25 April 2024
EMA/271149/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Mektovi

International non-proprietary name: Binimetinib

Procedure No. EMEA/H/C/004579/X/0029

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACSF	Array Clinical Service Formulation
ADME	Absorption, Distribution, Metabolism and Excretion
AE	Adverse event
AS	Active substance
AUCinf	Area under the concentration-time curve from zero to infinity
AUClast	Area under the concentration-time curve up to the last observed concentration
BA	Bioavailability
BCS	Biopharmaceutical Classification System
BE	Bioequivalence
BID	Twice daily (bis in die)
BMI	Body mass index
BRAF	serine/threonine-protein kinase B-Raf
CI	Confidence interval
Cmax	Maximum observed concentration
CQA	Critical Quality Attribute
CSR	Clinical Study Report
CV	Coefficient of variation
DoE	Design of experiments
ECG	Electrocardiogram
EDTA	Ethylene diamine tetra acetic acid
EMA	European Medicines Agency
EU	European Union
FC	Film-coated
GMR	Geometric mean ratio
HR	Heart rate
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
IS	Internal standard
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LE	Line Extension
LLOQ	Lower limit of quantification
LoQ	List of Questions
LT	Less than
MAA	Marketing Authorisation Application
MEK	Mitogen-activated protein kinase
MEK162	Binimetinib also coded W0074 or ARRAY-438162
MF	Matrix Factor
MO	Major Objection
NCI-CTCAE	National Institute Cancer-Common Terminology Criteria for Adverse Event

NCSF	Novartis Clinical Service Formulation
P3-MI	Phase 3-Market image
PCSA	Potentially clinically significant abnormal
Ph. Eur.	European Pharmacopoeia
PIC	Powder-in-capsule
PK	Pharmacokinetic(s)
PR	Pulse rate
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
QbD	Quality by design
QC	Quality control
QD	Once daily
QS-CSF	QS Pharma-Clinical Service Formulation
QTPP	Quality target product profile
R	Reference formulation
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
SD	Standard deviation
TEAE	Treatment emergent adverse event
TEAE	Treatment-emergent adverse event
Tmax	Time relative to maximum observed concentration
uHPLC	Utra-high performance liquid chromatography
UV	Ultraviolet
W00074	Binimetinib also coded MEK162 and ARRAY-438162

1. Background information on the procedure

1.1. Submission of the dossier

Pierre Fabre Medicament submitted on 8 September 2023 an extension of the marketing authorisation.

Extension application to add a new strength of 45 mg (film-coated tablets).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point (c) - Extensions of marketing authorisations

1.3. Information on Paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Janet Koenig

The application was received by the EMA on	8 September 2023
The procedure started on	28 September 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	19 December 2023

The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	25 January 2024
The MAH submitted the responses to the CHMP consolidated List of Questions on	20 February 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	27 March 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Mektovi on	25 April 2024

2. Scientific discussion

2.1. Problem statement

Binimetinib is approved in combination with encorafenib for the treatment of adult patients with unresectable or metastatic melanoma with BRAF V600 mutation.

Binimetinib is approved as a film-coated (FC) tablet at a strength of 15 mg. The recommended dose of binimetinib is 45 mg twice daily approximately 12 hours apart, when used in combination with encorafenib, corresponding to a total daily dose of 90 mg. They may be taken with or without food.

The purpose of this submission is to extend the current Marketing Authorisation (MA) to add a new oral FC tablet containing 45 mg of binimetinib. The proposed clinical use for the 45 mg film-coated tablet is for the same indications as the one approved for the 15 mg film-coated tablet. The lower tablet strength (i.e., 15 mg) will remain registered and available.

The objective of the new formulation program was to develop a new dose strength of 45 mg binimetinib to reduce the number of tablets taken per day from 6 (3 x 15 mg BID) to only two tablets (1 x 45 mg BID), and therefore to reduce the patient "tablet burden".

2.2. About the product

The European Commission granted a Marketing Authorization (MA) valid throughout the European Union for Mektovi (binimetinib) via the centralised procedure on 20/09/2018. Binimetinib is a small molecule adenosine triphosphate-uncompetitive inhibitor of the mitogen-activated protein kinases MEK1 and MEK2. ATC code: L01EE03. The current recommended dosing regimen for binimetinib is 45 mg (3 x 15 mg) twice daily (BID) in combination with encorafenib 450 mg (6 x 75 mg) once daily (QD).

2.3. Type of Application and aspects on development

This is a line extension for Mektovi to include a new strength.

To support the new formulation development, 2 biopharmaceutical clinical studies were conducted:

• A pilot study, W00074CI101: a randomised, single-center, open-label, single-dose, two-period, crossover study to investigate the relative bioavailability of binimetinib 45 mg and 3x15 mg tablets in healthy participants; 14 subjects completed the study and were evaluated for pharmacokinetics,

• A pivotal study, W00074CI103, a randomised, single-center, open-label, single-dose, two-period, crossover pivotal bioequivalence study comparing binimetinib 3x15 and 45 mg tablets in healthy participants; 37 subjects completed the study and 36 subjects completed the treatment and were included in PK analysis and evaluation of bioequivalence.

GCP compliance of the submitted studies was declared in the study reports. The applicant has listed inspections of clinical site conducted by competent European authorities. Monitoring reports from studies W00074CI101 and W00074CI103 have been provided. Site initiation, monitoring and closure reports have been included.

2.4. Quality aspects

2.4.1. Introduction

The finished product subject of this line extension (LE) is presented as film-coated tablets containing 45 mg of binimetinib. The LE concerns the addition of this new strength to the previously approved 15 mg strength.

Other ingredients for the tablet core are: lactose monohydrate, cellulose microcrystalline (E460i), silica colloidal anhydrous (E551), croscarmellose sodium (E468) and magnesium stearate (E470b).

Other ingredients for the film-coating of the 45 mg film-coated tablets are: poly(vinyl alcohol) (E1203), macrogol 4000 (E1521), calcium carbonate (E170)and talc (E533b).

The product is available in PVC/PVDC/Alu blisters as described in section 6.5 of the SmPC.

2.4.2. Active Substance

No new information on the active substance binimetinib has been provided with this line extension. The film-coated tablets, subject of this LE, contain binimetinib of the same quality as the active substance used in the approved presentations. The active substance is manufactured by the approved manufacturing sites.

The approved specification of the active substance is acceptable for manufacturing of the finished product and no additional tests are required.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is presented as an immediate release film coated tablet for oral administration. The tablets are provided in one dosage strength of 45 mg. The length of the film coated tablet is approximately 15 mm. The width of the film-coated tablet is approximately 6 mm. The tablet is ovaloid, biconvex, unscored, white to off-white, debossed with "45" on one side.

The qualitative composition of the binimetinib 45 mg film-coated tablet core is the same as binimetinib 15 mg film-coated tablet core. The quantitative composition of binimetinib 45 mg core tablet is similar to binimetinib 15 mg core tablet. A white film coating was chosen to distinguish the binimetinib 45 mg tablet from the binimetinib 15 mg tablet for which film coating is yellow.

The active substance has been described in detail. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards or EU No. 231/2012. Functionality related characteristics were defined for relevant excipients and are reflected in the excipient specifications. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. The formulation does not require the use of an overage.

A Quality by Design (QbD) approach was implemented for binimetinib 45 mg film-coated tablet. A comprehensive Quality Target Product Profile (QTPP) was defined as being bioequivalent to 3 tablets of the currently approved binimetinib 15 mg, in order to reduce the number of tablets taken per day, hence facilitating patient adherence.

The development of a standard manufacturing process by direct tabletting, followed by coating, has been described in sufficient detail. Design of experiments of the milling step, the compression step feasibility and the film coating step studies have been performed. The overall conclusion is that no parameters could be considered as critical, therefore, the risk level of all manufacturing process steps is low. No design spaces are claimed.

Based on the pilot relative bioavailability study results, a bioequivalence study was performed comparing the authorised 15 mg binimetinib tablet (x 3) and the 45 mg binimetinib tablet, as described in more details in the clinical section. The batches were found to be bioequivalent. Comparative dissolution testing of the binimetinib 45 mg tablet and binimetinib 15 mg tablet (x 3) showed similar profiles.

Taking into account the qualitative and quantitative similarity between the formulae of binimetinib 45 mg and binimetinib 15 mg tablets, the dissolution method development was adapted from the dissolution method of the binimetinib 15 mg film-coated tablet. The discriminatory power of the dissolution method has been demonstrated with respect to small changes in composition, and the dissolution method used for QC is acceptable. The dissolution specification is set according to the Reflection paper "Dissolution specification for generic oral immediate release products" (EMA/CHMP/CVMP/QWP/336031/2017).

The primary packaging is PVC/PVDC/Alu blister and is the same as the currently approved primary packaging for the binimetinib 15 mg film-coated tablet. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The finished product is manufactured by one already approved manufacturing site (Pierre Fabre Médicament Production (PFMP), France).

The manufacturing process consists of seven main steps: raw material sifting, dry blending, milling, blending and lubrication, compression, film-coating and packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process will be validated post-approval which is acceptable for a standard manufacturing process. An acceptable process validation protocol has been provided. Batches manufactured

so far demonstrate that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The critical steps have been sufficiently discussed. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance of tablet (visual), identification (UHPLC/UV), assay (UHPLC/UV), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.), water content (Ph. Eur.), degradation products (UHPLC/UV), microbiological examination (Ph. Eur.).

The specification limit for dissolution was initially not set in line with the requirements of the reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action (EMA/CHMP/CVMP/QWP/336031/2017) and a major objection was raised by the CHMP. The applicant was requested in this MO to tighten the specification in line with the provided dissolution data of the biobatch. The applicant provided additional justification for the initially proposed specification limit of 80 % (Q) after 30 min for the release and shelf-life specification in line with the biobatch performance and the MO was considered resolved.

The degradation impurities, elemental impurities and nitrosamine risk have been sufficiently discussed.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment, it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described in detail, including the principle of the method, the equipment parameters, the sample and standard preparation, the calculation formula, and a System Suitability Test. The validation data provided are in accordance with the requirements of the relevant ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 1 pilot-scale batch and 2 production-scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The applied primary packaging systems are standard for solid oral formulations. The specifications and information for the proposed container closure systems have been described sufficiently.

2.4.3.4. Stability of the product

Stability data from 1 pilot-scale batch and 2 production-scale batches of finished product stored for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested in accordance with the shelf-life specification outlined in **Error! Reference source not found.**. The analytical procedures used are stability indicating. At long term and accelerated conditions, the results remain within specification and no significant trend is observed. A slight increase in water content is observed, however, the results remain well within the specifications.

In addition, one pilot-scale batch of binimetinib 45 mg film-coated tablets was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The stability to artificial light stressing conditions was evaluated both on bulk product and on finished product in its primary packaging. Bulk binimetinib 45 mg film-coated tablets are slightly sensitive to light degradation, leading to a change in appearance (colour becomes beige) and a slight increase of a degradation product. Binimetinib 45 mg film-coated tablets stored in its primary packaging show no significant change in overall quality after exposure to the light sources. In conclusion, the primary packaging protects the finished product from light degradation.

Based on available stability data, the proposed shelf-life of 36 months with no specific storage conditions as stated in the SmPC (section 6.3) is acceptable.

2.4.3.5. Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

One quality MO was raised during the procedure, requesting the applicant to tighten the QC dissolution limit in line with the biobatch performance. The applicant resolved this MO by presenting relevant justification for keeping the limit as initially proposed.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.5. Non-clinical aspects

No new non-clinical data have been submitted as this line extension application concerns the addition of a new strength.

2.5.1. Ecotoxicity/environmental risk assessment

An ERA was not included in the dossier as there is no anticipated increase in the environmental exposure from this line extension to add a new strength of 45 mg as the daily dose remains unchanged.

2.5.2. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted, which was considered acceptable, as this line extension application concerns the addition of a new strength.

2.5.3. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 1: Tabular overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	W00074CI 101	5.3.1.2	To investigate the relative bioavailability of binimetinib 15 mg tablet (x3) and 45 mg tablet in healthy participants	A randomized, single-center, open-label, single-dose, two-period crossover study	Binimetinib tablets; Single dose 3 x 15 mg; Oral Binimetinib tablet Single dose 1 x 45 mg Oral	14	Healthy subjects	Single dose	Complete, Full
BE	W00074CI 103	5.3.1.2	To demonstrate the bioequivalence of binimetinib 45 mg tablets (Test formulation) in comparison to 15 mg tablets (x3) (Reference formulation) in healthy participants	A randomized, single-center, open-label, single-dose, two-period crossover bioequivalence study	Binimetinib tablets; Single dose 3 x 15 mg; Oral Binimetinib tablet Single dose 1 x 45 mg Oral	37	Healthy subjects	Single dose	Complete, Full
Abbreviations: ACSF = Array clinical service formulation; BA = Bioavailability; BE = Bioequivalence; NCSF = Novartis clinical service formulation; PK = Pharmacokinetic(s); QD = Once daily.									

2.5.4. Clinical pharmacology

The objective of the new formulation program was to develop a new dose strength of 45 mg binimetinib to reduce the number of tablets taken per day from 6 (3 x 15 mg BID) to only two tablets (1 x 45 mg BID), and therefore to reduce the patient "tablet burden". The qualitative composition of binimetinib 45 mg core tablet is the same as Mektovi 15 mg core tablet. A white film-coating was selected to distinguish easily the 2 dosage strengths. The quantitative composition of binimetinib 45 mg core tablet is close to Mektovi 15 mg core tablet. There was a minor difference in the film coating of binimetinib 45 mg tablet used in the 2 clinical biopharmaceutical studies (see quality part):

• In Study W00074CI101, the film coating of the binimetinib 45 mg tablet contained titanium dioxide,

• In Study W00074CI103, the titanium dioxide was replaced by calcium carbonate in the film coating of binimetinib 45 mg tablet.

2.5.4.1. Pharmacokinetics

Analytical methods

The analytical method P1593.02 is used for both studies W00074CI101 and W00074CI103. Binimetinib and its active oxidative metabolite AR00426032 have been determined in plasma. The samples were prepared by SPE and analysed by used quantitative LC-MS/MS (ESI+-MRM) method.

The pilot bioavailability study **W00074CI101** was carried out comparing 3 x15 mg binimetinib FCTs (Mektovi) to 1 x 45 mg binimetinib FCT (Mektovi new strength, but the film coating of the binimetinib 45 mg tablet contained titanium dioxide).

In this study, MEK162 and N-desmethyl MEK162 was determined in human plasma samples by LC-MS/MS method. The bioanalytical part of the studies is carried out at PPD, USA. The time of the clinical part was

from 31 AUG 2022 to 18 JAN 2023, and the first date of analysis to last date of analysis was 16 November 2021 to 23 November 2021, including re-assays and ISR analysis. (Maximum time-period between first sample collection and latest analysis: 59 days).

A total of 504 of 504 samples have been analysed in 4 sequences for determination of MEK162 and N-desmethyl MEK162 by HPLC/MS/MS. Calibration and quality control standards with the concentrations given below were used for method validation and sample analysis. Each batch included calibration curve standards 1.00, 2.00, 4.00, 16.0, 60.0, 250, 800, and 1000 ng/mL), quality control samples (3.00 ng/mL, 400 ng/mL, 750 ng/mL, and 40.0 ng/mL) and subject samples. The calibration curves (for both analytes) were found to be linear over the concentration range of 1.0 to 1000 ng/mL. The calibration lines of chromatographic response versus concentration were determined by the weighted least square regression analysis with a weighting factor of $1/x^2$. The coefficient of determination (r^2) was consistently > 0.996.

Between run precision and accuracy of the calibration standards for MEK 162 ranged from 2.3 % to 6.2 and 100.1 % to 106.3 %, respectively. Between run precision and accuracy of the quality control samples MEK 162 ranged from 2.5 % to 5.1 and 100.1 % to 106.3 %, respectively. Between run precision and accuracy of the calibration standards for N-desmethyl MEK162 ranged from 3.1 % to 10.9 % and 94.2 % to 107.5 %, respectively. Between run precision and accuracy of the quality control samples N-desmethyl MEK162 ranged from 4.2% to 7.5% (19.1% (did not meet acceptance criteria) and 99.0% to 4.9% respectively.

Suitable acceptance criteria for the exclusion of standards and QC and for re-assay have been submitted.

118 study samples corresponding to 9 % of the 1311 study samples analyzed, were re-assayed as ISR. 94.1% of IRS were found to be within ± 20% of the mean of initial and incurred concentrations.

Chromatograms of at least 20% of all subjects analysed, the associated calibration standards, including blank standard, zero standard and QC samples as well as the calibration curves have been presented. (No chromatograms from this study were individually integrated.)

The potential for carryover from a sample containing a high concentration of analyte to the following sample in an injection sequence was monitored by injecting duplicate extracted matrix blanks immediately after the ULOQ calibration standards in each run. There were no contributions from chromatographic peaks, at the expected retention time of the analyte in the blank samples, greater than 20% of the mean analyte response for the LLOQ calibration standards in any runs.

The pivotal bioequivalence study **W00074CI103** was carried out comparing 3 x15 mg binimetinib FCTs (Mektovi) to 1 x 45 mg binimetinib FCT (Mektovi new strength, titanium dioxide was replaced by calcium carbonate).

MEK162 and N-desmethyl MEK162 was determined in human plasma samples by LC-MS/MS method. The bioanalytical part of the studies is carried out at PPD, USA. The time of the clinical part was from 31 AUG 2022 to 18 JAN 2023, and the first date of analysis to last date of analysis was 06 January 2023 to 23 January 2023, including re-assays and ISR analysis. (Maximum time-period between first sample collection and latest analysis: 125 days). The blood samples were collected into K_2EDTA tubes. The plasma samples were stored in PP tubes at -80°C for shipping. A total of 1311 samples have been analysed in 11 sequences for determination of MEK162 and N-desmethyl MEK162 by HPLC/MS/MS. Calibration and quality control standards with the concentrations given below were used for method validation and sample analysis. Each batch included calibration curve standards (1.00, 2.00, 4.00, 16.0, 60.0, 250, 800, and 1000 ng/mL), quality control samples (3.00 ng/mL, 400 ng/mL, 750 ng/mL, and 40.0 ng/mL) and subject samples. The calibration curves were found to be linear over the concentration range of 1.0 to 1000 ng/mL. The calibration lines of

chromatographic response versus concentration were determined by the weighted least square regression analysis with a weighting factor of $1/x^2$. The coefficient of determination (r^2) was consistently > 0.999. Between run precision and accuracy of the calibration standards for MEK 162 ranged from 2.4 % to 4.4 and 99.7 % to 100.3 %, respectively. Between run precision and accuracy of the quality control samples MEK 162 ranged from 3.7 % to 8.4 and 100.7 % to 103.3 %, respectively. Between run precision and accuracy of the calibration standards for N-desmethyl MEK162 ranged from 3.4 % to 5.3 % and 97.8 % to 101.4 %, respectively. Between run precision and accuracy of the quality control samples N-desmethyl MEK162 ranged from 3.2% to 8.6% and 101.1% to 101.7% respectively. Suitable acceptance criteria for the exclusion of standards and QC and for re-assay have been submitted.

Chromatograms of all samples, the associated calibration standards, including blank standard, zero standard and QC samples as well as the calibration curves have been presented (data not shown).

The potential for carryover from a sample containing a high concentration of analyte to the following sample in an injection sequence was monitored by injecting duplicate extracted matrix blanks immediately after the ULOQ calibration standards in each run. There were no contributions from chromatographic peaks, at the expected retention time of the analyte in the blank samples, greater than 20% of the mean analyte response for the LLOQ calibration standards in any runs.

An analyte interference check was performed to determine if samples fortified with Paracetamol and Amoxicillin interfered with the quantitation of binimetinib and AR00426032 in human plasma. Results presented indicate there is no effect on the quantitation of binimetinib and AR00426032 in human plasma.

Bioavailability

Pilot study W00074CI101: a randomised, single-center, open-label, single-dose, two-period, crossover study to investigate the relative bioavailability of binimetinib 45 mg and 3x15 mg tablets in healthy participants; 14 subjects completed the study and were evaluated for safety and pharmacokinetics.

Protocol code: W00074CI101

EudraCT number: 2021-002075-19

Biotrial code: 1PF73

Sponsor: Pierre Fabre Médicament represented by the Institut de Recherche Pierre Fabre

Study location: Biotrial Rennes, 7-9, rue Jean-Louis Bertrand, CS 34246, 35042 Rennes, France

Study Periods

Study initiation date: 03 SEP 2021

Study completion date: 19 NOV 2021

The study protocol V2.0 was approved on 25 AUG 2021 by the CPP and on 11 AUG 2021 by the ANSM.

Study design

This was a randomized, single-center, open-label, single dose, two-period, crossover phase I study to investigate the relative bioavailability of binimetinib 3 x 15 mg and 45 mg tablets in healthy participants.

The R formulation was 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 T formulation was the tablet containing 45 mg of binimetinib as active substance in one tablet. Participants were randomized to one of 2 treatment sequences (RT or TR) containing 2 treatment periods, with at least a 7-day washout between each dose.

The study consisted 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, and a washout of at least 7 days between P1D1 and P2D1 (note: the washout period was exactly 7 days for all participants).

Study treatments were given by the oral route in fasted condition.

A total of 14 healthy male and female participants between ≥ 18 and ≤ 65 years of age with a body mass index (BMI) of ≥ 18.5 to < 30 kg/m2 and body weight ≥ 50 kg and < 100 kg were to be included in the study to allow for the completion of 12 participants evaluable for PK. Female participants had to be postmenopausal or sterilized and male participants with a female partner of childbearing potential were 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.

Blood samples (4 mL) were 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.

Test and reference products

Table 2: Study treatments

Study Treatment Name:	**Test Formulation: Binimetinib oral film-coated tablet**	**Reference Formulation: Binimetinib oral film-coated tablet (Mektovi®)**
Active ingredients	Binimetinib 45 mg	Binimetinib 15 mg
Excipients	Tablet core: Lactose monohydrate, cellulose microcrystalline, croscarmellose sodium, magnesium stearate, silica colloidal anhydrous Film-coating (Opadry II White): Polyvinyl alcohol – part hydrolyzed, macrogol 4000, titanium dioxide, 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
Route of Administration	Oral	Oral
Dosing instructions:	Study treatments were administered orally on D1 in the morning (i.e., around 8:00). Participants had to be instructed to take binimetinib with approximately 240 mL of water. Participants had to be instructed to swallow the tablet(s) whole and not to chew or crush them. Participants fasted from 10 hours before dosing until 4 hours after dosing (i.e., around 12:00) where they were served lunch. Dinner was served approximately 12 hours after dosing (i.e., around 20:00).	
Packaging and Labeling	Study treatments were provided as treatment units each comprised of 1 blister of 12 film-coated tablets of binimetinib 15 mg and 1 blister of 15 film-coated tablets of binimetinib 45 mg. Each pack and blister was labeled as required per country requirements in local languages. Details of labeling are provided in Section 7.5 of the protocol (Appendix 16.1.1).	
Manufacturer	Institut de Recherche Pierre Fabre – Toulouse Langlade 3 avenue Hubert Curien 31100 Toulouse France	

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)
Batch number	CL0175-A	G01000_A

The reference (R) formulation was the currently commercially available Mektovi tablet containing 15 mg of binimetinib as active substance, administered as three tablets for a total of 45 mg binimetinib. The test (T) formulation was the tablet containing 45 mg of binimetinib as active substance in one tablet.

Population(s) studied/ Demographic and Other Baseline Characteristics

Table 3: Summary of demographic characteristics (randomised set, N=14)

Parameter (Unit)	Statistics / Category	Overall (N=14)
Age (years)	n	14
	Mean ± SD	50.4 ± 13.47
	Min ; Max	30 ; 65
Sex	Female	3 (21.4 %)
	Male	11 (78.6 %)
Height (cm)	n	14
	Mean ± SD	171.9 ± 10.14
	Min ; Max	154 ; 187
Weight at screening (kg)	n	14
	Mean ± SD	73.17 ± 13.305
	Min ; Max	53.0 ; 98.4
BMI at screening (kg/m²)	n	14
	Mean ± SD	24.61 ± 2.901
	Min ; Max	19.5 ; 28.2

Reference: Binimetinib 3 x 15 mg tablet; Test: Binimetinib 1 x 45 mg tablet
SD: standard deviation; BMI: body mass index.
Sources: W00074CI101 - Version Date: 03FEB2022 - File Name: FA14_1_3_demog_sum_Ran_t.rtf - Listing 16.2.4.1
Sources: Database lock: 21DEC2021 - ADSL: 06JAN2022 - FA14_1_3_demog_sum_Ran_t.sas: 03FEB2022

Overall, 3 participants (21.4%) were female and 11 participants (78.6%) were male. The mean (± SD) age of the participants was 50.4 ± 13.5 years, ranging from 30 to 65 years. Their mean (±SD) height was 171.9 ± 10.1 cm (ranging from 154 to 187 cm) and their mean (± SD) weight at screening was 73.2 ± 13.3 kg (ranging from 53.0 to 98.4 kg), resulting in a mean (±SD) BMI at screening of 24.6 ± 2.9 kg/m2 (ranging from 19.5 to 28.2 kg/m2).

None of the participants in the randomized set was vaccinated against COVID-19; 7 participants (50.0%) had never smoked and 7 participants (50.0%) were former smokers; and 2 participants (14.3%) never drank alcohol and 12 participants (85.7%) currently consumed alcohol.

All 14 randomized participants completed the study, and all were present for P1 and P2.

Discontinued Subjects

No participant in the Randomized set was excluded from the Safety set or the PK set.

Table 4: Analysis sets

Analysis Set	Test/Reference (N=7)	Reference/Test (N=7)	Overall (N=42)
Screened set	7 (100 %)	7 (100 %)	42 (100 %)
Randomized set	7 (100 %)	7 (100 %)	14 (33.3 %)
Safety set	7 (100 %)	7 (100 %)	14 (33.3 %)
Pharmacokinetic set	7 (100 %)	7 (100 %)	14 (33.3 %)

Reference: Binimetinib 3 x 15 mg tablet; Test: Binimetinib 1 x 45 mg tablet

Protocol deviations

No important protocol deviations were reported during the study.

Pharmacokinetic variables

The following parameters were derived by non-compartmental analysis from the plasma binimetinib concentration-time profiles: Cmax, Tmax, AUClast, AUCinf (primary parameters); and apparent terminal elimination rate constant (λz), terminal elimination half-life (t½), time of last observed plasma concentration (Tlast), apparent total body clearance (CL/F), and apparent volume of distribution (Vz/F) (secondary parameters).

Additionally, the following PK parameters were derived by non-compartmental analysis from the plasma AR00426032 concentration-time profiles: Cmax, Tmax, AUClast, AUCinf; t½, Tlast.

The PK parameters were determined using Phoenix® WinNonlin® version 8.1 (Certara USA, Inc., Princeton, NJ).

Statistical methods

PK analysis:

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

Concentration-time profile plots were 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 were summarized by formulation and corresponding listings were prepared.

For binimetinib only:

• Scatter plots and box whisker plots were generated for the comparison of Cmax, AUClast and AUCinf.

• The geometric mean ratio between treatments of AUCs and Cmax of binimetinib were estimated together with 90 % CIs, using the corresponding contrast from an analysis of variance on the log-transformed parameters, with sequence, period and treatment as fixed effects and participant within sequence as random effect.

• Tmax was analyzed using non-parametric tests.

Safety analysis:

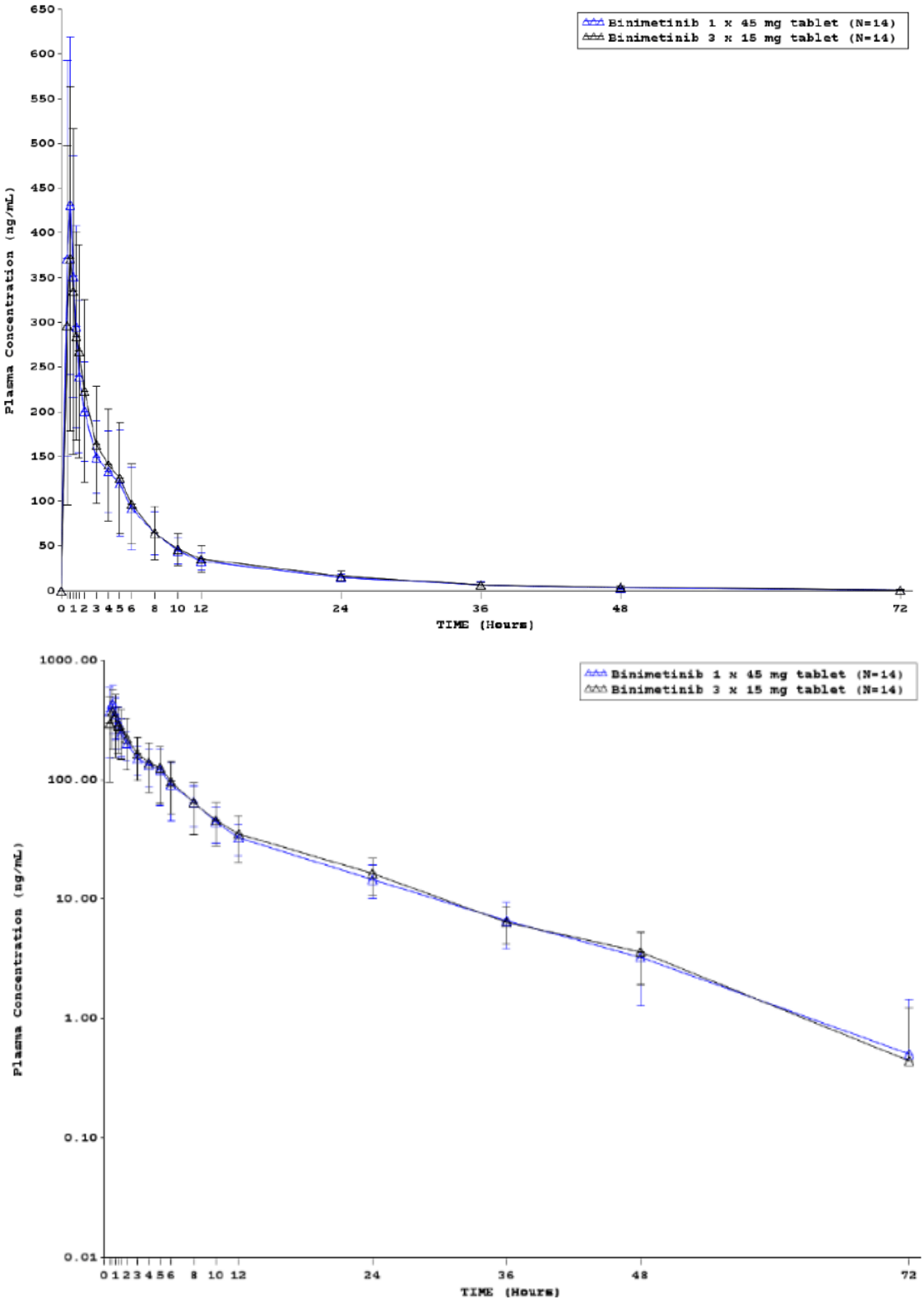
All AEs and TEAEs were described by preferred term and system organ class; AEs were described by formulation (before any treatment and after first intake of each treatment) and overall, and TEAEs were described by formulation.

Summary descriptive statistics were provided for other safety parameters (vital signs measurements, ECG, complete physical examination, weight, COVID-19 tests, visual examination, ophthalmologic examination, and laboratory tests).

Results

Mean concentration time profiles of binimetinib for test and reference are displayed in the figures below.

Figure 1:Linear Scale (Top Panel) and Semi-Logarithmic Scale (Bottom Panel) Arithmetic Mean (±SD) Binimetinib Concentration Time Profiles Following Administration of 45 mg Binimetinib as 3 x 15 mg Tablet (Current Commercial Formulation, Reference) and as 1 x 45 mg Tablet (Test) Formulations in 14 Healthy Participants(W00074CI101)



Pre dose levels of binimetinib were below the lower limit of quantitation in nearly all subjects.

All 14 randomized participants completed the study, and all were present for P1 and P2.

Results regarding the main pharmacokinetic parameters of binimetinib are displayed in the table below.

Table 5: Mean plasma PK parameters of binimetinib following single oral administration (PK set, N=14)

Formulation	Statistics	C_{max} (ng/mL)	T_{max} (h)	T_{last} (h)	AUC_{last} (h*ng/mL)	AUC_{inf} (h*ng/mL)
Binimetinib 1 x 45 mg tablet (N=14)	n	14	14	14	14	14
	Geometric Mean	415.5	0.7158	51.73	1843	1895
	Arithmetic Mean ± SD	456.4 ± 195.44	0.7738 ± 0.38596	53.14 ± 13.073	1889 ± 431.91	1941 ± 437.19
	SEM	52.23	0.10315	3.494	115.43	116.84
	CV%	42.8	49.8774	24.60	22.86	22.52
	Geometric CV%	49.0	39.0769	24.28	23.77	23.37
	Median	511.0	0.7500	48.00	1836	1908
	Q1 ; Q3	266.0 ; 566.0	0.5000 ; 0.7500	48.00 ; 72.00	1608 ; 2097	1671 ; 2134
	Min ; Max	198 ; 869	0.500 ; 2.000	36.0 ; 72.0	1100 ; 2650	1130 ; 2750
Binimetinib 3 x 15 mg tablet (N=14)	n	14	14	14	14	14
	Geometric Mean	394.0	0.8770	53.90	1871	1917
	Arithmetic Mean ± SD	429.1 ± 184.65	1.1083 ± 1.15638	54.86 ± 11.251	1943 ± 548.72	1986 ± 551.33
	SEM	49.35	0.30906	3.007	146.65	147.35
	CV%	43.0	104.3349	20.51	28.25	27.76
	Geometric CV%	44.9	64.7156	19.18	29.31	28.31
	Median	370.5	0.7500	48.00	1923	1937
	Q1 ; Q3	280.0 ; 617.0	0.6333 ; 1.0000	48.00 ; 72.00	1613 ; 2172	1695 ; 2220
	Min ; Max	199 ; 756	0.500 ; 5.000	48.0 ; 72.0	1120 ; 3110	1140 ; 3210

SD: standard deviation; SEM: standard error of the mean; CV: coefficient of variation; Q: quartile.

Table 6: Binimetinib PK parameters in Study W00074CI101

Parameters (Units)	Geometric means (geometric CV%)	
	Test Product: Binimetinib 45 mg tablet	Reference Product: Binimetinib 3 x 15 mg tablets
AUC_{last} (h.ng/mL)	1843 (23.8 %)	1871 (29.3 %)
AUC_{inf} (h.ng/mL)	1895 (23.4 %)	1917 (28.3 %)
C_{max} (ng/mL)	415.5 (49.0 %)	394 (44.9 %)
T_{max} (h)[1]	0.75 (0.50-2.00)	0.75 (0.50-5.00)

[1] Median (range)

Table 7: Estimation of Test/Reference Ratios and 90 % Confidence Intervals in Study W00074CI101

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference (%)	Confidence Intervals (%)
AUC_{last}	98	92– 106
AUC_{inf}	99	93-106
C_{max}	105	91-122

Following administration of the currently commercialized formulation (binimetinib 3 x 15 mg), geometric mean Cmax, AUClast and AUCinf values were 394.0 ng/mL, 1871 h*ng/mL and 1917 h*ng/mL, respectively.

Following administration of the test formulation (binimetinib 1 x 45 mg), geometric means of Cmax, AUClast and AUCinf were 415.5 ng/mL, 1843 h*ng/mL and 1895 h*ng/mL, respectively.

The 90% CIs of the binimetinib Cmax and AUCs and geometric mean ratios (Test/Reference) were all within the BE range of 80.00 to 125.00%.

An assessment of the relative bioavailability of binimetinib 3 x 15 mg film-coated tablets and binimetinib 45 mg film-coated tablet was performed. Although no formal statistical analysis was performed, the GMR and 90% CI for AUC and Cmax were inside the bioequivalence boundaries.

Bioequivalence

Pivotal study W00074CI103: a randomised, single-center, open-label, single-dose, two-period, crossover pivotal bioequivalence study comparing binimetinib 3x15 and 45 mg tablets in healthy participants

Protocol code: W00074CI103

EudraCT Number: 2022-000610-34

ClinicalTrials.gov: NCT05810740

Sponsor: Pierre Fabre Médicament

Study location: Biotrial Rennes, 7-9, rue Jean-Louis Bertrand, CS 34246, 35042 Rennes, France

Studied period (years):

Initiation date: 31AUG2022

Completion date: 18JAN2023

The protocol V1.2 was approved on 18JUL2022 by the CPP, and the protocol V2.0 was approved on 08NOV2022 by the CPP and on 28NOV2022 by the ANSM.

Study design

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

The Reference (R) formulation was 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 was the tablet containing 45 mg of binimetinib as active substance, administered as one tablet.

Participants were 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 consisted 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 were given by oral route in fasted conditions.

A total of 40 healthy participants between ≥ 18 and ≤ 65 years of age with a body mass index (BMI) of ≥ 18.5 to < 30 kg/m2 and body weight ≥ 50 kg and < 100 kg were planned to be included in the study to allow for the completion of 36 participants evaluable for PK.

Female participants had to be postmenopausal or sterilized, and male participants with a female partner of childbearing potential were 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.

Blood samples (4 mL) were drawn for the assay of plasma binimetinib and its metabolite AR00426032 at the following time-points: within 15 min before treatment administration (T0h), 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.

Test and reference products

Table 8: Test and Reference Product Information in Study W00074CI103

Product Characteristics	Test Product	Reference Product
Name	Binimetinib 45 mg	Binimetinib 15 mg
Strength	45 mg	15 mg
Dosage form	Film-coated tablet	Film-coated tablet
Manufacturer	PFMP Progipharm	PFMP Progipharm
Batch Number	G99003	G01018
Batch Size (Biobatch)	200 kg blend (corresponding to approximately 444 444 film-coated tablets)*	200 kg blend (corresponding to approximately 444 444 film-coated tablets)*
Measured contents (% of label claim)	97.6	100.6
Commercial Batch Size	200 kg blend (corresponding to approximately 444 444 film-coated tablets)	200 kg blend (corresponding to approximately 444 444 film-coated tablets)
Expiry date (Retest date)	March 2023	April 2024
Location of Certificate Analysis	CSR W00074CI103 Appendix 16.1.6	CSR W00074CI103 Appendix 16.1.6
Member State where the reference product is purchased from:		France
This product was used in the following trials:	W00074CI103	CMEK162A2103 ARRAY-162-105 MEK162A2110 ARRAY-162-106 CMEK162A2104 CMEK162A2105 CMEK162A2301 CMEK162B2301

Population(s) studied/ Demographic and Other Baseline Characteristics

Table 9: Summary of demographic characteristics (Randomised set, N=37)

Parameter (Unit)	Statistics / Category	Overall (N=37)
Age (years)	n	37
	Mean ± SD	42.3 ± 13.62
	Min; Max	19; 65
Sex	Female	4 (10.8 %)
	Male	33 (89.2 %)
Height (cm)	N	37
	Mean ± SD	174.2 ± 8.05
	Min; Max	149; 190
Weight at screening (kg)	N	37
	Mean ± SD	77.80 ± 11.293
	Min; Max	54.5; 99.6
BMI at screening (kg/m^2)	n	37
	Mean ± SD	25.58 ± 2.932
	Min; Max	19.4; 30.0

Reference: binimetinib 3 x 15 mg tablet; Test: binimetinib 1 x 45 mg tablet.
SD: standard deviation; SEM: standard error of the mean; BMI: body mass index.

A total of 135 participants were enrolled in order to include 37 participants. Ninety-eight (98) participants were not included. A total of 37 male and female participants were randomized and completed the study. Overall, 4 participants (10.8%) were female and 33 (89.2%) were male. The mean (±SD) age of the participants was 42.3±13.6 years, with participants' ages ranging from 19 to 65 years. The mean (±SD) height of participants was 174.2±8.1 cm (ranging from 149 to 190 cm) and the mean (±SD) weight of participants was 77.8±11.3 kg (ranging from 54.5 to 99.6 kg). This resulted in a mean (±SD) BMI at screening of 25.6±2.9 kg/m2, ranging from 19.4 to 30.0 kg/m2.

36 of the participants were evaluable for PK.

23 (62.2%) of participants in the Randomized Set had never smoked and 14 (37.8%) were former smokers; 10 (27.0%) of participants never drank alcohol and 27 (73.0%) reported current alcohol consumption within the accepted ranges specified in the protocol.

Discontinued Subjects (Study report 10.1)

One participant was enrolled in the study, but monitoring revealed that their signature was missing from the ICF (all other information was completed) and the participant could not be reached after multiple attempts. Because of this, it was agreed that this participant's data would be deleted and therefore was excluded from the analyses.

One (1) participant was infected with COVID-19 and was therefore not present for P2.

Table 10: Summary of participant disposition (enrolled set, N=135)

Status / Reason	Test/Reference	Reference/Test	Overall
Enrolled			135
Screened			50
Randomized	18	19	37
Completed treatment	17	19	36
Discontinued treatment	1	0	1
Other: COVID 19 test positive	1	0	1
Completed study	18	19	37
Discontinued study	0	0	0

Reference: binimetinib 3 x 15 mg tablet; Test: binimetinib 1 x 45 mg tablet.

Protocol deviations

Overall, 2 out of 37 participants (5.4%) presented important deviations. These deviations were as follows:

• One (1) participant did not complete the visit on P2D4, as well as ophthalmologic assessment of the EOS visit because the visit was performed off-site at participant's request. The rest of the EOS visit was performed as planned.

• One (1) participant did not complete 4 visits during the second period (P2D1-P2D4) due to positive COVID-19 test. The participant did not complete the second period and was therefore not included in the PK Set.

Table 11: Important protocol deviations (randomised set)

	Test/Reference (N=18) n	Reference/Test (N=19) n	Overall (N=37) n
At least one important protocol deviation*	1 (5.6 %)	1 (5.3 %)	2 (5.4 %)
Other procedure not done	0	1 (5.3 %)	1 (2.7 %)
Subject visit not performed	1 (5.6 %)	1 (5.3 %)	2 (5.4 %)

* Multiple important protocol deviations can occur by participant.
Reference: binimetinib 3 x 15 mg tablet; Test: binimetinib 1 x 45 mg tablet.

Pharmacokinetic variables

The following parameters were derived by non-compartmental analysis from the plasma binimetinib concentration-time profiles: maximum observed plasma concentration (Cmax), time to reach Cmax (Tmax), area under the plasma concentration-time curve (AUC) from time of administration to last observed plasma concentration (AUClast), AUC from time of administration to infinity (AUCinf); and, apparent terminal elimination rate constant (λz), terminal elimination half-life (t½), time of last observed plasma concentration (Tlast), apparent total body clearance (CL/F), residual area in percentage (AUC_%Extrap_obs), apparent volume of distribution (Vz/F) and mean residence time (MRT) (secondary parameters).

Additionally, the following PK parameters were derived by non-compartmental analysis from the plasma AR00426032 concentration-time profiles: Cmax, Tmax, AUClast, AUCinf; t½, Tlast, λz, MRT.

The PK parameters were determined using Phoenix® WinNonlin® version 8.1 (Certara USA, Inc., Princeton, NJ).

Statistical methods

PK analysis:

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

Concentration-time profile plots were 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 were summarized by formulation and corresponding listings were prepared.

For binimetinib only:

• Scatter plots and box whisker plots were generated for the comparison of Cmax, AUClast and AUCinf.

• To demonstrate the BE between the two formulations, primary PK parameters (AUClast, AUCinf and Cmax) were 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 were provided for the ratio of T to R (3 x 15 mg formulation as R and 45 mg formulation as T). BE was declared if the 90% CI for the ratio of T to R geometric means was within the range of 0.80 to 1.25 for all primary endpoints.

• Tmax was analyzed using non-parametric tests for paired data.

Safety Analysis

All AEs and treatment emergent AEs (TEAEs) were described by preferred term and system organ class. TEAEs were described by formulation and all AEs were listed.

Summary descriptive statistics were provided for other safety parameters (vital signs measurements, ECG, complete physical examination, weight, COVID-19 tests, visual examination, ophthalmologic examination, and laboratory tests).

2.5.5. Discussion on clinical pharmacology

The objective of the new formulation program was to develop a new dose strength of 45 mg binimetinib to reduce the number of tablets taken per day from 6 (3 x 15 mg BID) to only two tablets (1 x 45 mg BID), and therefore to reduce the patient "tablet burden". To support the new formulation development, 2 biopharmaceutical clinical studies were conducted: a pilot bioavailability study, W00074CI101, and a pivotal bioequivalence study, W00074CI103.

The conducted randomised, single-center, open-label, single-dose, two-period, crossover study (W00074CI101) to investigate the relative bioavailability of binimetinib 45 mg and 3x15 mg tablets in healthy participants is considered adequate.

Study W00074CI103 was a randomised, single-center, open-label, single-dose, 2-sequence, 2-period, crossover pivotal bioequivalence study comparing binimetinib 3x15 and 45 mg tablets in healthy participants.

The Reference (R) formulation was 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 was the tablet containing 45 mg of binimetinib as active substance, administered as one tablet. The employed design is overall considered adequate for the PK objectives. The mean and individual plots of concentrations versus time have been submitted within the CSR. Truncation of AUC at 72 h is considered sufficiently representative of extent of absorption for drugs with long half-life.

With regard to AUC and Cmax, the acceptance range of 80% to 125% was met.

Median Tmax values observed at 0.75 and 1.00 hours for test and reference respectively, were only slightly different between the 2 formulations. The Tmax for both the test product and the reference product is shorter than the Tmax determined in earlier studies (1.5 h according to SmPC). The Applicant discussed that these differences observed in the median Tmax between healthy subjects (administered under fasting conditions) and patients (administered irrespective of food or in fasted conditions) can be attributed to binimetinib PK variability (high variability in Cmax), differences in blood sampling schedule (different number of samples collected around Tmax) and instructions regarding food intake. As already shown in study CMEK162A2103, Tmax increased from 0.875 h to 1.25 h after a low fat meal (LFM) or to 2.03 h after a high fat meal but AUC remained unchanged between conditions (LFM vs. HFM).

Based on the results from study W00074CI103 the new 45 mg strength can be considered bioequivalent to 3 tablets of 15 mg administered simultaneously.

2.5.6. Conclusions on clinical pharmacology

The new tablets of Mektovi 45 mg strength can be considered bioequivalent to 3 tablets of 15 mg administered simultaneously. From a clinical pharmacology point of view, the application is acceptable.

2.5.7. Clinical efficacy

No new efficacy data were submitted.

2.5.8. Clinical safety

2.5.8.1. Patient exposure

Safety data is provided from 14 participants randomized in the relative bioavailability study W00074CI101 and from 37 subjects in the bioequivalence study W00074CI103. Both studies included healthy participants that received single doses of binimetinib. The safety evaluations in both studies were based upon the incidence, nature and severity of TEAEs reported throughout the study and on changes in clinical laboratory parameters, vital signs, electrocardiograms (ECGs) and ophthalmologic examinations.

2.5.8.2. Adverse events

An overview of TEAEs reported in **study W00074CI101** is presented in the following table.

There was no SAE, no death, and no important medical event.

No AE required the withdrawal of a participant. No TEAE was related to COVID-19.

All AEs were treatment-emergent. A total of 4 TEAEs were reported in 2 participants (14.3%):

• 3 TEAEs reported in 1 participant (7.1%) after administration of binimetinib 3 x 15 mg tablets in the TR sequence.

• 1 TEAE reported in 1 participant (7.1%) after administration of binimetinib 1 x 45 mg tablet in the RT sequence.

The 4 TEAEs included nasopharyngitis, retinal exudates, chalazion; all were of NCI-CTCAE grade 2, and eye irritation which was of NCI-CTCAE grade 1.

Only the TEAE of retinal exudates was suspected to be related to study treatment.

All 4 TEAEs were reported as recovered/resolved at the end of the study.

Table 12: Summary of treatment-emergent adverse events (safety set, N=14) (W00074CI101)

	Binimetinib 1 x 45 mg tablet (N=14)		**Binimetinib 3 x 15 mg tablet (N=14)**		**Overall (N=14)**	
	n	**[E]**	**n**	**[E]**	**n**	**[E]**
At least one TEAE	1 (7.1 %)	1	1 (7.1 %)	3	2 (14.3 %)	4
At least one TEAE with grade ≥ 3*	0		0			0
At least one related TEAE	0	0	1 (7.1 %)	1	1 (7.1 %)	1
At least one related TEAE with grade ≥ 3*	0		0			0
At least one TEAE leading to any dose reduction	0		0			0
At least one TEAE leading to permanent treatment discontinuation	0		0			0
At least one related TEAE leading to permanent treatment discontinuation	0		0			0
At least one serious TEAE	0		0			0
At least one TEAE leading to death	0		0			0
At least one related TEAE leading to death	0		0			0

*NCI-CTCAE grade version 5.0.
TEAE: treatment-emergent adverse event; n: number of participants with at least one TEAE; [E]: number of occurrences of TEAEs.
A TEAE was an AE that started or worsened during the on-treatment period.
%: (n/N)*100.

An overview of TEAEs reported in **study W00074CI103** is presented in the following table.

No AE required the withdrawal of a participant from the study.

A total of 12 treatment emergent adverse events (TEAE) were reported in 8 participants (21.6%). One participant reported 1 TEAE each after both administration of binimetinib 1 x 45 mg tablet and binimetinib 3 x 15 mg tablet:

• 5 TEAEs in 4 participants (10.8%) after administration of binimetinib 1 x 45 mg tablet.

• 7 TEAEs in 5 participants (13.9%) after administration of binimetinib 3 x 15 mg tablet.

The 12 TEAEs were COVID-19 infection (N=2), ocular discomfort, retinal vascular disorder, abdominal pain, orthostatic hypotension, tooth abscess, viral infection, vision blurred, pruritus, frequent bowel movements, and toothache. Of these, COVID-19 (N= 2), retinal vascular disorder, tooth abscess, viral infection, and toothache were of NCI-CTCAE grade 2, the remaining TEAEs were NCI-CTCAE grade 1. Only the TEAE of orthostatic hypotension and the TEAE of blurred vision were considered related to study treatment.

All 12 TEAES were reported as recovered/resolved at the end of the study.

Table 13: Summary of treatment-emergent adverse events (safety set, N=37) (W00074CI103)

	binimetinib 1 x 45 mg tablet (N=37)		**binimetinib 3 x 15 mg tablet (N=36)**		**Overall (N=37)**	
	n	**[E]**	**n**	**[E]**	**n**	**[E]**
At least one TEAE	4 (10.8 %)	5	5 (13.9 %)	7	8 (21.6 %)	12
At least one TEAE with grade>=3*	0		0			0
At least one related TEAE	1 (2.7 %)	1	1 (2.8 %)	1	2 (5.4 %)	2
At least one related TEAE with grade>=3*	0		0			0
At least one TEAE leading to any dose reduction	0		0			0
At least one TEAE leading to permanent treatment discontinuation	0		0			0
At least one related TEAE leading to permanent treatment discontinuation	0		0			0
At least one serious TEAE	0		0			0
At least one TEAE leading to death	0		0			0
At least one related TEAE leading to death	0		0			0

*NCI-CTCAE grade version 5.0.
TEAE: treatment-emergent adverse event; n: number of participants with at least one TEAE; [E]: number of occurrences of TEAEs.
A treatment-emergent adverse event is an adverse event that starts or worsens during the on-treatment period.
%: (n/N)*100.

2.5.8.3. Serious adverse event/deaths/other significant events

There was no SAE, no death, and no important medical event.

2.5.8.4. Laboratory findings

In **Study W00074CI101**, no clinically significant changes or abnormal values were observed in hematology, blood chemistry, coagulation, urinalysis, vital signs or electrocardiogram (ECG) parameters. No abnormal physical examination or visual assessment result was considered clinically significant.

Two participants had potentially clinically significant abnormal (PCSA) vital signs values during the study.

Occurrences of orthostatic hypotension and abnormal heart rate (HR) were rare, with 2 participants presenting orthostatic hypotension, and 3 participant presenting abnormal HR increase. No episode of orthostatic hypotension or abnormal HR increase was considered clinically significant.

In **Study W00074CI103,** 15 participants had PCSA vital sign values throughout the study. These were considered transient and not clinically significant. Seven (7) episodes of orthostatic hypotension were reported in 5 participants. Of these, 1 was considered clinically significant and related to study treatment. Of the 9 episodes of abnormal pulse rate (PR) reported in 8 participants, none were considered clinically significant.

No clinically significant changes were observed in hematology, blood chemistry, coagulation, urinalysis, vital signs, or ECG parameters. No physical examination (including dermatological examination) or visual assessment results were abnormal.

2.5.8.5. In vitro biomarker test for patient selection for safety

n/a

2.5.8.6. Safety in special populations

n/a

2.5.8.7. Immunological events

n/a

2.5.8.8. Safety related to drug-drug interactions and other interactions

n/a

2.5.8.9. Discontinuation due to adverse events

No subject discontinued due to adverse events.

2.5.8.10. Post marketing experience

No new data on safety have been reported.

2.5.9. Discussion on clinical safety

Safety data is provided from two studies (W00074CI101 and W00074CI103) in which healthy participants were give single doses of binimetinib.

Most of the reported AEs were of mild grade. There was no serious adverse event (SAE), no death, and no important medical event. No adverse event (AE) required the withdrawal of a participant from the studies. All TEAES were reported as recovered/resolved at the end of the studies.

Only the TEAEs of retinal exudates, of orthostatic hypotension and of blurred vision were considered to be related to study treatment.

Detected PCSA vital signs values were transient and not considered clinically significant. One episode of orthostatic hypotension was considered clinically significant and related to study treatment. No clinically significant changes were observed in haematology, blood chemistry, coagulation, urinalysis, vital signs, or ECG parameters. No physical examination (including dermatological examination) or visual assessment results were abnormal or considered clinically significant.

Overall, the safety profile of the binimetinib 45mg tablet is considered to be in line to that of the currently available 15 mg tablet. No new safety concerns have been identified.

From a general safety perspective, the informative value of data coming from single-dose administrations in healthy individuals is limited. From a comparative perspective, as outlined above, there is no trend suggesting a different safety or tolerability profile when the proposed new strength vs. three tablets of the currently marketed strength are given. This is expected since bioequivalence has been demonstrated.

2.5.10. Conclusions on the clinical safety

No new safety concerns have been identified. Taking into account that bioequivalence has been shown, the safety profile of the proposed strength can be assumed to be equivalent to that of the existing 15 mg strength.

2.6. Risk Management Plan

Not applicable.

2.7. Pharmacovigilance

Not applicable.

2.7.1. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.8. Product information

2.8.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed considering that excluding the minor strength-specific details detailed in section 6, the Package Leaflets of the 15 mg and of the 45 mg strengths are fully identical.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The purpose of this submission is to add a new strength of binimetinib (45 mg film-coated tablet). The proposed clinical use for the 45 mg film-coated tablet is for the same indications as approved for the 15 mg film-coated tablet.

The objective of the new formulation program was to develop a new dose strength of 45 mg binimetinib to reduce the number of tablets taken per day from 6 (3 x 15 mg BID) to only two tablets (1 x 45 mg BID), and therefore to reduce the patient "tablet burden".

This application refers to a line extension with no change in approved indications.

The main clinical studies are one bioavailability study W00074CI101 and the bioequivalence study W00074CI103. Both studies were phase I, single-dose, open-label, randomized studies conducted in healthy subjects.

3.2. Favourable effects

Bioequivalence was demonstrated with regards to Cmax and AUC in study W00074CI103, comparing the 45 mg FC tablet with three 15 mg FC tablets under fasted conditions.

3.3. Uncertainties and limitations about favourable effects

There are no pending uncertainties that have a critical impact on the benefit/risk balance assessment.

3.4. Unfavourable effects

From a general safety perspective, the informative value of data coming from single-dose administrations in healthy individuals is limited. From a comparative perspective there is no trend suggesting a different safety or tolerability profile when the proposed new strength vs. three tablets of the currently marketed strength are given. This is expected since bioequivalence has been demonstrated. No new safety concerns have been identified.

3.5. Uncertainties and limitations about unfavourable effects

There are no pending uncertainties.

3.6. Effects Table

Not applicable.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The benefits of the new strength are acknowledged.

3.7.2. Balance of benefits and risks

As bioequivalence has been demonstrated for the 45 mg tablet, a positive B/R balance comparable to the reference strength can therefore be concluded.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of Mektovi is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Mektovi new strength, is favourable in the following indication(s):

Binimetinib in combination with encorafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Mektovi subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.