVO [e.g., optic disc cupping, visual field defects, intraocular pressure (IOP) > 21 mmHg].
16. Subfoveal choroidal thickness outside of 40µm - 475µm range.
17. Neuromuscular disorders that were associated with elevated creatine kinase (CK) (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy).
18. Underwent major surgery ≤ 3 weeks prior to starting study treatment or who had not recovered from side effects of such a procedure.
19. Known history or ongoing alcohol abuse within 4 weeks prior to dosing of study treatment.

    Note: alcohol consumption is prohibited 1 week prior to dosing.
20. Known regular use of recreational drugs within 4 weeks prior to dosing of study treatment.

    Note: evidence of alcohol abuse/drug use (criterion No. 19 and including this criterion No. 20) as indicated by the laboratory tests conducted during screening or baseline evaluations.
21. Smoker or use of tobacco products or products containing nicotine in the last 4 weeks prior to first dosing of study treatment.

    Note: smokers will be defined as any participant who reports the use of a product containing nicotine during the preceding 30 days or has a positive urine cotinine test > 200 ng/mL.
22. Medical, psychiatric, cognitive or other conditions that may have compromised the participant's ability to understand the participant information, give informed consent, comply with the study protocol or complete the study.

Criteria for inclusion / exclusion:

Exclusion (continued):

23. Malignancy with the following exceptions:
    a. Adequately treated basal cell or squamous cell carcinoma of the skin (adequate wound healing is required prior to study entry).
    b. Primary malignancy which had been completely resected and was in complete remission for ≥ 5 years.
24. History of retinal degenerative disease.
25. Participation in any clinical investigation within 4 weeks prior to dosing or longer if required by local regulation, or within seven half-lives of the investigational agent taken (whichever is longer).
    Note: participants who had taken part in a clinical investigation receiving any form of binimetinib should have completed a 3-week washout prior to baseline.
26. Donation or loss of 400 mL or more of blood within 4 weeks prior to dosing.
27. Inability to swallow.
28. Any vaccination within 4 weeks prior to dosing.
29. Participant is under any administrative or legal supervision.

During the time window authorized for the screening visit (i.e., between 21 and 2 days before admission to the first treatment period), the Investigator may order a re-test of any parameter evaluated during the initial screening visit if he/she needs to evaluate the evolution of said parameter(s) or to confirm the value observed.

Rechecking of any parameter is to be limited to one time except when the measurement has not been obtained in accurate conditions.

Concomitant medications and study restrictions:

Concomitant treatments are not permitted throughout the study (i.e., until after the PK blood sampling and safety evaluations at time (t) 72h after the last study treatment administration), except HRT for postmenopausal women.

Participants will be requested to abstain from consumption of grapefruit, grapefruit hybrids, pomelos, pomegranate, star fruit, Seville oranges and charbroiled meats for 7 days (D-7) prior to the first dosing and throughout the study (i.e., up to t72h after the last study treatment administration). Juices and products containing the above-mentioned fruits are also required to be avoided during this time.

Smokers (as defined in exclusion criterion No. 21) will not be included in this study. The use of tobacco products or products containing nicotine is prohibited for 4 weeks before the first dosing and throughout the study (i.e., up to t72h after the last study treatment administration).

Alcohol consumption is prohibited for 1 week before the first dosing (D-7) and throughout the study (i.e., up to t72h after the last study treatment administration).

Participants will be requested to abstain from strenuous physical activity and consumption of food and stimulating beverages containing xanthine derivatives (i.e., no coffee, tea, chocolate or cola drinks) for 48 hours prior to dosing (D-2) and throughout the study (i.e., up to t72h after the last study treatment administration).

Study Schedule:

Screening:

Participants will be screened for eligibility between 21 and 2 days before the first study treatment administration of the first period.

Written informed consent will be obtained before any study procedure is performed.

The screening will consist of verification of inclusion and exclusion criteria, demography (sex, age at screening, year of birth and ethnicity), medical history, alcohol history, smoking history, drug/alcohol/tobacco/substance usage (i.e., urine drug screen, alcohol breath test and urine cotinine test), prior medications/therapies/procedures, COVID-19 vaccination status, height and weight (to calculate BMI), complete physical examination, vital signs (supine and standing systolic and diastolic BP and PR, body temperature), visual examination, ophthalmologic examination, 12-lead ECG, standard cardiac echocardiography, HBsAg, HCV Ab and HIV tests, COVID-19 test, serum FSH and estradiol for postmenopausal women (except if treated with HRT), serum pregnancy test for all female participants, hematology, clinical chemistry, coagulation, urinalysis, assessment of concomitant medications/therapies; adverse event (AE) assessment.

Screening (continued):

During the time window authorized for the screening visit (i.e., between 21 and 2 days before admission to the first treatment period), the Investigator may order a re-test of any parameter evaluated during the initial screening visit if he/she needs to evaluate the evolution of said parameter(s) or to confirm the value observed.

Rechecking of any parameter is to be limited to one time except when the measurement has not been obtained in accurate conditions.

The results of screening must be known to the Investigator prior to the participant's admission to the first treatment period.

Treatment periods:

In each treatment period (P1 and P2), eligible participants will be admitted to the research facilities on D-1, 1 day prior to receiving the dose of study medication, and the following procedures will be performed: verification of inclusion and exclusion criteria, drug/alcohol/tobacco/substance usage (i.e., urine drug screen, alcohol breath test and urine cotinine test), prior medications/therapies/procedures (P1D-1 only), weight, complete physical examination, vital signs (supine and standing systolic and diastolic BP and PR, body temperature), visual examination, 12-lead ECG, COVID-19 test, serum pregnancy test for all female participants, hematology, clinical chemistry, coagulation, urinalysis, assessment of concomitant medications/therapies, AE assessment and sequence randomization (P1D1 only). Rechecking of any parameter is to be limited to one time except when the measurement has not been obtained in accurate conditions.

In the morning of D1, allocated treatment will be administered following at least 10 hours of fasting.

Vital signs will be assessed at pre-dose and on D2 and D4 (24 and 72h post-dose) and 12-lead ECGs will be performed at pre-dose and on D2 (24h post-dose). Complete physical examination will be performed on D2 (24h post-dose) and visual examination will be performed on D2 and D4 (24 and 72h post-dose). Hematology, clinical chemistry, coagulation and urinalysis will be performed on D2 and D3 (24 and 48h post-dose). PK blood samples will be taken at pre-dose within 15 min before treatment administration (0h), and at t +0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48 and 72h post-dose.

Concomitant medications/therapies and AEs will be assessed continuously, from when the participant first provides informed consent until the EOS visit.

Meals will be served as indicated in the schedule of assessments.

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.

Follow-up:

An EOS visit will occur 30 (± 3) days after the last study treatment administration or discontinuation. The EOS visit will cover weight, complete physical examination, vital signs (supine and standing systolic and diastolic BP and PR, body temperature), visual examination, ophthalmologic examination, 12-lead ECG, COVID-19 test, serum pregnancy test for all female participants, hematology, clinical chemistry, coagulation, urinalysis, assessment of concomitant medications/therapies, and AE assessment.

Criteria for evaluation:

Pharmacokinetic Assessments	Blood samples (4 mL) will be drawn for the assay of plasma binimetinib and its metabolite AR00426032 at the following time-points: within 15 min before treatment administration (0h), and at t+0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48 and 72h post-dose in each dosing period. The following parameters will be derived by non-compartmental analysis from the plasma binimetinib concentration-time profiles: C_{max}, T_{max}, AUC_{last}, AUC_{inf} (primary parameters); and apparent terminal elimination rate constant (λ_z), terminal elimination half-life ($t_{½}$), time of last observed plasma concentration (T_{last}), apparent total body clearance (CL/F), residual area in percentage (AUC_%Extrap_obs), apparent volume of distribution (V_z/F) and mean residence time (MRT) (secondary parameters). Additionally, the following PK parameters will be derived by non-compartmental analysis from the plasma AR00426032 concentration-time profiles: C_{max}, T_{max}, AUC_{last}, AUC_{inf}, $t_{½}$, T_{last}, λ_z, MRT. The PK parameters will be determined using Phoenix® WinNonlin® version 8.1 or higher (Certara USA, Inc., Princeton, NJ).

Safety Assessments	Safety will be evaluated from: • Clinical safety (reported AEs, complete physical examinations, weight, vital signs, visual examinations, ophthalmologic examinations, standard 12-lead ECGs). • Laboratory safety assessments (standard hematology, clinical chemistry, coagulation analyses, urinalysis and COVID-19 tests). A serum pregnancy test will be performed for all female participants at screening, on D-1 of each period and at the EOS visit. AEs will be monitored throughout the study, i.e., from when the participant first provides informed consent until the EOS visit [30 (± 3) days after the last study treatment administration or discontinuation].
Statistical methods:	Statistical analysis of clinical parameters and PK parameters will be performed under the responsibility of Biotrial. PK analysis: Plasma concentrations (binimetinib and AR00426032) will be summarized over time by formulation and corresponding listings will be prepared. Concentration-time profile plots will be prepared on linear and log-linear coordinates for each participant with both formulations on the same graph, as well as arithmetic mean (± standard deviation [SD]) with both formulations on the same graph. Binimetinib and AR00426032 PK parameters will be summarized by formulation and corresponding listings will be prepared. For binimetinib only: • Scatter plots and box whisker plots will be generated for the comparison of C_{max}, AUC_{last} and $AUC_{inf.}$ • To demonstrate the bioequivalence between the two formulations, primary PK parameters (AUC_{last}, AUC_{inf} and C_{max}) will be analyzed separately using linear mixed effects model with log-transformed PK parameter as the dependent variable, sequence, period and formulation as fixed effects and participant with sequence 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 45 mg formulation as Test). Bioequivalence will be declared if the 90% CI for the ratio of Test to Reference geometric means is within the range of 0.80 to 1.25 for all primary endpoints. • T_{max} will be analyzed using non-parametric tests for paired data. Safety Analysis All AEs and TEAEs will be described by preferred term and system organ class. TEAEs will be described by formulation and overall and all AEs will be listed. Summary descriptive statistics will be provided for other safety parameters (vital signs measurements, ECG, complete physical examination, weight, COVID-19 tests, visual examination, ophthalmologic examination, and laboratory tests).

2. SCHEDULE OF ACTIVITIES (SOA)

		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																						
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

		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**	
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																					
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		

a. At least 7 days between P1D1 and P2D1.
b. 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.
c. 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).
d. Sex, age at screening, year of birth and ethnicity.
e. Urine drug screen, alcohol breath test and urine cotinine test.
f. 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. At screening visit and D-1, 3 supine BP measurements will be performed within 5 minutes. An average for each parameter (SBP, DBP, HR) will be obtained.

g. 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.
h. Full ophthalmologic examination by ophthalmologist to be performed at screening (within 2 weeks before randomization) and EOS (within 1 week up to 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.
i. 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.
j. Within 2 weeks before randomization .
k. 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.
l. 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).
m. For all female participants, serum pregnancy tests are to be performed at screening, D-1 of each period and at the EOS visit.
n. 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.
o. 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.
p. aPTT and prothrombin ratio.
q. 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)
r. 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.
s. 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].
t. In addition, a snack will be provided in the afternoon of D1 and lunch will be provided on D2.

LIST OF ABBREVIATIONS

ACSF	Array clinical service form
ADME	Absorption, distribution, metabolism and excretion
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of specific interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé (French Drug Agency)
aPTT	Activated partial thromboplastin time
ARS	Agence Régionale de Santé (Regional Health Agency)
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC_{last}	Area under the plasma concentration-time curve from time of administration to the last observed plasma concentration
AUC_{inf}	Area under the plasma concentration-time curve from time of administration to infinity
B	Breakfast
BE	Bioequivalence
BID	Twice daily (*bis in die*)
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
BRAF	Virus-induced rapidly accelerated fibrosarcoma murine sarcoma viral oncogene homolog B
°C	Degree Celsius
CDER	Food and Drug Administration Center for Drug Evaluation and Research
CI	Confidence interval
CK	Creatine kinase
CL/F	Apparent total body clearance
C_{max}	Maximum observed plasma concentration
COVID-19	Coronavirus disease 2019
CPMP	Committee for Proprietary Medicinal Products
CPP	Comité de Protection des Personnes (Independent Ethics Committee)

CRA	Clinical research associate
CSR	Central serous retinopathy; or Clinical study report
CTD	Clinical Trial Document
CVintra	Intra-individual variations
CYP	Cytochrome P450
D	Day
Di	Dinner
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
e.g.	*Exempli gratia* (for example)
EMA	European Medicines Agency
EOS	End-of-study
ERK	Extracellular signal-regulated kinase
etc.	*Et cetera* (and the rest)
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GLP	Good Laboratory Practice
hCG	Human chorionic gonadotropin
H	Hour
HBs Ag	Hepatitis B surface antigen
HCV Ab	Hepatitis C virus antibody
HIV	Human immunodeficiency virus
HR	Heart rate
HRT	Hormone replacement therapy
ICF	Informed consent form
ICH	International Council on Harmonization
i.e.	*Id est* (that is)
IEC	Independent Ethics Committee
IOP	Intraocular pressure
IRPF	Institut de Recherche Pierre Fabre
IV	Intravenous

K2EDTA	Dipotassium ethylenediaminetetraacetic acid
kg	Kilogram
L	Liter
LLOQ	Below the lower limit of quantification
Lu	Lunch
LVEF	Left ventricular ejection fraction
λ_z	Apparent terminal elimination rate constant
m^2	Square meter
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase kinase
mg	Milligram
min	Minute
mIU	Milli-international unit
mL	Milliliter
mmHg	Millimeter of mercury
MRT	Mean residence time
msec	Millisecond
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NCSF	Novartis clinical service form
NCS	Not clinically significant
ng	Nanogram
NOAEL	No observed adverse effect level
OTC	Over-the-counter
P	Period
P3-MI	Phase 3-market image
PCR	Polymerase chain reaction
PCSA	Potentially clinically significant abnormal(ity)
pg	Picogram
PK	Pharmacokinetics
PR	Pulse rate
QTcF	QT interval corrected using Fridericia's method
R	Reference
RAF	Rapidly accelerated fibrosarcoma
RAS	Rat sarcoma virus

RBC	Red blood cell (erythrocyte)
RVO	Retinal vein occlusion
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SEM	Standard error of the mean
SoA	Schedule of activities
SUSAR	Suspected unexpected serious adverse reaction
t	Time
T	Test
$t_{1/2}$	Terminal elimination half-life
T_{last}	Time of last observed plasma concentration
T_{max}	Time to reach C_{max} (time at peak plasma level)
TEAE	Treatment-emergent adverse event
TOST	Two one-sided t-test
UGT1A1	Uridine diphosphate glucuronosyltransferase 1 family, polypeptide A1
ULN	Upper limit of normal range
Vz/F	Apparent volume of distribution
WOCBP	Woman of childbearing potential
WHO	World Health Organization
WMA	World Medical Association

3. INTRODUCTION

3.1. Study Rationale

The current commercially available MEKTOVI® (binimetinib) 15 mg tablets are provided as immediate release film-coated tablets for oral administration. For the treatment of adult patients with unresectable or metastatic melanoma with virus-induced rapidly accelerated fibrosarcoma murine sarcoma viral oncogene homolog B (BRAF) V600 mutation, the recommended dosing regimen is 45 mg twice daily (*bis in die*, BID). No food effect with the commercial formulation of 15 mg was demonstrated.

In order to reduce the patient's burden, a new strength tablet containing 45 mg of binimetinib as active ingredient is being developed. As a result, the number of binimetinib tablets to be taken by the patients will be reduced from 6 tablets (6 x 15 mg) to 2 tablets (2 x 45 mg) per day.

Binimetinib is a Class 4 compound in the Biopharmaceutics Classification System, therefore changes in the formulation require a bioequivalence (BE) study in case of post-approval changes.

Given that binimetinib did not reveal any relevant signal of genotoxic or mutagenic risk in preclinical studies, with an acceptable safety profile following single oral dose administration up to 45 mg (binimetinib Investigator's Brochure latest version [1]), this study will be performed in healthy participants, a population in which extrinsic factors influencing the pharmacokinetics (PK) are expected to be at a minimum.

3.2. Introduction

3.2.1. Background

Binimetinib is an orally bioavailable, selective and potent mitogen-activated protein kinase kinase (MEK) 1 and MEK 2 inhibitor. As a MEK inhibitor, this compound has the potential to benefit participants with advanced cancers by inhibiting the oncogene rat sarcoma (RAS) / rapidly accelerated fibrosarcoma (RAF) / MEK / extracellular signal-regulated kinase (ERK) pathway. Binimetinib has previously been examined in the treatment of rheumatoid arthritis based on the role of the RAS/RAF/MEK/ERK pathway in inflammatory processes.

3.2.2. Pharmacology

Binimetinib in combination with encorafenib is approved in Europe for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. In addition, binimetinib in combination with encorafenib and cetuximab is approved in Japan for the treatment of unresectable advanced or recurrent colorectal cancer with BRAF mutations progressing after chemotherapy.

Binimetinib has been or is also currently being investigated mainly in combination with a variety of additional compounds, including encorafenib, paclitaxel and inhibitors of phosphoinositide 3-kinase, RAF, epidermal growth factor receptor, protein kinase C, cyclin-dependent kinase 4/6 and type 1 insulin-like growth factor receptor in patients with selected advanced or metastatic solid tumors, including, among other tumors, melanoma, biliary, colorectal, and ovarian cancers. The clinical development program of binimetinib encompasses patients with selected advanced or metastatic solid tumors, including neuroblastoma RAS viral oncogene homolog- and BRAF-mutant melanoma, BRAF- and Kirsten RAS viral oncogene homolog-mutant non-small cell lung cancer, high-grade platinum-

resistant ovarian cancer, low-grade serous ovarian cancer, biliary, colorectal, and pancreatic cancers.

Numerous *in vitro* and *in vivo* studies were performed to evaluate and confirm the ability of binimetinib to affect its intended targets, MEK1/2, and produce beneficial pharmacodynamics and efficacy outcomes.

For more details, please see the Investigator's Brochure [1].

3.2.3. Non-clinical Metabolism and Pharmacokinetics

In rat and monkey absorption, distribution, metabolism and excretion (ADME) studies, with radiolabeled binimetinib administered orally as a suspension as well as intravenously (IV), the average absorption was ~50% in rat and ~50-100% in monkey. The rate of absorption was faster in the monkey ADME study [time to reach maximum observed plasma concentration (T_{max}) = 0.67h] than in the rat ADME study (T_{max} = 4.7h), although in other rat single-dose PK studies the rate of absorption has been higher (T_{max} as low as 0.33h).

Binimetinib is highly bound to plasma proteins across species (97.2% in humans), and preferentially distributes to the plasma.

The average oral bioavailability in both nonclinical ADME studies was similar to absorption, indicating a minimal first pass effect in rats and monkeys. In single-dose PK studies, oral bioavailability in preclinical species (mice, rats, dogs and monkeys) ranged from 26.7% in monkeys to 76% in rats. Overall, the area under the plasma concentration-time curve (AUC) and maximum observed plasma concentration (C_{max}) values increased in an approximately dose-proportional manner in mice, rats and monkeys.

Following single- and repeat-dose administration of binimetinib to Sprague-Dawley rats for up to 6 months, females had approximately 2-fold higher exposures than males at equivalent doses. C_{max} and AUC from time of administration to infinity (AUC_{inf}) values increased with the dose, but the increase was less than dose proportional. Cynomolgus monkeys receiving binimetinib for 28 days or 9 months showed no consistent differences in exposure between females and males. No significant changes in exposure versus day were observed.

The primary metabolites of binimetinib across species and *in vitro* systems occurred through direct glucuronidation, oxidative N-demethylation (AR00426032), and cleavage of the N-O bond of the alkyl sidechain to form an amide. In human liver microsomes and recombinant cytochrome P450s (CYPs), the major oxidative metabolite was AR00426032. *In vitro*, CYP1A2 and CYP2C19 catalyzed the formation of AR00426032.

For more details, please see the Investigator's Brochure [1].

3.2.4. Toxicology

The safety of binimetinib has been evaluated in acute and repeat-dose studies in Sprague-Dawley rats and cynomolgus monkeys in accordance with international regulatory guidelines for preclinical toxicity studies and in adherence to current Good Laboratory Practice (GLP). In general, administration of binimetinib at doses up to 100 mg/kg was tolerated in rats and up to 3 mg/kg was tolerated in monkeys in a panel of safety studies.

There was no evidence of a genotoxic potential seen in the GLP bacterial reverse mutation (Ames) test, in the *in vitro* mouse lymphoma assay or the *in vivo* mouse micronucleus study.

In the rat embryo-fetal developmental toxicity study, no binimetinib-related mortality was seen. Binimetinib was well tolerated at 10 mg/kg; gestational body weight gain and fetal body weights were significantly reduced in the 30 and 100 mg/kg dose groups and food consumption

was reduced in all dose groups. The number of ossified fetal sternebrae was significantly decreased in the 30 and 100 mg/kg dose groups. Based on the results, the no observed adverse event level (NOAEL) in rats with respect to embryo-fetal developmental abnormalities is 10 mg/kg binimetinib. In the rabbit embryo-fetal developmental toxicity study, binimetinib related-mortality was seen in the 10 and 20 mg/kg dose groups.

Based on the results, the NOAEL in rabbit with respect to embryo-fetal developmental abnormalities is 2 mg/kg binimetinib.

No fertility or multi-generational reproductive toxicology studies have been performed with binimetinib.

For more details, please see the Investigator's Brochure [1].

3.2.5. Previous Human Experience

As of 20 January 2022, a total of 3483 participants have received at least 1 dose of binimetinib, either as a single agent or in combination with other targeted agents, standard chemotherapy agents or immunomodulating agents. These participants constitute the binimetinib safety population, which includes 243 healthy participants, 17 participants with hepatic dysfunction, 6 participants with renal dysfunction, 164 participants with rheumatoid arthritis and 3053 participants with advanced cancer. For more details, please see the Investigator's Brochure [1].

ADME studies:

The PK of binimetinib is characterized by moderate to high variability, accumulation of approximately 1.5-fold, and steady state concentrations reached within 15 days. Binimetinib T_{max} tends to range from 1.5 to 2 hours. Binimetinib PK has been shown to be approximately dose-proportional from 30 mg BID to 80 mg BID (Study ARRAY-162-111 [2]).

The human ADME study (CMEK162A2102 [3]) indicated that approximately 50% of the binimetinib dose was absorbed. The primary metabolic pathways include glucuronidation [up to 61.2% via uridine diphosphate glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1)], N-dealkylation, amide hydrolysis [up to 17.8% via CYP1A2 and CYP2C19]. The excretion route was 31.7% of unchanged binimetinib in feces and 18.4% in urine. Estimated renal clearance of unchanged binimetinib was 6.3% of the total dose. The impact of UGT1A1 inhibitors or inducers has not been clinically assessed.

The active metabolite AR00426032 has been monitored in several clinical studies; the results indicate that AR00426032 is <20% of binimetinib exposure.

Based on a population PK analysis, age, body weight and gender do not have a clinically important effect on the systemic exposure of binimetinib.

Four relative bioavailability studies were carried out:

- Clinical Study ARRAY-162-104 [4] assessed the relative bioavailability of single dose 40 mg binimetinib capsules and formulated binimetinib tablets in healthy participants in a fasted state, with no statistically or clinically significant difference in binimetinib exposure observed.
- Clinical Study CMEK162A2101J [5] assessed the relative bioavailability of binimetinib Novartis clinical service form (NCSF) and Array clinical service form (ACSF) tablets following a single oral dose given as 3 × 15 mg tablets in healthy participants. The ACSF and NCSF drug product formulations are identical except that the drug substance used in

NCSF drug product was made with a slightly different process and at a different manufacturer. Binimetinib exposure was similar between the NCSF and ACSF tablets. The Phase 3-market image (P3-MI) formulation used in pivotal clinical studies is identical to the ACSF/NCSF formulation except that P3-MI drug product is coated with a slightly lower quantity of cosmetic film coat.

- Clinical Study CMEK162A2110 [6] evaluated the relative bioavailability of a binimetinib liquid formulation (crushed tablets in suspension) and 3 × 15 mg tablets following a single oral dose in healthy participants. A slightly higher peak plasma binimetinib concentration was observed following the liquid formulation, while total exposure (AUC) remained unchanged. These results indicate that binimetinib administered as a 45 mg single dose using the liquid formulation is an adequate formulation to be used in future clinical studies, including those conducted in a pediatric population.
- Clinical study W00074CI101 [7] investigated the relative bioavailability of binimetinib 3 x 15 mg and 45 mg tablets in fourteen (14) healthy participants under fasted condition. The preliminary results demonstrated that the geometric mean ratios (Test/Reference) for binimetinib C_{max}, AUC_{last} and AUC_{inf} between 0.98 and 1.05 indicated that the bioavailability of the test formulation is not different from the reference formulation. Moreover, median T_{max} values observed were not different between the 2 formulations.
  Overall, the plasma PK profiles of binimetinib appear to be similar with the new strength tablet (Test: 1 x 45 mg tablet) and the currently commercialized formulation (Reference: 3 x 15 mg tablets).
  Single oral administrations of 45 mg binimetinib, as 1 x 45 mg tablet and 3 x 15 mg tablets in a crossover design with a washout of 7 days between the 2 administrations, were safe and well tolerated for the majority of participants. One (1) out of the 14 participants presented, after receiving these single doses, an AE of moderate severity (already described and potentially expected for this class of family treatment, i.e., MEK inhibitors), considered emergent and related to IMP (retinal exudates), which resolved spontaneously without treatment and without sequelae. Overall, this pilot study has given appropriate results to design the current pivotal bioequivalence study.

Food effect and drug interaction studies:

Food-effect clinical studies have indicated that the influence of food on the PK of binimetinib is mild and not clinically relevant; therefore, binimetinib can be taken without regard to food (ARRAY-162-104 [4] and CMEK162A2103 [8]). Results from a drug interaction study with binimetinib and midazolam suggested that continuous intake of binimetinib produced no relevant CYP3A4 induction (CMEK162A2105 [9]). Binimetinib solubility *in vitro* has been shown to be pH-dependent. Results from a drug interaction study in healthy participants indicate that the extent of binimetinib exposure is not altered in the presence of the proton-pump inhibitor rabeprazole (ARRAY-162-105 [10]). *In vitro* studies also demonstrated that binimetinib is a P-glycoprotein and breast cancer resistance protein substrate, but the effects of inhibitors of these substrates on the PK of binimetinib *in vivo* are unknown.

Although encorafenib is a relatively potent reversible inhibitor of UGT1A1, when binimetinib was co-administered with encorafenib no differences in binimetinib exposure were observed clinically.

Safety:

Data collected in the nonclinical and clinical programs, as well as class effects with MEK inhibitors overall, indicate that binimetinib exposure may be associated with rash-like events, gastrointestinal events (including diarrhea, nausea and vomiting, stomatitis/mucositis), reversible elevations of creatine kinase (CK), aspartate aminotransferase (AST) and alanine aminotransferase (ALT), hemorrhage, edema, cardiac events, retinal events, and interstitial lung disease or non-infectious pneumonitis. Ocular toxic effects occurred infrequently, with blurred vision being the most frequent single ocular event (4%). The vast majority of events were grade 1-2 and either asymptomatic, managed with supportive care or improved or resolved with dose reduction or temporary interruption of binimetinib. Less frequently, ejection fraction decrease and hypertension have also been observed with binimetinib [11].

For more details, please see the Investigator's Brochure [1].

3.3. Benefit/Risk Assessment

3.3.1. Overall Risk/Benefit Assessment

The inclusion and exclusion criteria have been chosen to enable a uniform study population and to minimize possible risks due to the administration of binimetinib.

In the completed clinical studies, single doses of 45 mg/kg have been tested and well tolerated [1]. In addition, the recommended dose of binimetinib, which has had marketing authorization since September 2018, is 45 mg BID [12].

The participants in this study will receive a single dose of binimetinib as 3 x 15 mg tablets and a single dose of binimetinib as one 45 mg tablet.

The participants will not benefit from taking part in this study; the data from this study will support the development of binimetinib as a 45 mg tablet in order to reduce the burden on patients who must currently take 6 x 15 mg tablets daily.

Given that this study involves single dose administration in healthy participants, the main adverse events (AEs) that may be anticipated based on the safety profile of binimetinib are gastrointestinal events (nausea, diarrhea), nervous system disorders (headache, presyncope), dermatologic events (rash, acne) and eye events (vision blurred) [13].

Other common to very common identified risks with binimetinib mainly after repeated doses are blood and lymphatic system disorders (anemia), cardiac disorders (ejection fraction decreased, left ventricular dysfunction), eye disorders (chorioretinopathy, detachment of retinal pigment epithelium, eyelid edema, macular edema, periorbital edema, retinal detachment, retinal vein occlusion, retinopathy, serous retinal detachment, subretinal fluid, blurred vision, visual acuity reduced, visual impairment), gastrointestinal disorders (abdominal pain, diarrhea, nausea, vomiting), general disorders and administration site conditions (fatigue, peripheral edema, pyrexia, asthenia, face edema, generalized edema, edema, xerosis), investigations (AST increased, blood CK increased, ALT increased), musculoskeletal and connective tissue disorders (muscle spasms, muscular weakness, musculoskeletal pain, myalgia), nervous system disorders (dizziness, dysgeusia), respiratory, thoracic and mediastinal disorders (epistaxis, pulmonary embolism), skin and subcutaneous disorders (dermatitis acneiform, dry skin, rash, erythema, erythematous rash, macular rash, maculo-papular rash, papular rash, skin fissures), and vascular disorders (hypertension) [1]. Other potential risks are listed in the Investigator's Brochure [1]. These AEs are unlikely to occur with the administration of single doses of binimetinib.

There can be risks, special discomforts or symptoms in connection with the measures performed in this study. Specifically, these are, e.g., risks associated with blood draws or skin reactions to electrocardiogram (ECG) adhesive electrodes.

The risks resulting from blood draws are circulatory reactions that may result in changes in blood pressure (BP), dizziness, or nausea, or possibly fainting or seizure. Some blood draws will be taken using an indwelling venous cannula. This may occasionally cause local irritation such as swelling, hardening or inflammation of the vein, formation of blood clots, or bleeding into the surrounding tissue (bruising). Nerve damage may occur that may lead in rare instances to long-lasting paresthesia, impaired touch sensation and to persistent pain. In this regard motor disturbances such as impaired mobility of the affected arm may also occur. When using adhesive ECG electrodes, people with overly sensitive skin may experience itching and redness beneath the adhesive patches (electronic leads). These reactions are usually harmless and resolve once the electrode leads are removed.

The study will be carried out in a center specialized in early phase studies with experienced medical staff and adequate facilities. From admission on Day (D)-1, until discharge on D3 of each of the 2 treatment periods, the participants will be confined and under constant medical monitoring. To ensure the safety of the participants, AEs, vital signs parameters, ECG and laboratory parameters will be carefully monitored.

Participants with a known history of clinically significant drug allergies are excluded from the study, as are participants with a history or current evidence of central serious retinopathy (CSR), retinal vein occlusion (RVO) or ophthalmopathy that may be considered a risk for either of those conditions, a history of retinal disease, or a history of neuromuscular disorders associated with elevated CK.

The risks associated with this study are considered elucidated and well controlled by cautionary measures.

3.3.2. Coronavirus Disease 2019 (COVID-19) Risk Assessment

The risk of exposure to people infected with COVID-19 cannot be completely excluded, as the participants may need to be exposed to public areas (e.g., commute to the site and at the site).

Risk mitigation:

- Risk assessment by the Investigator and Sponsor before deciding to start the trial.
- Record participants' COVID-19 vaccination status at screening.
- Test for COVID-19 prior to each stay at the study site.
- Closely monitor symptoms and signs for COVID-19.
- Reduce the public exposure while ambulatory.

COVID-19 screening procedures will be performed according to Biotrial procedures as deemed necessary by the Investigator. COVID-19 tests will be performed at screening, D-1 of each period and at the end-of-study (EOS) visit.

4. OBJECTIVES, ENDPOINTS AND ESTIMANDS

Objectives	Endpoints
Primary	
• To demonstrate the bioequivalence of binimetinib 45 mg tablet Test formulation in comparison to 3 x 15 mg tablet Reference formulation in healthy participants under fasted conditions.	• Plasma concentrations of binimetinib and corresponding non-compartmental derived PK parameters [area under the plasma concentration-time curve (AUC) from time of administration to last observed plasma concentration (AUC_{last}), AUC from time of administration to infinity (AUC_{inf}), maximum observed plasma concentration (C_{max}), AUC Test (T)/Reference (R) ratios].
Secondary	
• To measure secondary PK parameters of binimetinib and PK parameters of the metabolite (AR00426032).	• Secondary PK parameters of binimetinib: Time to reach C_{max} (T_{max}) and terminal half-life ($t_{1/2}$, λ_z), residual area (AUC_%Extrap_obs), mean residence time (MRT).
• 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.	• PK parameters of AR00426032: AUC_{last}, AUC_{inf}, C_{max}, T_{max}, $t_{1/2}$, λ_z, mean residence time (MRT). • Incidence, nature and severity of treatment-emergent adverse events (TEAEs). • TEAEs leading to dose interruption or discontinuation. • Treatment-emergent serious adverse events (treatment-emergent SAEs). • Changes in clinical laboratory parameters, vital signs, electrocardiograms (ECGs), ophthalmologic examinations.

Estimands:

The primary estimands are to demonstrate the bioequivalence of binimetinib 45 mg-tablet in comparison to the currently commercialized 3 x 15 mg tablets in healthy participants under fasted conditions.

Forty (40) healthy participants will be enrolled to obtain a minimum of 36 evaluable healthy participants, who will receive within a crossover design the 2 formulations under fasted conditions.

To demonstrate the bioequivalence between the two formulations, primary PK parameters (AUC_{last}, AUC_{inf} and C_{max}) will be analyzed separately using linear mixed effects model with log-transformed PK parameter as the dependent variable. Point estimates and 90% confidence intervals (CIs) will be provided for the ratio of Test to Reference (45 mg formulation as Test

and 3 x 15 mg formulation as Reference). Two one-sided t-tests will be used to test the ratio of Test to Reference. Bioequivalence will be declared if the 90% CI for the ratio of Test to Reference geometric means is within the range of 0.80 to 1.25 for all primary endpoints. T_{max} will be analyzed using non-parametric methods for paired data.

5. STUDY DESIGN

5.1. Overall Design

This will be a randomized, single-center, open-label, 2-sequence, 2-period crossover Phase I study in healthy participants. The aim is to demonstrate the bioequivalence of binimetinib 45 mg tablets Test formulation in comparison to 3 x 15 mg tablet Reference formulation in healthy participants under fasted conditions.

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, administered as one tablet.

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

Thus, 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 oral route in fasted conditions.

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.

Details of the timing of each clinical visit and the assessments to be performed at each visit are summarized in the schedule of activities (SoA, Section 2).

5.2. Number of Participants

A total of 40 healthy participants will be included in the study to allow for the completion of 36 participants evaluable for PK.

Participants who drop out may be replaced as described in Section 8.6. Replacement participants will be assigned to the same treatment sequence as the participants they are replacing, in order to allow for the completion of 36 evaluable participants.

5.3. Number of Study Centers

The study will be performed at one investigational site in France.

5.4. End of Study Definition and Duration of Participation

The study will be completed when all participants will have undergone the end of study visit [i.e., 30 (± 3 days) after the last study treatment administration or discontinuation of the last participant].

The maximum duration of the study for a participant will be approximately 2 months between the screening visit and the EOS visit. Following the completion of the study, a 3-month exclusion period will apply to the participant before they are allowed to take part in another clinical study.

5.5. Scientific Rationale for Study Design

Binimetinib is a Class 4 compound in the Biopharmaceutics Classification System, therefore changes in the formulation require a bioequivalence (BE) study in case of post approval changes [14]. Thus, this study will be conducted as a randomized, open-label, two-period crossover design to demonstrate the bioequivalence of binimetinib 45 mg tablets Test formulation in comparison to 3 x 15 mg tablet Reference formulation in healthy participants under fasted conditions.

This study design is also standard for a BE study and is consistent with Food and Drug Administration (FDA) and EMA guidelines.

Based on the half-life of 15 mg binimetinib tablets, a washout period of at least 7 days will be used between each dosing days in the 2 treatment periods, in order to ensure that drug concentrations are below the lower limit of quantification (LLOQ) prior to the next dose administration.

Healthy participants will be included in this study. The binimetinib safety profile is well known as described in the Investigator's Brochure [1]. In addition, preliminary results of clinical study W00074CI101 (see section 3.2.5) in healthy participants has demonstrated that the 2 single oral administrations binimetinib at 45mg (as 1 x 45 mg tablet and 3 x 15 mg tablets) separated by a 7-day washout period were safe and was well tolerated.

The primary estimands are described in Section 4.

The primary objective of this study is to demonstrate bioequivalence between the test **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 study design is open-label without placebo control because the primary estimand is an objective measurement (PK), investigating the Bioequivalence, that does not require blinding or a placebo control.

5.6. Justification for Dose

For the treatment of adult patients with unresectable or metastatic melanoma with BRAF V600 mutation, the recommended dosing regimen is 45 mg BID [12]. A single dose of 45 mg, i.e., half the recommended daily dose, is appropriate with this type of study design as it provides sufficient information for the extent of absorption and will thus be investigated in the present bioequivalence study.

5.7. Identification of Source Data

Electronic data capture (EDC) via electronic case report forms (eCRFs) will be used for this study, as described in Section 10.1.1. Data will be collected on source documents and entered by the study personnel into the eCRFs in a timely manner.

6. STUDY POPULATION

Each participant must take part in the informed consent process and sign and date the informed consent form (ICF) before any procedures specified in this protocol are performed.

Nevertheless, if necessary and after agreement of the Sponsor, any measures identical to those planned in the protocol for the participants' screening that have already been performed within the protocol time window authorized for the screening examinations could be used in the study, in order to minimize the constraints on the participants.

6.1. Inclusion criteria

All the following inclusion criteria must be met for a participant to be eligible to be included in this study:

1. Provide a signed and dated ICF.
2. Healthy participant.

   Note: defined as an absence of clinically significant abnormalities and any active medical conditions, as identified by a detailed medical history, complete physical examination, vital signs, clinical laboratory tests, cardiac and ophthalmologic evaluation as assessed by the Investigator.
3. Male and female between ≥ 18 and ≤ 65 years of age (at the day of consent signature).
4. Female participants must be postmenopausal or sterilized.

   Note: due to preclinical data of teratogenicity and lack of data on human pregnancies with binimetinib, women of childbearing potential are excluded from this study.

   Women are considered postmenopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum follicle stimulating hormone (FSH) levels > 40 mIU/mL and estradiol < 20 pg/mL [except if treated with hormone replacement therapy (HRT)] or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks prior to dosing. In case of doubt on the menopausal status, the participant will not be included. In the case of oophorectomy alone, the reproductive status of the woman should be confirmed by a follow-up hormone level assessment to consider her of non-childbearing potential.
5. Men with a female partner of childbearing potential will be required to use an effective method of birth control or practice abstinence for the entire study duration and for up to 30 days following the last dose of the study treatment.

   Note: the following birth control is recommended: condom for the male participant and an intrauterine device with spermicide or oral or implanted hormonal contraception for the female partner.
6. Body mass index (BMI) of ≥ 18.5 to < 30 kg/m^2, with body weight ≥ 50 kg and < 100 kg.

7. Vital signs within the following ranges or if out of normal ranges, considered as not clinically significant by the Investigator except for high diastolic BP:

   (After at least 5 minutes rest in the supine position)

   a. Supine systolic BP ≥ 90 mmHg and ≤ 140 mmHg
   b. Supine diastolic BP ≥ 50 mmHg and ≤ 90 mmHg.
   c. Supine pulse rate (PR) ≥ 45 to ≤ 100 beats per minute (bpm).
   d. Body temperature between ≥ 35.0°C and ≤ 37.5°C.
   e. Orthostatic hypotension has to be ruled out based on the following criteria after standing for 5 minutes:
      i. More than a 20 mmHg decrease in systolic BP or 10 mmHg decrease in diastolic BP.
      ii. Clinical signs/symptoms of postural hypotension (dizziness, syncope, etc.), regardless of vital signs.

8. Participants must have safety laboratory values within the normal ranges or if out of normal ranges considered as not clinically significant by the Investigator except for the following parameters:

   a. Total bilirubin ≤ upper limit of normal (ULN).
   b. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT) ≤ ULN and alkaline phosphatase (ALP) ≤ 1.1 X ULN.
   c. Serum creatinine within normal range, except on P1D-1 and P2D-1 (≤ 1.1 X ULN).
   d. Serum amylase and lipase ≤ ULN.
   e. Fasting glucose, coagulation panel (prothrombin ratio) within normal range and activated partial thromboplastin time (aPTT) ≤ 1.1 X ULN.

NB: It should be noted that for the parameters acceptable at ≤ 1.1 X ULN, if more than one parameter exceeds ULN, the subject will be excluded.

9. Able to communicate well with the Investigator and comply with the requirements of the study.
10. Participants must be willing to comply with dietary and fluid restrictions (from D-7 to 72 hours after the last study treatment administration, see Section 6.3).
11. Willing to remain in the clinical research unit as required by the protocol.
12. Covered by a health insurance system where applicable, and/or in compliance with the recommendations of the national laws in force relating to biomedical research.

6.2. Exclusion criteria

Participants meeting any of the following criteria will not be eligible to be included in this study:

1. Concurrent severe and/or uncontrolled medical conditions (e.g., uncontrolled diabetes, active or uncontrolled infection) that could cause unacceptable safety risks or compromise compliance with protocol.

2. Pregnant or currently breastfeeding women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.
3. A past medical history of clinically significant ECG abnormalities or a family history (grandparents, parents, and siblings) of prolonged QT interval syndrome.
4. Impaired cardiovascular function.

   Note: including any one of the following:

   a. Left ventricular ejection fraction (LVEF) < 50% or below the institutional lower limit of the normal range (whichever was higher) as determined by standard cardiac echocardiography.
   b. Inability to determine the QT interval on ECG.
   c. Complete left bundle branch block.
   d. Use of a ventricular-paced pacemaker.
   e. Congenital long QT syndrome.
   f. History of or presence of clinically significant ventricular or atrial tachyarrhythmia.
   g. Clinically significant resting bradycardia (< 40 bpm).
   h. History of clinically documented myocardial infarction.
   i. History of angina pectoris.
   j. History of known structural abnormalities (i.e., cardiomyopathy).
   k. Other clinically significant cardiovascular disease (e.g., congestive heart failure, atherosclerosis, labile hypertension or uncontrolled hypertension).
   l. Abnormal ECG defined as:
      i. PR interval > 220 msec, QRS complex > 110 msec, QT interval corrected using Fridericia's method (QTcF) > 450 msec (male) and > 470 msec (female).
      ii. Any ST/T wave abnormalities.
      iii. Any atrial or ventricular arrhythmias, which are of clinical significance and may have had an impact on the safety of the participant or the study as determined by the Investigator.
      iv. Any cardiac conduction abnormalities.
5. History of fainting spells or orthostatic hypotension episodes.
6. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism or excretion of drugs or which may jeopardize the participant in case of participation in the study.

   Note: The Investigator should be guided by evidence of any of the following:

   a. History of inflammatory bowel syndrome, gastritis, ulcers, gastrointestinal or rectal bleeding.
   b. History of major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, cholecystectomy or bowel resection.

c. History of, or clinical evidence of, pancreatic injury or pancreatitis.

d. Clinical evidence of liver disease or liver injury as indicated by abnormal liver function tests such as ALT, AST, GGT, ALP, or serum bilirubin.

e. Malabsorption syndrome.

f. History of impaired renal function or elevated creatinine values indicating impaired renal function.

g. Evidence of urinary tract obstruction or difficulty in voiding at screening.

7. History of autonomic dysfunction or Gilbert syndrome.
8. History of immunocompromised status, including a positive human immunodeficiency virus (HIV) infection (enzyme-linked immunosorbent assay and western blot) test result.
9. A positive test for hepatitis B surface antigen (HBsAg) or hepatitis C virus antibody (HCV Ab) or positive COVID-19 test result or other clinically relevant viral infections.
10. Significant illness within the 2 weeks prior to dosing.
11. History of clinically significant drug allergy.
12. History of atopic allergy (asthma, urticaria, and eczematous dermatitis).
13. Use of any prescription drugs or over-the-counter (OTC) medications (except acetaminophen, i.e., paracetamol) and vitamins, supplements, and herbal remedies within 2 weeks prior to dosing.
14. Participants taking acetaminophen (i.e., paracetamol) on a daily basis for more than 2 consecutive days within 1 week prior to dosing should not be enrolled.
15. History or current evidence of central serous retinopathy (CSR), retinal vein occlusion (RVO) or ophthalmopathy as assessed by ophthalmologic examination at baseline that would be considered a risk factor for CSR/RVO [e.g., optic disc cupping, visual field defects, intraocular pressure (IOP) > 21 mmHg].
16. Subfoveal choroidal thickness outside of 40µm - 475µm range.
17. Neuromuscular disorders that were associated with elevated CK (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy).
18. Underwent major surgery ≤ 3 weeks prior to starting study treatment or who had not recovered from side effects of such a procedure.
19. Known history or ongoing alcohol abuse within 4 weeks prior to dosing of study treatment.

    Note: alcohol consumption is prohibited 1 week prior to dosing.

20. Known regular use of recreational drugs within 4 weeks prior to dosing of study treatment.

    Note: evidence of alcohol abuse/drug use (criterion No. 19 and including this criterion No. 20) as indicated by the laboratory tests conducted during screening or baseline evaluations.

21. Smoker or use of tobacco products or products containing nicotine in the last 4 weeks prior to first dosing of study treatment.

    Note: smokers will be defined as any participant who reports the use of a product containing nicotine during the preceding 30 days or has a positive urine cotinine test > 200 ng/mL.

22. Medical, psychiatric, cognitive or other conditions that may have compromised the participant's ability to understand the patient information, give informed consent, comply with the study protocol or complete the study.
23. Malignancy with the following exceptions:
    a. Adequately treated basal cell or squamous cell carcinoma of the skin (adequate wound healing is required prior to study entry).
    b. Primary malignancy which had been completely resected and was in complete remission for ≥ 5 years.
24. History of retinal degenerative disease.
25. Participation in any clinical investigation within 4 weeks prior to dosing or longer if required by local regulation, or within seven half-lives of the investigational agent taken (whichever is longer).

    Note: participants who had taken part in a clinical investigation receiving any form of binimetinib should have completed a 3-week washout prior to baseline.
26. Donation or loss of 400 mL or more of blood within 4 weeks prior to dosing.
27. Inability to swallow.
28. Any vaccination within 4 weeks prior to dosing.
29. Participant is under any administrative or legal supervision.

During the time window authorized for the screening visit (i.e., between 21 and 2 days before admission to the first treatment period), the Investigator may order a re-test of any parameter evaluated during the initial screening visit if he/she needs to evaluate the evolution of said parameter(s) or to confirm the value observed.

Rechecking of any parameter is to be limited to one time except when the measurement has not been obtained in accurate conditions.

6.3. Lifestyle restrictions

Participants will be requested to abstain from consumption of grapefruit, grapefruit hybrids, pomelos, pomegranate, star fruit, Seville oranges and charbroiled meats for 7 days (D-7) prior to the first dosing and throughout the study. Juices and products containing the above-mentioned fruits, as well as orange juice, are also required to be avoided during this time.

Smokers (as defined in exclusion criterion No. 21, see Section 6.2) will not be included in this study. The use of tobacco products or products containing nicotine is prohibited for 4 weeks before the first dosing and throughout the study (i.e., up to t72h after the last study treatment administration).

Alcohol consumption is prohibited for 1 week before the first dosing (D-7) and throughout the study.

Participants will be requested to abstain from strenuous physical activity and consumption of food and stimulating beverages containing xanthine derivatives (i.e., no coffee, tea, chocolate or cola drinks) for 48 hours prior to dosing (D-2) and throughout the study.

An overnight fast will be imposed so that no food is taken within at least 10 hours before study treatment administration. Participants will remain fasted for at least 4 hours after dosing.

For each treatment period, meals will be served in the unit: lunch at an appropriate time on D-1, dinner on D-1 ending at least 10 hours before dosing, lunch on D1 4 hours after dosing, a snack in the afternoon of D1, and dinner on D1 approximately 12 hours after dosing, and breakfast, lunch and dinner at appropriate times on D2, and breakfast on D3.

All meal times during hospitalization will be reported in the eCRF.

All meals and fluids taken after the treatment will be standardized with regards to composition and time of administration during the sampling period.

During the in-house periods, meals will be standardized and identical for all participants and all periods.

The start time and end time of the standardized dinner meal consumed and the percentage of the meal consumed on the day prior to dosing (D-1 of each period) will be documented on the eCRF.

The start time and end time of meals consumed and the percentage of the meals consumed for lunch and dinner on the dosing days (P1D1 and P2D1) will also be recorded.

Drinking of water will be allowed *ad libitum* except from 1 h before up until 2 h after dosing.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized (i.e., participants who do not meet one or more of the inclusion/exclusion criteria at screening or on P1D-1, or who are not randomized for other reasons, e.g., consent withdrawal). A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes informed consent and visit date, demography, screen failure details, eligibility criteria, and any adverse event (AE/SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once, and a complete screening assessment panel will be performed.

7. STUDY TREATMENTS

7.1. Study Treatments Administered

Table 1 provides an overall summary of the study treatment administered during the study, further information is provided in the Investigator's Brochure [1].

Table 1: Study treatments

Study Treatment Name:	**Test Formulation: Binimetinib 45 mg, film-coated tablet**	**Reference Formulation: Binimetinib film coated tablet** (MEKTOVI®) [12]
Active ingredients	Binimetinib	Binimetinib
Excipients	Tablet core: Lactose monohydrate, cellulose microcrystalline, croscarmellose sodium, magnesium stearate, silica colloidal anhydrous Film-coating (Opadry II TF-White): Polyvinyl alcohol – part hydrolyzed, macrogol 4000, talc	Tablet core: Lactose monohydrate, cellulose microcrystalline, silica colloidal anhydrous, croscarmellose sodium, magnesium stearate Film-coating (Opadry II Yellow): Polyvinyl alcohol, macrogol 3350, titanium dioxide, talc, iron oxide yellow, iron oxide black
Dosage formulation:	Film-coated tablet	Film-coated tablet
Unit dose strength/Dosage level:	45 mg / 45 mg (1 tablet)	15 mg / 45 mg (3 tablets)
Route of Administration	Oral	Oral
Dosing instructions:	Study treatments will be administered orally on D1 in the morning. Participants should be instructed to take binimetinib with approximately 240 mL of water. Participants should be instructed to swallow the tablet(s) whole and not to chew or crush them. Participants will fast from 10 hours before dosing until 4 hours after dosing where they will be served lunch. Dinner will be served approximately 12 hours after dosing.	
Packaging and Labeling	Study treatments will be provided as treatment units each comprised of 1 blister of 14 film-coated tablets of binimetinib 45 mg and 1 blister of 12 film-coated tablets of binimetinib 15 mg. Each pack and blister will be labeled as required per country requirements in local languages. Details of labeling are provided in Section 7.5.	

7.2. Method of Treatment Assignment

Each participant will be identified in the study by a participant code that will be assigned upon enrolment. Participants will be considered enrolled in the study as soon as they have signed an ICF.

The participant code will contain 8 digits, corresponding to the country number, the center number and the participant's number according to chronological order (the order in which they signed the ICF).

Screen-failed participants keep their participant number. New participants must always be allotted a new participant number.

The sequences will be randomized as follows:

- Binimetinib 1 x 45 mg tablet (T) / binimetinib 3 x 15 mg tablet (R)
- Binimetinib 3 x 15 mg tablet (R) / binimetinib 1x 45 mg tablet (T)

For each participant, the Sponsor will provide one study treatment box, identified by a study treatment code and containing 2 blisters (one per period). There will be 2 types of study treatment boxes, randomly assigned:

- Blister 1 = R + blister 2 = T.
- Blister 1 = T + blister 2 = R.

The assignment of the treatment kit numbers (101 to 152) to participants will be done in ascending order of inclusion, on D1 pre-dose in Period 1 only and will also be used for Period 2 (each kit contains the treatments for Period 1 and Period 2). This activity will be managed by a Pharmacy staff member.

The first participant included will receive the first treatment box and so on for the other participants.

Participants withdrawn from the study will retain their participant number. New participants must always be assigned a new participant number. The replacement participant will receive the replacement treatment (R101 to R152).

For example: for the participant who is assigned the treatment number 105, their replacement participant will receive the treatment number R105.

Treatment numbers and replacement treatment numbers are shown in Table 2.

Table 2: Treatment Numbers

Treatment Number	Replacement Treatment Number
101 to 152	R101 to R152

Blinding

Not applicable, as this is an open-label study.

7.3. Dose administration

The study treatments will be administered only to participants included in this study following the procedures set out in the present clinical study protocol.

Treatments will be given orally on D1 in the morning after a 10-hour overnight fast in each period. Participants should be instructed to take binimetinib with approximatively 240 mL of water. Participants should be instructed to swallow the tablet(s) whole and not to chew or crush them.

Participants will be dosed in an upright position; during the next 4 hours, they will remain predominantly in a supine position, but will be allowed to walk short distances, such as to the toilet.

Follow-up evaluation (EOS visit) will be performed D30 (±3 days) after the last study treatment administration, or discontinuation.

7.4. Dose Modification

None.

7.5. Supply, Packaging and Labeling of the investigational products

A sufficient quantity, to be defined by Biotrial, of study treatments to perform the study and to ensure retention samples requested per FDA Guidance [15] will be supplied as well as an acknowledgement of receipt form. The Institut de Recherche Pierre Fabre will provide a certificate of analysis and a batch release certificate for those batches of study treatment used in the study. As soon as the pharmacist receives delivery of the study treatments, he/she will check the contents and immediately return documents to the Investigational Medicinal Products Department of the Institut de Recherche Pierre Fabre (IRPF) and/or designee (acknowledgment of receipt, and temperature recording graph of the Temptale®) that accompanies the parcel containing study treatment, duly completed and signed. Documents included in the parcel will be kept in the Investigator's file.

The study treatments will be packed and labeled for clinical use purpose by Institut de Recherche Pierre Fabre or designee according to the European Union-Good Manufacturing Practice, including its annex 13, and all local regulations.

The study treatments will bear the following information on the labels:

Treatment unit box labeling

- Sponsor's name and address.
- Product name.
- Pharmaceutical form.
- Dosage.
- Administration route.
- Number of units.
- Batch and/or code number.
- Protocol number and EudraCT number.
- Treatment number.
- Statement "FOR CLINICAL TRIAL USE ONLY."
- Storage conditions.
- Expiry date.

Treatment unit blister labeling

- Name of the Sponsor.
- Protocol number.
- Packaging batch number.
- Treatment number.
- Expiry date as month/year (EXP: MM/YYYY).
- Dosage & concentration of the tested product.
- Period.

The Investigator, or designee, will only dispense study treatments to participants included in this study. The dispensing for each participant will be documented in the participant's eCRF.

Further details will be provided in the study-specific Pharmacy Manual.

7.6. Storage of the investigational products

Binimetinib 45 mg tablets will be stored below 25°C. For binimetinib 15 mg tablets there are no specific storage instructions. All study treatments will be stored in a secure and locked storage area with limited access, with temperature control and monitoring.

Further details will be provided in the study-specific Pharmacy Manual.

The pharmacist at Biotrial will be responsible for the correct storage and handling of the study treatments.

Deviations from the storage requirements, including any actions taken, must be documented.

7.7. Accountability, reconciliation and return of the investigational products

The Investigator must maintain a complete and current dispensing and inventory record. The Investigator is accountable for all test articles supplied by the Sponsor. The dispenser uses this information to maintain an accurate and complete dispensing and inventory record. The designated copies of the completed dispensing and inventory record will be returned to the Sponsor.

Regulatory agencies require accounting for the disposition of all investigational drugs received by each clinical site. Information on drug disposition required by law consists of the date received, date administered, quantity administered, and the participant to whom the drug was administered.

Study treatments are shipped to the investigational site as needed. Drug accounting will be reviewed by the site monitor during routine monitoring visits. Each time a dose is prepared for a participant, the following information should be recorded: the participant's study number, the total dose prepared, the number of tablets used, the number of the lot from which the dose was prepared, and the initials of the person preparing the dose.

At the completion or termination of the study, a final drug accountability review and reconciliation must be completed, and any discrepancies must be investigated and their resolution documented.

All full, partially full, and empty study treatment containers must be returned by Biotrial to the Sponsor or destroyed by Biotrial after the Monitor has performed accountability (this does not include retention samples) and after Sponsor approval and with the appropriate form.

Upon completion or termination of the study, a sample of all study supplies will be retained at the study site according to applicable regulations. Once the retention period has elapsed, any remaining unused drug will be returned to the Sponsor in the original containers, or destroyed, as directed in writing by Sponsor.

Retention samples will be collected in compliance with the current FDA guidance [15].

7.8. Recall

In case of recall of study treatments (decided by the Competent Authorities or the Sponsor), the Investigator will be immediately informed by the Sponsor.

The Investigator, in collaboration with the Sponsor representatives [Study Manager, clinical research associate (CRA)] must urgently:

- Put in quarantine all study treatments concerned by the recall.
- Stop the administration of the concerned study treatments to the participants.

The Study Manager/CRA organizes the return of the recalled products to the Investigational Medicinal Product Management Service of IRPF or designee, according to the Sponsor procedures.

7.9. Study Treatment Retention

A sufficient quantity of Binimetinib 45 mg tablets and MEKTOVI® (binimetinib 15 mg tablets) will be supplied by Sponsor to perform the study and to ensure retention samples requested per FDA Guidance [15]. The Sponsor's representative will provide a certificate of analysis for the batches of IMP used in the study.

7.10. Treatment Compliance

All doses will be administered in the clinical unit under direct supervision of the Investigator or designee.

After administration of each study treatment, a hand check and a mouth check will be performed to verify that the participant has swallowed the dose. All drug administration information will be recorded in the eCRF and in the drug accountability form.

The definition of overdoses is provided in Section 9.4.6; the definitions of medication errors, abuse and misuse are provided in Appendix 2. Overdoses, medication errors, abuse or misuse will be collected as part of study treatment dosing information and/or as a protocol violation, as required.

7.11. Prior Treatments

Reasonable efforts will be made to determine all relevant treatments [prescription drugs or OTC medications (except acetaminophen, i.e., paracetamol) and vitamins, supplements, and herbal remedies] received by the participant within 2 weeks before study treatment administration. Intake of acetaminophen (i.e., paracetamol) by the participant within 1 week before study treatment administration should also be determined. The participants' COVID-19 vaccination status at the time of the screening visit will be determined.

As indicated in Section 6.2, the intake of prescription drugs, OTC medications (except acetaminophen, i.e., paracetamol) and vitamins, supplement and herbal remedies within 2 weeks before dosing and the intake of acetaminophen, i.e., paracetamol, on a daily basis for more than 2 consecutive days within 1 week before dosing are prohibited. Any vaccination is prohibited within 4 weeks prior to dosing. In addition, participation in any clinical investigation within 4 weeks prior to dosing or longer if required by local regulations, or within seven half-lives of the investigational agent taken (whichever is longer), is prohibited, and participants who had taken part in a clinical investigation receiving any form of binimetinib should have completed a 3-week washout prior to baseline.

All relevant information must be recorded on the participant's eCRF.

7.12. Concomitant Treatments

Concomitant treatments are not permitted throughout the study (i.e., until after the PK blood sampling and safety evaluations at t72h after the last study treatment administration), except

HRT for postmenopausal women. Concomitant medications / therapies will be assessed continuously (see Section 2, SoA).

For any participant, if the use of any concomitant treatment becomes necessary (e.g., the treatment of an AE) before the end of the PK and safety evaluations at t72h after the last study treatment administration, the treatment must be recorded on the eCRF, including the reason for treatment, generic name of the drug, dosage, route, and date and time of administration. If a treatment is administered, the Sponsor's medical monitor must be promptly notified in order to assess the participant's eligibility for continuing study participation.

8. DISCONTINUATION CRITERIA AND RELATED PROCEDURES

8.1. Withdrawal criteria

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, which corresponds to the EOS visit [i.e., 30 (± 3 days) after the last study treatment administration or discontinuation]. See the SoA (Section 2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The EOS visit is not required for participants who did not receive any dose of study treatment. The participant will be permanently discontinued both from the study treatment and from the study at that time.

If a participant withdraws from the study at his/her own request, he/she will be asked to write and sign a statement of consent withdrawal.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

8.2. Stopping rules

For this study, stopping rules will be used and **any stopping rules will result in an immediate stop to dosing**. This could be a final end of dosing or a temporary halt. Restart is possible without a substantial amendment if review leads to a conclusion which is fully within predefined conditions for the relevant stopping criterion and after agreement of the French authorities. Any submitted substantial amendment (If needed to re-start the study) should include a rationale for the proposed dosing and for the continuation of the trial and details of any adjustments to the protocol including additional safety monitoring, if applicable.

Stopping rules are:

- At the individual level:
    - A ‘serious’ adverse reaction (i.e., a SAE considered at least possibly related to the study treatment administration).
    - A ‘severe’ non-serious adverse reaction (i.e., severe non-serious AE considered as, at least, possibly related to the study treatment administration).
    - Any AE assessed as related to study treatment that would lead to undue risk if dosing with study drug continued or escalated, in the judgment of the principal Investigator.
    - ECG: prolongation of QTcF to > 500 ms or of > 60 ms over baseline, drug--related.
    - Safety laboratory tests: Increase in ALT/AST ≥ 5 x ULN.
    - Safety laboratory tests: Increase in ALT/AST ≥ 3 x ULN and total bilirubin ≥ 2x ULN.

- A significant ophthalmologic abnormality related to the tested drug, which contra-indicates a second drug administration according to the principal Investigator.

- At the study level:
  - A 'serious' adverse reaction (i.e., a SAE considered at least possibly related to the study treatment administration) in one participant.
  - 'Severe' non-serious adverse reactions (i.e., severe non-serious AEs considered as, at least, possibly related to the study treatment administration) in two participants in the same cohort, independent of within or not within the same system organ class.
  - Any AE assessed as related to study drug that would lead to undue risk if dosing with study treatment continued or escalated, in the judgment of the principal Investigator.

8.3. Discontinuation of Study Treatment

Participants may voluntarily discontinue from the study treatment for any reason at any time.

If a participant decides to discontinue from study treatment, the Investigator must make every effort (e.g., telephone, email, letter) to determine the primary reason for this decision and record this information in the participant's chart and on the appropriate eCRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reasons (see Sections 8.4 and 8.5).

The Investigator should discontinue study treatment for a given participant if, on balance, he/she believes that continuation would be detrimental to the participant's well-being (see Section 8.2).

Participants who discontinue study treatment before completing all two study periods should NOT be considered withdrawn from the study and may be considered not evaluable for PK (see Section 8.6). They should return for a visit within 30 (± 3) days after the last study treatment dose, at which time all of the assessments listed for the EOS visit will be performed. The EOS visit eCRF page should be completed, giving the date and reason for not completing the study. If participants fail to return for the EOS visit for unknown reasons, every effort (e.g., telephone, email, letter) should be made to contact them as specified in Section 8.4.

See the SoA (Section 2) for data to be collected at the time of discontinuation of study treatment and follow-up and for any further evaluations that need to be completed.

8.4. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The center must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- If necessary, the participant will be replaced (see Section 8.6).

Discontinuation of the study as a whole is handled as part of Appendix 1.

8.5. Withdrawn participant data collection

The principal Investigator and/or other Investigator involved in the study will document on the termination page of the eCRF and in the participant's medical records the primary reason for the participant's withdrawal as follows:

- The participant's withdrawal. See Section 8.1.
- Lost to follow-up. See Section 8.4.
- Adverse event: if an AE occurs and is considered by the Investigator liable to threaten the health of the participant or if a serious disease occurs and necessitates the prescription of a medication incompatible with the pursuit of the study treatment, the Clinical Study Manager should immediately be informed by phone or fax or e-mail and a report explaining the discontinuation will be forwarded to him/her as soon as possible. Information related to the withdrawal due to the AE will be filled out in the eCRF.
- Protocol deviation (erroneous inclusion): the decision to maintain or not the participant in the study will be taken jointly by the Investigator and the Sponsor.
- Physician decision.
- Non-compliance with the study treatment.
- Other reasons: if none of the above-mentioned reasons are applicable, then the reason will be specified (technical problems, study/site terminated by Sponsor …).

See the SoA (Section 2) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

All withdrawals will be reported to the Sponsor.

For all drop-outs, the EOS visit (if applicable) will be arranged as described in Section 8.3, and will document the progress of their condition. In every case, the eCRF must be filled in up to the last visit performed.

8.6. Replacement of participants

Participants will be replaced on a case-by-case basis after discussion between the Sponsor and the Investigator.

- Participants who discontinue study treatment

  In case of moderate or severe AE causing the participant to withdraw, a joint decision between the Sponsor and the Investigator will be made on the appropriateness of replacing the participant or not.

The Investigator and the Sponsor will decide whether participants who withdraw from the study for any reason other than safety will be replaced.

- Participants who vomit within 4 hours after dosing

  In case of vomiting, PK sampling post-vomiting should not be done.

- Participants who require concomitant medication

  Administration of concomitant medication could lead to the replacement of the participant.

  Decisions regarding replacement of participants requiring concomitant medication have to be discussed with the Sponsor on a case-by-case basis.

- Participants for whom one or more of the planned PK samples could not be collected / tested

  Replacements will be decided case-by-case by the Sponsor who will be informed as soon as possible (at the latest within 24 hours), in order to confirm the replacement.

Replacement of participants will only be done if fewer than 36 participants are evaluable for PK.

If replacement of participants is necessary, the replacement participants will be randomized to the same treatment sequence as the participants they are replacing.

9. PROCEDURES

9.1. Investigational schedule

The schedule of assessments is described in Section 2 (SoA).

When several procedures are scheduled at the same theoretical time, the 12-lead ECG will be obtained first, followed by vital signs. The time windows allowed for the post-dose study procedures are provided in Appendix 5.

For pre-dose assessments, the time window will be 45 minutes. When no doses are planned, no time window is required.

The PK blood samples will be collected at the scheduled time within the windows noted in Section 9.3.1.

Rechecking of any parameter is to be limited to one time except when the measurement has not been obtained in accurate conditions.

9.2. Total volume of blood collected

Table 3 summarizes the number and volume of blood samples collected during the study:

Table 3: Volume of blood

Type	Sample (mL)	Number of samples	Volume (mL)
Hepatitis B surface antigen, hepatitis C antibody and HIV	3.5	1	3.5
Hematology	3	8	24
Clinical chemistry (including when applicable screening FSH and estradiol in serum)	3.5	8	28
Coagulation	2.7	8	21.6
PK blood samples	4	36	144
Pregnancy test in serum (when applicable)	3.5	4	14
Total volume (mL)			235.1 mL

Less than 450 mL of blood (which correspond to a blood donation) will be collected during the study within the 2 months of the study.

9.3. Pharmacokinetic Evaluation

9.3.1. Pharmacokinetic Assessment Methods and Timing

Blood samples of approximately 4 mL will be collected for plasma determinations of binimetinib and its metabolite AR00426032.

Serial blood samples (n=18 by period) will be collected over 72 hours: at pre-dose within 15 min before treatment administration (0h), then t+0.5h (± 1 min), 0.75h (± 1 min), 1h (± 3 min), 1.25h (± 3 min), 1.5h (± 3 min), 2h (± 5 min), 3h (± 5 min), 4h (± 5 min), 5h (± 5 min), 6h (± 5 min), 8h (± 5 min), 10 (± 5 min), 12 h (± 5 min), 24h (± 15 min), 36h (± 30 min), 48h (± 120 min) and 72h (± 120 min) post-dose.

Each blood sample will be drawn by direct venepuncture or via an intravenous catheter into K_2EDTA tubes. If an indwelling catheter is used for blood collection, approximately 1 mL will be drawn and discarded before sampling. Care must be taken to collect blood slowly without causing hemolysis.

When a sampling time is close to meal time, the sample will be collected before the meal.

The exact actual date and time of dose should be recorded in the eCRF.

The exact actual date and time of each sample collection should be recorded in the eCRF and used for the PK calculations.

If vomiting occurs within the 4 hours post dose, the exact time of the first vomiting episode must be recorded in the eCRF.

Complete information regarding blood sample collection and processing, handling and shipment will be provided in the study-specific Laboratory Manual. The primary and back-up aliquots will be stored at -70°C until shipment.

9.3.2. Sample shipment and storage

The samples will be shipped in a container filled with enough dry ice to ensure that the samples are kept frozen.

Study samples will be shipped to the bioanalytical laboratory on dry ice, as separate shipments for the primary and back-up samples.

9.3.3. Bioanalytical method

Plasma concentrations of binimetinib and its metabolite AR00426032 will be evaluated in the same run, using a validated method, which includes solid phase extraction plasma sample preparation and liquid chromatography coupled to tandem mass spectrometry.

9.3.4. Pharmacokinetic Criteria

The PK parameters will be determined using Phoenix® WinNonlin® version 8.1 or higher (Certara USA, Inc., Princeton, NJ).

The following plasma PK parameters will be calculated for binimetinib, by standard non-compartmental methods for those participants with sufficient plasma concentration data:

- C_{max}: maximum observed plasma concentration.
- T_{max}: time to reach maximum observed plasma concentration.
- T_{last}: time of last observed plasma concentration.
- $AUC_{last:}$ Area under the plasma concentration-time curve from time of administration to the last observed plasma concentration.
- AUC_{inf}: Area under the plasma concentration-time curve from time of administration to infinity.
- λ_z: apparent terminal elimination rate constant.
- $t_{1/2:}$ terminal elimination half-life calculated as follows: $t_{1/2} = Ln(2)/\lambda_z$.
- MRT: mean residence time.
- CL/F: apparent total body clearance.

- Vz/F: apparent volume of distribution.
- AUC_%Extrap_obs: residual area expressed in percentage.

Additionally, the following PK parameters will be derived by non-compartmental analysis from the plasma AR00426032 concentration-time profiles: C_{max}, T_{max}, AUC_{last}, AUC_{inf}, λ_z, $t_{1/2}$, MRT, T_{last}.

The metabolite-parent ratio based on AUC_{inf} (MRAUC), accounting for differences in molecular weights will be calculated.

The list of parameters may be adjusted, if needed, during the analysis.

9.4. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 2.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study (see Section 8).

The records of AEs must describe the nature (diagnosis, signs and symptoms), severity, date/time of onset, date/time of end, outcome and actions taken with study treatment, and relationship to study treatment (in the Investigator's opinion). It must be specified whether the event is serious or not and if yes, at least one seriousness criterion must be specified. The severity of AEs will be evaluated using the National Cancer Institute - Common Terminology Criteria for Adverse Events version 5.0 (NCI-CTCAE V5.0 [15]).

9.4.1. Time Period and Frequency for Collecting AE/SAE Information

All AEs, including SAEs, will be collected for each participant from the signing of the ICF until the EOS visit [30 (± 3) days after the last study treatment administration or discontinuation] at the time points specified in the SoA (Section 2).

Medical occurrences that begin before obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF, not the AE section.

All SAEs will be recorded and reported to the Sponsor or designee immediately (i.e., without delay) and under no circumstance should this exceed 24 hours, as indicated in Section 9.4.2. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation for the participant or after the end of the study. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be related to the study treatment or study participation, the Investigator must promptly notify the Sponsor, but not report the event in the eCRF.

9.4.2. Method of Detecting, Recording and Reporting AEs and SAEs

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, whatever the relationship to the study treatment or study procedures, or that caused the participant to discontinue the study treatment.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended (participant's spontaneous reporting) and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

The methods of recording, evaluating, and assessing causality of AE and SAE are the following.

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- For a recurrent AE that resolves and subsequently recurs, each recurrence must be recorded as a separate AE.
- For a continuous AE (i.e., unresolved between participant assessments), any change in severity (improvement or worsening) or seriousness must be recorded with the indication of the start and (if applicable) the end of the change within the same AE eCRF form.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Sponsor in lieu of completion of the AE/SAE eCRF page/SAE form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Severity

The Investigator will make an assessment of severity for each AE and SAE reported during the study, and grade them using NCI-CTCAE V5.0 [16].

For any term that is not specifically listed in the NCI-CTCAE scale, severity should be assigned a grade of 1 through 5 using the following NCI-CTCAE guidelines:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

An event is defined as 'serious' when it meets at least 1 of the predefined seriousness criteria as described in the definition of an SAE (see Appendix 2), NOT when it is rated as severe.

Assessment of Causality

The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
  - Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure [1] and/or Product Information [12], for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to Pierre Fabre Corporate Vigilances Division. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Pierre Fabre Corporate Vigilances Division.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Details regarding the grading of the causal relationship of an AE/SAE with study medication are provided in Appendix 2.

Procedures for completing and transmitting SAE notification form are provided below:

SAE Reporting to Pierre Fabre via Paper SAE form

- E-mail transmission of the SAE form immediately and within 24 hours (with all the available information about the event) is the preferred method to transmit this information to the Pierre Fabre Corporate Vigilances Division.
- Contacts for SAE reporting: HQ.pharmacovigilance@pierre-fabre.com

AEs must be documented as soon and as completely as possible on the "Adverse Events" pages in the eCRF. Follow-up information must be entered as soon as available.

AEs that occur during the study should be treated by established standards of care that will protect the life and health of the participants. If such treatment constitutes a deviation from the protocol, the participants should be withdrawn from the study and the reason must be documented in the eCRF.

9.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs (as defined in Appendix 2), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.4).

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any *post-mortem* findings including histopathology.
- New or updated information will be recorded using a new SAE form.
- The Investigator will submit any updated SAE data to the Sponsor's Corporate Vigilances Division within 24 hours of receipt of the information.

9.4.4. Regulatory Reporting of Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met. Thus, all SAEs, regardless of study treatment or relationship to study treatment and occurring once the ICF has been signed, must be reported by the Investigator to the Sponsor as soon as he/she is informed of the event (no later than within 24 hours).

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Independent Ethics Committee (IEC), and Investigators.

The Sponsor will inform the French Regulatory Authority (ANSM), the IEC and the relevant Regional Health Agency (ARS) without delay of any new safety medical fact (See definition in Appendix 2) and if necessary, of the appropriate measures taken for ensuring the safety of the participants. The Sponsor will inform the ANSM of any new safety medical facts at the following address: vig-essaiscliniques@ansm.sante.fr.

All suspected unexpected serious adverse reactions (SUSARs), SAEs, and serious adverse drug reactions (SADRs) will be submitted to ANSM without delay at the following address: declarationsusars@ansm.sante.fr.

For all studies, Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure.

9.4.5. Pregnancy

Only female partners of male participants are concerned in this section, as only post-menopausal female participants will be included in this study.

Details of all pregnancies in the female partners of male participants will be collected on the Pregnancy form after the start of study treatment and until the 30 days after the last study treatment administration.

Pregnancies discovered in the period after the signature of the ICF but before any study treatment exposure are not to be reported to the Sponsor unless associated to a seriousness criterion (e.g., SAE study-protocol related procedure).

If a female partner of a male participant becomes pregnant, the participant must inform the Investigator, and both should receive counseling as to the continuation of the pregnancy.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy using the Pregnancy form and should follow the procedures outlined below:

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the participant is in the study, during or after exposure to study treatment. This applies only to male participants who receive study treatment.
- The Investigator will record pregnancy occurrence on the Pregnancy form and submit it to the Sponsor within 24 hours of learning of pregnancy.
- After obtaining the necessary signed ICF to collect pregnancy data from the pregnant female partner of a male study participant directly (required within 72 hours), additional pregnancy information will be submitted to the Sponsor on a new Pregnancy form.
- The pregnant female will be followed until the completion/termination of the pregnancy. Information on the status of the mother and the neonate will be forwarded to the Sponsor using the Pregnancy form. The outcome of the pregnancy and the impact on the baby's health will be followed as long as it is needed. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or stillbirth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy-related SAE considered related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 9.4.2. While the Investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Pregnancy Reporting to Pierre Fabre via paper Pregnancy form

- E-mail transmission of the pregnancy form, within 24 hours, is the preferred method to transmit this information to the Pierre Fabre Corporate Vigilances Division.
- Contacts for pregnancy reporting: HQ.pharmacovigilance@pierre-fabre.com.

9.4.6. Overdose

For this study, any dose of binimetinib greater than 45 mg within a 24-hour time period will be considered an overdose. The Sponsor does not recommend specific treatment for an overdose (see Investigator's Brochure [1]).

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until binimetinib can no longer be detected systemically (at least 3 days). In the absence of seriousness criteria, the overdoses, and associated AEs if any, are reported only on the AE form of the eCRF. **If the definition** of seriousness criteria **is met**, the SAE reporting form must be also completed and transmitted to the Sponsor.
3. Document the quantity of the excess dose as well as the duration of the overdose in the AE form of the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

9.4.7. Medication errors

In the absence of seriousness criteria, medication errors, and associated AEs if any, are reported only on the AE form of the eCRF.

If the definition of seriousness criteria is met, the SAE Notification form must also be completed and transmitted to the Sponsor.

- E-mail transmission of the SAE form immediately and within 24 hours (with all the available information about the event) is the preferred method to transmit this information to the Pierre Fabre Corporate Vigilances Division.
- Contacts for SAE reporting: HQ.pharmacovigilance@pierre-fabre.com

9.5. Safety Assessment

Rechecking of any parameter is to be limited to one time except when the measurement has not been obtained in accurate conditions.

9.5.1. Physical Examination

The timing of the complete physical examinations, body weight and height and BMI is provided in Section 2 (SoA). BMI is calculated from the participants' height and weight.

The physical examinations will be performed by the Investigator or his/her representatives.

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, dermatological and neurological, musculoskeletal in addition to head, eyes, ears, nose, throat, neck and lymph nodes systems. Height and weight will also be measured and recorded. The physical examination will NOT include pelvic, rectal or breast examinations.

Further examination of other body systems may be performed in case of evocative symptoms at the Investigator's discretion.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Any abnormality identified at baseline should be recorded as medical history.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in the participant's notes. New or worsened clinically significant abnormalities should be recorded as AEs on the AE eCRF.

9.5.2. Visual and Ophthalmological Examinations

9.5.2.1. Visual Assessment

Visual assessment (general inspection of the eyes, examination of motility and alignment, any visual disturbances such as blurred vision or loss of vision) will be performed on site by the Investigator.

The timing of the assessments is summarized in Section 2 (SoA).

9.5.2.2. Ophthalmologic Examination

The full ophthalmologic examination will be performed by an ophthalmologist and will include best corrected visual acuity for distance testing, optical coherence tomography and/or fluorescein angiography, slit lamp examination, IOP and fundoscopy with attention to retinal abnormalities.

The timing of the assessments is summarized in Section 2 (SoA).

9.5.3. Vital Signs

9.5.3.1. Parameters

Measured parameters: Supine and standing systolic BP, diastolic BP and PR, body temperature.

9.5.3.2. Method of Assessment

Qualified staff members will perform BP measurements. If possible, BP measurements will be taken from the same arm (opposite the arm that is used for blood sample collection) by an automated BP monitor using the oscillometric method (e.g., Dinamap®). If there is a clinically important change in BP from the previous recording, 1 additional measurement will be taken to confirm the change.

BP and PR will be measured using an automatic device for each participant, after at least 5 minutes at rest in the supine position and after standing for 5 minutes. Body temperature will be measured using an appropriate thermometer.

The timing of the assessments is summarized in Section 2 (SoA).

9.5.4. Standard 12-lead ECG

9.5.4.1. Parameters

- Measured parameters: heart rate (HR), PR interval, QRS duration, QRS axis, QT interval.
- Derived parameters: one correction of the QT interval will be investigated: QTcF.
- Observations and comments on the quality of the trace if needed, on normality or abnormality.

9.5.4.2. Method of Assessment

The timing of the assessments is summarized in Section 2 (SoA).

The measurements will consist of triplicate 12-lead digital ECGs (conducted within approximately 5 to 10 minutes total time). ECGs should be performed before blood collection at equivalent nominal time points.

Participants must rest in the supine position for at least 5 minutes before the ECG recording is started. The ECG may be recorded during the period of rest required before the measurements of supine blood pressure and pulse rate. A qualified physician will review the ECGs promptly and any clinically important finding will be recorded in the appropriate section of the eCRF. The Investigator is responsible for providing the interpretation of all ECGs.

9.5.5. Laboratory safety parameters

9.5.5.1. Blood Safety Analysis

The following parameters will be determined:

- **Hematology:**

Erythrocytes (red blood cells, RBCs), 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.

- **Clinical chemistry:**

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.

A blood pregnancy test (hCG) will be performed at the screening visit, D-1 of each period and at the EOS visit.

For postmenopausal female participants, serum FSH and estradiol will be performed at screening to confirm postmenopausal status (except, if the participant is treated with HRT).

- **Coagulation:**

aPTT and prothrombin ratio.

9.5.5.2. Urinalysis parameters

Dipstick determination of 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.

9.5.5.3. Method of Assessment

Samples of blood will be collected in fasted conditions at the visits summarized in Section 2 (SoA).

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

All abnormal laboratory tests with values considered clinically significant during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

Samples of urine will be collected at the visits summarized in Section 2 (SoA).

9.5.5.4. Laboratory Safety Determinations

Laboratory tests will be performed by Centre Eugène Marquis, Laboratoire de Biologie, Avenue Bataille Flandres-Dunkerque, CS 44229, 35042 Rennes Cedex, France.

9.5.6. COVID-19 tests

COVID-19 antigenic tests will be performed at the time points indicated in Section 2 (SoA). A COVID-19 polymerase chain reaction (PCR) test will be performed on P1D-1, if required.

9.6. Demographic and Baseline Characteristics

9.6.1. Demography and Other Participant Information

The following information will be collected at the time points indicated in Section 2 (SoA):

- Informed consent (before any procedures specified in this protocol are performed).
- Verification of inclusion and exclusion criteria (see Sections 6.1 and 6.2, respectively).
- Demography (sex, age at screening, year of birth and ethnicity).
- Medical history.
- Alcohol history.
- Smoking history.
- Prior medications / therapies / procedures.
- COVID-19 vaccination status.
- Concomitant medications / therapies.

9.6.2. Standard Cardiac Echocardiography

A standard cardiac echocardiogram will be performed for orientation regarding cardiac function and will only assess LVEF by Simpson and presence/absence of potential abnormalities. In case of abnormal findings, those findings will be reported on the safety report completed by the cardiologist during the analysis.

The principal Investigator or designated site physician will review and sign all echocardiogram reports.

Results must be summarized in writing and classified as normal; abnormal, clinically relevant; or abnormal, not clinically relevant. Once signed, the original echocardiogram report will be retained with the participant's source documents.

The timing of the assessment is summarized in Section 2 (SoA).

9.6.3. Serology, Drug Screen, Alcohol Breath Test, Urine Cotinine Test, and Hormonology

Blood tests will be carried out to test for the presence of HBs Ag, HCV Ab and HIV.

Urinary screening will be carried out to test for benzodiazepines, cocaine, cannabinoids, morphine, amphetamines, methamphetamines and ecstasy.

Alcohol breath tests will be performed.

Urine cotinine tests will be performed (considered positive only if > 200 ng/mL due to possible exposure to secondhand smoke).

Serum FSH and estradiol tests will be performed for postmenopausal women (except if treated with HRT).

The timing of the assessments is summarized in Section 2 (SoA).

10. DATA MANAGEMENT AND STATISTICS

10.1. Data entry and management

10.1.1. Data collection

EDC via eCRFs will be used for this study. For each participant who signed an ICF, an eCRF must be completed and signed electronically by the Investigator or co-investigator. This also applies to screen failures and those participants who fail to complete the study. If a participant withdraws from the study, the reason must be noted on the eCRF. Case report forms are to be completed on an ongoing basis.

Study data will be collected by the Investigator or dedicated study personnel. Data will be collected on source documents and entered by the study personnel into the eCRFs in a timely manner.

External data (including at least PK concentrations, ECGs, and safety laboratory results), as described in the Data Management Plan, will not be captured on the eCRF. However, for ECGs and safety laboratory results, the clinical significance (significant or not significant) of the results will be entered in the eCRF.

Validated results from bioanalysis of treatment concentrations in plasma will be transmitted by the bioanalytical center to the subcontractor in charge of PK analysis. The study treatment concentrations and final PK parameters will be uploaded in the final database from an electronic data file respectively provided by the bioanalytical laboratory and the subcontractor.

All the documents must be archived for a minimum of 25 years or according to the Sponsor's procedures, whichever is longer.

10.1.2. Data coding

Biotrial will ensure coding for AEs, prior and concomitant medications and medical history in compliance with the Medical Dictionary for Regulatory Activities (MedDRA) and the World Health Organization (WHO) Drug Global Dictionary, using the most recent versions of MedDRA and WHODrug Global Dictionary. The data coding will be validated by a Physician.

10.1.3. Data validation

Biotrial will prepare the data validation document.

Biotrial will be responsible for data entry and their validation (according to the Sponsor's requirements).

Biotrial will organize a data review meeting before database lock.

The scope of data cleaning and the data to be locked will be described in the study-specific Data Management Plan (or in any other specific plan).

For the database lock at study end, all data will be entirely validated and locked and access for users will be modified to read-only to prevent any further changes to the data.

10.2. Statistical considerations

10.2.1. Sample size

The primary objective of this study is to demonstrate bioequivalence between the test **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, μ(Test)/ μ(Reference), for the C_{max}, AUC_{last}, and AUC_{inf} 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 either ≥0.80 or ≤1.25.
For each PK parameter designated as a primary endpoint, a two one-sided t-test (TOST) [17] 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% 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 EMA guideline on the investigation of bioequivalence [14].

Based on these criteria, assuming intra participant CV (CVintra) of C_{max} to be around 25% as observed on the pilot study [7] 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.

10.2.2. Statistical methods

The Statistical Analysis Plan (SAP), including the PK analysis plan, will be prepared by the Sponsor or delegates and finalized prior to the first visit of the first participant. The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. Any major modifications related to the primary endpoint definition or analysis will also be described in a protocol amendment.

The statistical analyses will be performed by the Biostatistics Unit of Biotrial Biometrics using SAS® software version 9.4 or higher (SAS Institute Inc., Cary, NC, USA).

PK data will be analyzed by Biotrial 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 variables: 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, and quartiles for PK parameters).
- Qualitative variables: sample size, absolute and relative frequencies per class.

All listings will be presented by participant (except for PK listings, by formulation and participant).

No interim analysis is planned.

Further details of the statistical analysis will be described in the SAP and agreed upon by the Sponsor.

10.2.3. Description of data sets

10.2.3.1. Definition of data sets

The Enrolled set will be defined as all participants who signed the ICF for the study.

The Screened set will be defined as all enrolled participants having successfully completed the screening period.

The Randomized set will be defined as all randomized participants.

The Safety set will be defined as all included participants having taken at least one dose of study treatment, including those who did not complete the study.

The Pharmacokinetic set will be defined as 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.

The analysis sets will be validated during the data review meeting.

10.2.3.2. Description of the sets

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, the number of participants who discontinued classified by reason of withdrawal, and the number of participants in each analysis set will be performed by sequence and overall. Corresponding individual listings will be prepared.

Listings with analysis sets, EOS status and visit dates will also be generated. A specific listing with discontinued participants will be prepared, as well as a listing of participants excluded from analysis sets.

10.2.4. Demographic and baseline characteristics

The following analysis will be performed on the Randomized set.

The participants' demographic characteristics and baseline characteristics will be summarized by sequence and overall and listed.

Tables by sequence and overall with the number of participants having at least one medical or surgical history and a corresponding listing will be prepared.

Tables by sequence and overall with number of participants having at least one previous treatment will be prepared. The same table will be prepared for concomitant treatments.

Details of drug dosing and meals will be listed.

10.2.5. Protocol deviations

A summary table of important protocol deviations by sequence and overall and the corresponding listing will be prepared.

10.2.6. Pharmacokinetic analysis

The analysis will be performed on the Pharmacokinetic Set.

Relevant PK parameters will be calculated for binimetinib and AR00426032 (see Section 9.3.4) by standard non-compartmental methods for those participants with sufficient plasma concentration data.

Plasma concentration and PK parameters

Plasma concentrations (binimetinib and AR00426032) will be summarized over time by formulation and corresponding listings will be prepared.

Concentration-time profile plots will be prepared on linear and log-linear coordinates for each participant with both formulations on the same graph, as well as arithmetic mean (±SD) with both formulations on the same graph.

Binimetinib and AR00426032 PK parameters will be summarized by formulation and corresponding listings will be prepared.

For binimetinib only:

- Scatter plots and box whisker plots will be generated for the comparison of C_{max}, AUC_{last} and AUC_{inf}.
- To demonstrate the bioequivalence between the two formulations, primary PK parameters (AUC_{last}, AUC_{inf} and C_{max}) will be analyzed separately using linear mixed effects model with log-transformed PK parameter as the dependent variable, sequence, period and formulation as fixed effects and participant with sequence 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 45 mg formulation as Test). Bioequivalence will be declared if the 90% CI for the ratio of Test to Reference geometric means is within the range of 0.80 to 1.25 for all primary endpoints.
- T_{max} will be analyzed using non-parametric tests.

10.2.7. Safety analysis

10.2.7.1. Criteria

- AEs.
- Vital signs/temperature.
- Standard 12-lead ECG.
- Hematology, blood chemistry, coagulation, urinalysis.
- Complete physical examination, weight.
- Visual examination.
- Ophthalmologic examination.
- COVID-19 tests.

10.2.7.2. Statistical methodology

Descriptive analysis of safety parameters will be performed on the Safety set.

AEs will be considered treatment-emergent if they start or worsen during the on-treatment period.

TEAEs will be summarized by system organ class and preferred term in tables with:

- The number of participants with at least one TEAE and the number of TEAEs for each formulation.

Analyses taking into account severity and drug relationship to treatment will be also carried out. All AEs will be listed.

The description will be performed by formulation and measurement time (when applicable) for measurements during the two treatment periods, and overall for measurements performed at screening and EOS visits.

For vital signs and ECG parameters, potentially clinically significant abnormalities (PCSA) will be specified in the SAP and participants with PCSA values will be summarized.

The presence of orthostatic hypotension and abnormal HR increase will be derived and the number and percentage of participants with at least one orthostatic hypotension/ abnormal HR increase will be presented by formulation and measurement time, as well as a corresponding listing.

Visual and ophthalmologic abnormalities and dermatological abnormalities will be described, and corresponding listings will be generated.

Laboratory data (hematology, biochemistry, coagulation and urinalysis) will be described. For laboratory tests covered by the NCI-CTCAE (version 5.0 [16]), 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.

For laboratory tests where grades are not defined by NCI-CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

All laboratory parameters will be listed.

11. REFERENCES

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12. APPENDICES

Appendix 1: Regulatory and legal considerations

RIGHT OF ACCESS TO DATA AND SOURCE DOCUMENTS

Monitoring

The Investigator will allow the representative of the Sponsor and the study Monitor:

- To check and to verify the site, the facilities and the material used for the study.
- To meet all members of the team involved in the study.
- To consult all the documents relevant to the study.
- To check that the eCRFs have been correctly completed.
- To have direct access to source documents for comparison of data therein with the data in the eCRFs.
- To check that AEs have been documented.
- To verify that the study is carried out in compliance with the protocol.

This study will be monitored at regular intervals, by mutual agreement of the Investigator and Monitor.

All information dealt with during these visits will be treated as strictly confidential.

The Investigator will provide the Sponsor with the following:

- Study status updates at regular intervals.
- Adequately completed eCRFs.

Audit - Inspection

The Investigator will be informed that an audit will be carried out, at the request of the Sponsor, before, during or after the study.

The Investigator will be informed that the Regulatory Authorities may also carry out an inspection. In this case, the Investigator must inform the Sponsor as soon as he receives the notification of inspection.

The Investigator must allow the representatives of the Regulatory Authorities and persons responsible for the audit to:

- Inspect the site, facilities and material used for the study.
- Meet all members of his team involved in the study.
- Have direct access to study data and source documents.
- Consult all the documents relevant to the study.

QUALITY CONTROL AND QUALITY ASSURANCE

Written procedures describing data flow, data entry or electronic capture, data cleaning and processing, and required quality control must be utilized.

Trained site personnel must conduct data entry, or data must be transferred electronically from the device into the EDC system.

The entered/electronically transferred data will be systematically checked by the clinical research organization (Biotrial) staff, either by using error messages printed from validation programs or by manual checks carried out based on database listings. Data checks for data consistency and plausibility must be defined and implemented in the EDC system. Queries are raised and resolved electronically within the EDC system.

After the completion of the data cleaning and data review process and full resolution of the data queries, the database will be locked. Any changes to the database after that time may only be made by joint written agreement between the Sponsor and the Investigator.

The Investigator must guarantee the confidentiality of the study data in the medical files by implementing security measures to prevent unauthorized access to the data and to the computer system.

STUDY SUSPENSION, TERMINATION, AND COMPLETION

The Sponsor may suspend or terminate the study or any part of the study at any time for any reason.

If the Investigator suspends or terminates the study, the Investigator will promptly inform the Sponsor and the regulatory authorities and provide them with a detailed written explanation. The Investigator will also return all test articles, test article containers, and other study materials to the Sponsor.

Upon study completion, the Investigator will provide the Sponsor and IEC with final reports and summaries as required by regulations.

ETHICS AND REGULATORY ASPECTS

Current texts

The study will be carried out in accordance with:

- The most recent recommendations of the World Medical Association (WMA).
- The International Council on Harmonization (ICH) recommendations: Good Clinical Practice (GCP) [E6 (R2)], (CPMP/ICH/135/95), 2016.
- Decree of 26th April 2006 (n°2006-477) relative to biomedical research and French law n°2002-303 of 4th March 2002 regarding participant's rights.
- French law n°78-17 of 6th January 1978 relative to Data processing, Data files and individual liberties, modified by law n°2016-41 of 26 JAN 2016, ruling n°2016-800 of 16 JUN 2016 and updated by deliberation n°2016-262.
- European directive 2005/28/CE dated 8 April 2005 (GCP) translated in French law by the Decision of 24 Nov 2006 setting the GCP for biomedical research on drugs for human use.
- Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data.
- Guidance for Industry; Handling and Retention of BA and BE samples; U.S. Department of Health and Human Services; Food and Drug Administration Center for Drug Evaluation and Research (CDER); May 2004.

Participant Information and Consent

An unconditional prerequisite for a participant's participation in the trial is his/her written informed consent. The volunteer's written informed consent to participate in the trial must be given before any trial-related activities are carried out. Nevertheless, if necessary and after agreement of the Sponsor, any measures identical to those planned in the protocol for the participants' screening that have already been performed within the timelines given by the protocol for the screening exams could be used for the protocol in order to minimize the constraints on the participants.

Participants will be verbally informed by an Investigator of all pertinent aspects of the trial: the nature of the study, its aim, its possible risks and restrictions, its duration and the fee that they will receive. The protocol will be explained during a meeting prior to the study and each participant must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time. At this meeting, an information sheet will be given to each participant. The language used in doing so must be chosen so that the information can be fully and readily understood by lay persons.

The participant should carefully read before signing and dating the informed consent form. He/She can ask all necessary questions to the Investigator. After having obtained answers to his/her satisfaction and being given sufficient time to think about their decision (up to a few days), the participant can then decide whether or not to take part in the study. The informed consent form must be signed and personally dated by both the participant and the Investigator. A copy of the signed document should be given to the participant.

On request by the Sponsor, a copy of the signed information sheets and informed consent forms will be retained in a sealed envelope by the Investigator and delivered to the Sponsor at the end of the study for archiving. Under no circumstances will this envelope be opened by the Sponsor.

It may only be examined at the request of Regulatory Authorities. A copy will be kept by the Investigator for 25 years or according to the Sponsor's procedures, whichever is longer (the third copy is given to the participant).

The completed "participant screen log" will be signed by the Investigator to attest that consent has been obtained from all participants.

Whenever important new information becomes available that may be relevant to the participant's consent, the written participant information sheet and any other written information provided to participants will be revised by the Sponsor and be submitted again to the IEC for review and favorable opinion/authorization. The agreed, revised information will be provided to each participant in the trial for signing and dating. The Investigator will explain the changes from the previous version.

Submission to the authorities

Ethics Committee (CPP)

It is the responsibility of the Sponsor to seek and obtain the favorable opinion of the CPP (Comité de Protection des Personnes, i.e., Independent Ethics Committee). This activity is delegated to Biotrial.

The present clinical trial will not be initiated until this favorable opinion is obtained.

ANSM authorization

It is the responsibility of the Sponsor to seek and obtain the ANSM (French Drug Agency) authorization for conducting the present clinical trial. This activity can be delegated to Biotrial.

The present clinical trial will not be initiated until the ANSM authorization is received.

Protocol Amendments

Any significant change (substantial modification) in the study requires a protocol amendment for authorization or for information. Concerning a protocol amendment sent to ANSM and/or IEC for authorization, an Investigator must not make any changes to the study without regulatory authorities and Sponsor approval except when necessary to eliminate apparent immediate hazards to the participants. A protocol change intended to eliminate an apparent immediate hazard to participants may be implemented immediately, but the change must then be documented in an amendment, reported to the regulatory authorities/IEC within 5 working days, and submitted in the required time frame. All protocol amendments must be reviewed and approved following the same process as the original protocol.

Regulatory requirements

In compliance with French law, approval as a site for clinical research without direct individual therapeutic benefit was granted to Jean-Marc Gandon by the Minister for Health to Biotrial Rennes center (site n°05001M).

DATA PROCESSING AND ARCHIVING OF DOCUMENTS AND DATA RELATIVE TO THE RESARCH

After the study, the Investigator will keep all information relevant to the study for 25 years, or according to the Sponsor's procedures, whichever is longer.

CONFIDENTIALITY AND AGREEMENTS

Confidentiality

Before starting the study, the Investigator must confirm receipt of adequate documentation from the Sponsor so as to be able to decide whether or not to perform the study.

All documents and information given to the Investigator by the Sponsor with respect to the study are strictly confidential.

The Investigator and his colleagues agree to use them only with the framework of this study, in order to carry out the protocol. This agreement is binding as long as the confidential information has not been disclosed to the public by the Sponsor.

The Investigator may use the technical protocol to obtain the informed consent of study participants. It must not be disclosed to other parties without the written authorization of the Sponsor.

The Investigator keeps a confidential participant identification list for the study. The Investigator must maintain source documents for each participant in the study.

Data on participants collected in eCRFs during the study will be documented in an anonymous fashion. All information in the eCRFs must be traceable to these source documents.

REPORT AND PUBLICATION

Report:

The results of the study will be reported in a Clinical Study Report. This report will be prepared by Biotrial according to existing Standard Operating Procedures (ICH Biotrial or Sponsor own format).

In compliance with the regulations, the final report will be produced within one year of completing the study and in agreement with the work order.

The final report will be provided to all Investigators having included participants in the study.

The clinical study report will be provided as Word and PDF files. Also, SAS transfer files of the data will be provided electronically. All data will be presented CTD-compliant.

Publication:

The Investigator will only use the information in the context of the study. The information cannot be used without the Sponsor's authorization. Hence, all or part of the information should only be divulged, submitted for publication or claimed for industrial proprietary act with the written consent of the Sponsor.

Appendix 2: Adverse event and serious adverse event definitions

Definitions

AE Definition
• An AE is any untoward medical occurrence from signature of informed consent in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (e.g., hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from informed consent signature, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • Any new or worsening of the AE that is assessed by the Investigator as related to the disease progression must be reported as an AE. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or severity of the condition. • New conditions detected or diagnosed after informed consent signature even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. The event of an overdose itself meets the definition of an Adverse Event and should be reported as an AE/SAE.

Events NOT Meeting the AE Definition
• Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- **Adverse Drug Reactions**

An adverse drug reaction (ADR) is a response to a medicinal product which is noxious and unintended. A causal relationship between a medicinal product and an AE is at least a reasonable possibility. An adverse reaction, in contrast to an AE, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Serious Adverse Events or Serious Adverse Drug Reactions

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- **Requires inpatient hospitalization or prolongation of existing hospitalization**
- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

  Any hospitalization, or prolongation of hospitalization due to the circumstances listed below will not be notified as a SAE to the Sponsor by the Investigator:
  - planned (as per protocol) medical/surgical procedure including 24 hours hospitalization after the first treatment administration,
  - preparation for routine health assessment/procedure (e.g., routine colonoscopy),
  - planned medical/surgical admission (planned prior to entry into study trial, appropriate documentation required),
  - administrative or social reasons (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances)

c. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

d. Is a congenital anomaly/birth defect

e. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Suspected Unexpected Serious Adverse Reaction

A SUSAR is an unexpected SAE having a reasonable possibility of a causal relationship with the study drug.

New Safety Medical Fact

According to:

- French law n°2012-300 of 12 MAR 2015 and decree n°2016-1537 of 16 NOV 2016 (modified by decree n°2017-884 of 09 MAY 2017) relative to research on human persons, articles R1123-46 to R1123-62.

A new safety medical fact is any new safety data which could lead to a new evaluation of the benefit/risk balance of the research or the study treatment or which could be sufficient to consider changes to the administration of the study treatment, the conduct of the research, the documents relating to the research, or to stop or amend the protocol or similar studies. Biotrial and the Sponsor will follow the instructions for ensuring the safety of the participants and for the submission/reporting of the new safety medical fact to the French health authorities that are defined in the Safety Management Plan.

Other Reportable Information: Certain information, although not considered an SAE, must be recorded, reported, and followed up as indicated for an SAE. This includes:

- Overdose of an investigational product as specified in this protocol (see Section 9.4.6) with or without an AE.
- Medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product, with or without an AE.

Medication Error, Misuse and Abuse

Medication error refers to an unintentional error in dispensing or administration of the study treatment not in accordance with the protocol.

Misuse is defined as any situation where the study treatment is intentionally and inappropriately used not in accordance with the protocol.

Abuse is defined as the persistent or sporadic intentional excessive use of the study treatment, which is accompanied by harmful physical or psychological effects.

Causal relationship with trial medication

The relationship of an AE to the investigational product is a clinical decision by the Investigator based on all available information at the time of the completion of the eCRF and is graded as follows:

1. **No reasonable possibility:** a reaction for which sufficient information exists to indicate that the etiology is unrelated to the study treatment; the participant did not receive the study medication or the temporal sequence of the AE onset relative to administration of the study medication is not reasonable or the event is clearly related to other factors such as the participant's clinical state, therapeutic intervention or concomitant therapy.
2. **Reasonable possibility:** a reaction that follows a reasonable temporal sequence from administration of the drug or in which the drug level has been established in body fluids or tissues, that follows a known or expected response pattern to the suspected drug, and that is confirmed by improvement on stopping or reducing the dosage of the drug, and reappearance of the reaction on repeated exposure (re-challenge).

Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study treatment, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female participant with 1 of the following:
   - Documented hysterectomy.
   - Documented bilateral salpingectomy.
   - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above (e.g., mullerian agenesis, androgen insensitivity), the Investigator's discretion should be applied to determine study entry.

Note: documentation can come from the site personnel: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
  A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement.
- Females on HRT and whose menopausal status is in doubt will not be included.

Contraceptive guidance:

The contraceptive measures to be used by the participants in this study are described in the inclusion criteria (see Section 6.1).

Collection of pregnancy information:

The collection of pregnancy information is described in Section 9.4.5.

Appendix 4: Vital Signs and Electrocardiogram (ECG) normal ranges

Normal ranges applicable for vital signs:

Parameter	Normal ranges
Systolic Blood Pressure	[90-140] mmHg
Diastolic Blood Pressure	[50-90] mmHg
Pulse Rate	[45-100] beats/min
Orthostatic hypotension: decrease in systolic BP > 20 mmHg or diastolic BP > 10 mmHg when changing from the supine to the standing position. Note: Clinical signs and symptoms of postural hypotension (dizziness, syncope, etc.,) should be also evaluated, regardless of vital signs.	
Body temperature	[35.0-37.5] ºC

Normal ranges applicable for ECG:

Parameter	Normal ranges
QRS Duration, Aggregate	≤110 msec
PR Interval, Aggregate	≤220 msec
ECG Mean Heart Rate	[45-100] beats/min
QTcF Interval, Aggregate	≤450 msec (males) ≤470 msec (females)

Appendix 5: Time windows for performing safety and pharmacokinetic (PK) assessments

Procedure	Time Point	Time Window
Safety laboratory assessments (hematology, clinical chemistry, coagulation, urinalysis)	Inferior or equal to H2	± 15 min
	]H2-H6]	± 30 min
	]H6-H24]	± 60 min
	Superior to H24	± 120 min
12-lead ECG	[5-10[min	± 2 min
	[10-15] min	± 5 min
	]15-30] min	± 10 min
	]30 min-H2]	± 15 min
	]H2-H6]	±30 min
	]H6-H24]	± 60 min
	Superior to H24	± 120 min
PK blood collection	[H0.5-H0.75]	±1 min
	[H1-H1.5]	±3 min
	[H2-H12]	±5 min
	H24	± 15 min
	H36	± 30 min
	[H48-H72]	± 120 min
Vital Signs	Inferior or equal to H2	± 15 min
	]H2-H6]	± 30 min
	]H6-H24]	± 60 min
	Superior to H24	± 120 min