4 November 2024
EMA/339228/2024
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on `Trametinib film-coated tablet 0.5 and 2mg product-specific bioequivalence guidance' (EMA/CHMP/41624/2023)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	ACPS-Network GmbH
2	Alembic Pharmaceuticals Ltd
3	ELPEN Pharmaceutical Co. Inc
4	Lotus Pharmaceuticals Limited
5	Midas Pharma GmbH
6	Synthon B.V.
7	Viatris Inc.

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	**Comment:** ACPS-Network is a clinical pharmacology consultancy platform that supports the early development of novel drug substances and products. ACPS-Network welcomes the opportunity to comment on the draft product-specific bioequivalence guidance (PSG) for trametinib. In brief, considering the known properties of trametinib as a molecular-targeted kinase inhibitor, ACPS-Network proposes a conventional BE study in healthy volunteers with a single-dose, cross-over study design rather than a repeated-dose cross-over in cancer patients as presently proposed in the draft PSG. Specification and justification of this proposal is detailed in the comments below.	**Accepted that a single dose cross-over study can be conducted in healthy subjects (see below; first specific comment)**
2	**Comment:** Based on available safety and tolerability information from published literature and Alembic's previous PK studies on Trametinib, it is proposed to consider BE evaluation in healthy subjects upon single dose administration, instead of that upon multiple doses in stable patients with melanoma or NSCLC.	**Accepted that a single dose cross-over study can be conducted in healthy subjects (see below; first specific comment)**
4	**Comment:** Multiple dose crossover bioequivalence study on patient population is recommended in the draft product specific guidance. However, literatures are available in the public domain confirming that, bioequivalence studies on single dose of Trametinib have been conducted on healthy adult population and no safety concern reported. According to the EMA guidance on bioequivalence, we would like to propose a single dose, single-period,	**Accepted that a single dose cross-over study can be conducted in healthy subjects (see below; first specific comment)**

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	parallel, oral bioequivalence study in healthy, adult, human male subjects and female subjects of non-childbearing potential under fasting conditions.	
5	**Comment:** Midas Pharma welcomes the opportunity to comment on the trametinib product-specific bioequivalence draft guidance. Midas Pharma is an international pharmaceutical company offering products and services across the full industry value chain. In brief, Midas Pharma proposes to conduct the BE study with healthy volunteers in a single-dose, cross-over study design rather than the repeated-dose cross-over design in cancer patients as presently proposed in the draft. Trametinib film-coated tablet is an immediate-release oral product, for which, per EMA BE guideline (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), a single-dose 2x2 cross-over study can be accepted as it is the most suitable and sensitive design to detect differences in the rate and extent of absorption between the test and the reference product. Further details are provided in the following comments.	**Accepted that a single dose cross-over study can be conducted in healthy subjects (see below; first specific comment)**
6	**Comment:** The draft product-specific guidance for 0.5 mg and 2 mg trametinib film-coated tablets (EMA/CHMP/41624/2023, 22 Feb 2024) indicates that a multiple dose crossover study in patients with melanoma or non-small lung carcinoma is necessary to show bioequivalence due to safety reasons. The subject population and study design for BE studies should be selected with the aim of permitting detection of differences in the in vivo release characteristics between pharmaceutical products. In order to reduce variability not related to differences between products, the studies should normally be performed in healthy subjects unless the drug carries safety concerns. For trametinib two single-dose studies have been published in healthy male and female volunteers of non-childbearing potential with a 2	**Accepted that asingle dose cross-over study can be conducted in healthy subjects (see below; first specific comment)**

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	mg dose. Based on publicly available information, these studies were performed without safety concerns (Tan et al., 2022 and 2023). In addition, the FDA has recently changed their product-specific guidance for trametinib from requiring a patient population (Jan 2016) to a healthy volunteer population (May 2022). A study in healthy volunteers would also allow a single-dose study design. Therefore, Synthon respectfully request the Agency to consider changing the recommendation from a patient-based multiple-dose study into a single-dose crossover study in healthy volunteers (males and females of non-childbearing potential).	
7	**Comment:** Viatris is pleased to provide comments to EMA's draft product-specific bioequivalence guidance, which outlines the Agency's recommendations for a multiple dose cross-over study in stable patients with melanoma or non-small cell lung carcinoma (NSCLC) for establishing bioequivalence. For the reasons discussed in detail below, we propose that a single dose-cross over study in healthy adult volunteers is the more appropriate bioequivalence study design recommendation given the safety profile and the sensitivity of a single-dose study. Study in healthy volunteers is recommended to establish bioequivalence of trametinib and, a single dose PK study is more sensitive than multiple dose PK study for the demonstration of bioequivalence. Hence, in conclusion, single dose PK study in healthy volunteers is recommended to demonstrate bioequivalence.	**Accepted that a single dose cross-over study can be conducted in healthy subjects (see below; first specific comment)**

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 16 Bioequivalence study design	1	**Comment:** 1. Trametinib film-coated tablets are an immediate-release oral product. For such products, in accordance with the EU BE guideline (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), a single-dose 2x2 cross-over study can be accepted to be the best suited while the most sensitive design to detect differences in the rate and extent of absorption between the test and the reference product. 2. Trametinib is a non-genotoxic, small-molecule drug that acts as a reversible, highly selective MEK1/MEK2 kinase. Because of this specificity, there is no prior reason to preclude healthy subjects from a single-dose cross-over investigation with trametinib, provided that caution is taken when selecting and monitoring trial participants. Indeed, while molecular-targeted, trametinib's pharmacological action may be expected to be highly specific, resulting in less risk of damage to non-target tissues and functions. Several state-of-the art reviews discuss and conclude that healthy volunteers can take part in early and/or later development studies of non-genotoxic, molecular-targeted small molecules also in oncology, without undue harm. e.g. Iwamoto et al., 2012 [Clin Pharmacol Ther. 2012;92(5):571-4]; Karakunnel et al., 2018 [J Transl Med. 2018;16(1):336]; Ahmed et al., 2022 [Clin Transl Sci. 2020 Jan;13(1):31-40]. 3. The proposal for revision of the PSG is in line with the recommended single-dose cross-over study design in healthy	**Accepted** In the clinical development of trametinib, trametinib was only administered to patients with cancer. Based on careful review of all safety data in patients and in healthy subjects following trametinib exposure, including data from the literature, CHMP considers that trametinib can be administered to healthy subjects without undue harm in a single dose cross-over study. However, to prevent worsening of ocular conditions, subjects with central serous retinopathy, retinal vein thrombosis, or any risk factors for these conditions, including uncontrolled glaucoma or a history of hyper viscosity or hyper coagulability syndromes, should be excluded from the bioequivalence study. The product specific guideline has been changed accordingly.

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		volunteers adopted in several BE PSGs for similar drugs: e.g. Alectinib (2020), Bosutinib (2023), Cabozantinib (2019), Crizontinib hard capsules (2017), Dasatinib (2020), Gefitinib (2020), Ibrutinib (2022), Pazopanib (2017), Sorafenib (2021), Sunitinib (2015), Vandetanib (2017). This is no default ruling: For the HER2-inhibitor lapatinib, which carries a well-established risk of hepatotoxicity, the EMA PSG precluded the conduct of BE studies in healthy volunteers. However, for trametinib, there is no compelling reason for such a precautionary measure. 4. Also, for trametinib, a first FDA PSG draft in 2016 proposed a randomised, open-label, once daily repeated dosing, 2x2 cross-over trial in patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations. Review led to a substantially revised draft PSG (May 2022) favouring a randomised, open-label, single-dose, 2x2cross-over trial in healthy volunteers investigating the highest strength of 2 mg, i.e. a design that is agreement with our proposal here. 5. Moreover, the Originator, who may be expected to have the best access to all safety-relevant data in this regard, recently carried out biopharmaceutical single-dose studies in healthy volunteers. Two late-stage, life-cycle management studies were undertaken by the Originator with single doses of 2 mg trametinib administered twice in cross-over to healthy volunteers to investigate the effects of a light meal on bioavailability (Tan et al., 2023; N: 26) or the effects of a lower DMSO content to permit less strict low-temperature storage (Tan et al., 2022; N: 65). In both studies, safety and tolerability were closely monitored and reported in detail.	

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		Overall, tolerability under these experimental conditions was excellent. see Tan et al., 2022. Clin Pharmacol Drug Dev. 2022;11(10):1203-1210 Tan et al., 2023. Clin Pharmacol Drug Dev. 2023;12(3):333-342. Although the database of healthy subjects is small, it is sufficiently explicit that no safety concerns ought to preclude healthy subjects from enrolment in a single-dose cross-over BE investigation. 6. Patient management in clinical trials is standardised per study protocol, not individualised. In patients with advanced cancer, adhering to the strict requirements of BE studies can be difficult since the patients' personal well-being may clash with the broader group-ethical goal of making generic drugs available to others (see also Menikoff J. JAMA. Published online June 20, 2024. doi:10.1001/jama.2024.7677). With a single-dose cross-over study in healthy volunteers, the highest BE sensitivity for formulation effects can be secured without exposing trial subjects to undue risk. There is no reason to consider this principle not applicable to trametinib. 2. For BE studies with the purpose of comparing a test and reference formulation, the highest strength (not the highest clinical dose) is recommended to be used. **Proposed change:** DELETE: multiple dose INSERT: Single dose | Cross-over DELETE: patients: stable patients with melanoma or non-small cell lung carcinoma (NSCLC) INSERT: Healthy volunteers DELETE: Background: stable patients with melanoma or non-small cell lung carcinoma (NSCLC).	

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		Strength: 2 mg. DELETE: Background: 2 mg once daily is the recommended dose in patients. Individuals on a lower dose can participate in the bioequivalence study as long as the same dose is administered to them throughout the study. Number of studies: DELETE: one multiple dose study INSERT: one single-dose study. Other critical aspects: INSERT: Subjects with pertinent mutations or any sign or history of malignancy or premalignancy will be excluded from enrolment. Follow-up to be extended up to 1 month after last dosing. DELETE: Minimum 14 days of trametinib administration prior to PK sampling. DELETE: Co-medication of medicines that could affect the pharmacokinetics of trametinib should be avoided, if possible, and if not, their use should be well documented. DELETE: A bioequivalence study for trametinib during combination therapy with dabrafenib is acceptable.	
Line 16 Bioequivalence assessment	1	**Comment:** In line with the proposed single-dose design. **Proposed change:** Main pharmacokinetic variables: DELETE: AUC0-tau and Cmax,ss INSERT: AUC0-72 and Cmax.	**Accepted**
Line 16	2	**Comment:** The draft guidance1 recommends multiple-dose, cross-over, fasting, bioequivalence study in stable patients with melanoma or non-small cell lung carcinoma (NSCLC). It also mentions that	**Accepted that a single dose cross-over study can be conducted in healthy subjects (see above; first specific comment)**

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		a study in patients is recommended due to safety reasons. From a regulatory point of view, as per current EMA guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr)3, the subject population for bioequivalence studies should be selected with the aim of permitting detection of differences between pharmaceutical products. In order to reduce variability not related to differences between products, the studies should normally be performed in healthy volunteers unless the drug carries safety concerns that make this unethical. This model, in vivo healthy volunteers, is regarded as adequate in most instances to detect formulation differences and to allow extrapolation of the results to populations for which the reference medicinal product is approved (the elderly, children, patients with renal or liver impairment, etc.). Trametinib upon single dose administration, is well tolerated by normal healthy subjects. Following is the summary from published literature with respect to safety of trametinib in normal healthy subjects: • Article by Tan E.Y. et al. (2022)4: This was open-label, phase 1, single-dose, randomized, 2-treatment, 2-period crossover study in 60 healthy volunteers, bioavailability of a single 2-mg tablet of Trametinib containing 9% DMSO (test formulation), corresponding to the lowest DMSO content in the tablet after storage at 25°C for 36 months, was evaluated vs bioavailability of a 2-mg tablet containing 11% DMSO (reference formulation). Safety results: No AEs led to study drug discontinuation. Overall, 55% (33/60) of subjects experienced at least 1 AE of any grade. One subject reported a grade 3 headache. The most commonly reported AEs irrespective of treatment relation (≥5%) were headache	

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		(13.3%; 8/60), constipation (10.0%; 6/60), abdominal pain, diarrhea, upper respiratory tract infection (7%; 4/60 each), back pain, and dyspepsia (5.0%; 3/60 each). A total of 11.7% (7/60) of subjects reported at least one treatment-related AE (headache [6.7%, 4/60]; diarrhea [5.0%, 3/60]; abdominal pain [3.3%, 2/60]; nausea [1.7%, 1/60]). None of the treatment-related AEs were grade ≥3. No AEs led to study drug discontinuation. No SAEs and no deaths were reported during the study. Safety conclusion: The majority of AEs were mild. One subject experienced grade 3 headache, and no grade 4 or grade 5 AEs were reported. From this comparative bioavailability study in healthy subjects, it is concluded that, single dose of Trametinib tablets 2mg is safe & well tolerated in normal healthy subjects. • Article by Tan E.Y. et al. (2023)5: This was randomized, open-label, 2-part, 2 × 2 crossover, phase 1 study to evaluate the effect of a low-fat low-calorie (LFLC) meal on the relative bioavailability of a trametinib 2-mg tablet or dabrafenib 150-mg capsule in was evaluated in 56 healthy participants. Participants received either trametinib, administered orally as a single 2-mg tablet on days 1 and 29, or dabrafenib, administered as two 75-mg capsules (for a total dose of 150 mg) on days 1 and 8. Sequence 1 involved administration of the assigned study drug under fed conditions (period 1), followed by fasted conditions (period 2), whereas sequence 2 involved the opposite sequence. The end-of-study visit was conducted on day 57 for participants treated with trametinib or on day 15 for participants treated with dabrafenib and was followed by a safety follow-up call ≈30 days after the last administration of either drug. Safety results: Safety results	

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		of trametinib single dose under fasting conditions have been reported here, and those for dabrafenib can be reported from the reference article: Overall, 12 (40.0%) participants experienced at least 1 AE. The most common AEs were catheter site pain, diarrhea, and headache (2 [6.7%] participants each). Permanent discontinuation due to an AE occurred in 2 participants; of these, 1 participant randomly assigned to receive trametinib under fed and fasted conditions tested positive for coronavirus disease 2019 on day 28 that was reported resolved on day 51 and was not deemed to be related to the study drug. Another participant randomly assigned to receive trametinib under fed and fasted conditions experienced a severe AE of chorioretinopathy on day 28, which was resolved on day 87 and was deemed to be related to the study drug. No serious AEs or deaths occurred during the study. • USFDA product specific recommendation on trametinib6: USFDA also suggests single dose cross over bioequivalence study in normal healthy subjects. Following additional safety measure is recommended: Subjects with a history of, or current evidence of, either central serous retinopathy or retinal vein thrombosis, or both, or any risk factors for these conditions, including uncontrolled glaucoma or a history of hyper viscosity or hyper coagulability syndromes, should be excluded from the bioequivalence study. Male subjects (including those who have had vasectomies) with female partners of reproductive potential should use condoms throughout the study and for at least 4 months after the last dose.	

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		• Alembic's previous studies of Trametinib tablets 2mg in healthy subjects: • Pilot study 1 (#092-22): Single dose, four-arm, parallel, fasting study in 32 healthy male and female subjects of no reproductive potential Safety results: Total 3 adverse events were reported during the post-study laboratory evaluation by 2 of 32 subjects. Out of these 2 subjects, 1 subject had decreased hemoglobin (Test-1 treatment) and another subject (reference treatment) had increased aspartate aminotransferase and alanine aminotransferase. These adverse events were mild in nature and subjects were followed-up until the resolution of adverse events. Overall, Trametinib tablets 2mg test and reference products were safe and well tolerated by healthy subjects under fasting condition. • Pilot study 2(#031-23): Single dose, randomized, balanced, two-treatment, two-sequence, two-period, cross-over oral bioequivalence study of two formulations in 24 normal healthy male and female subjects of no reproductive potential. Safety results: One subject did not return for three consecutive ambulatory PK sample collection in period-2 and was dropped from the study. During post-study laboratory evaluations 5 of 24 subjects showed following AEs: 1 subject (reference treatment) showed increased SGPT, SGOT and GGT, and 4 (2 with test and 2 with reference) subjects showed decreased hemoglobin. All these subjects are to be followed-up until resolution of AEs. Overall, both test and reference products were well tolerated by healthy subjects under fasting condition. • Pilot study 3 (#040-23): Single dose, four-arm, parallel, fasting study in 40 healthy male and female	

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		subjects of no reproductive potential. Safety results: Total 2 (Test-2 and Test-4) of 40 subjects showed decreased Hemoglobin during post-study laboratory evaluations. This AE was mild in nature and the subjects were followed-up until its resolution. Overall, test and reference products were safe and well tolerated by healthy subjects under fasting condition. From a scientific point of view based on totality of evidence (published literature and previous experience of Alembic), it appears that trametinib tablets 2mg single dose under fasting condition is well tolerated by normal healthy subjects. Single dose studies, being most suitable to assess actual formulation difference is preferred to evaluate bioequivalence. References: 1. EMA Product Specific Bioequivalence Guidance, Trametinib filmcoated tablets 0.5mg and 2mg, 22Feb2024, EMA/CHMP/41624/2023, CHMP, Start of public consultation: 11Mar2024, End of public consultation: 30Jun2024 (https://www.ema.europa.eu/en/documents/scientific-guideline/trametinib-film-coatedtablet-05-2mg-product-specificbioequivalence-guidance_en.pdf) 2. Summary of Product Characteristics (SmPC), Mekinist film-coated tablets 0.5 mg and 2mg, date of latest renewal: 14Feb2019 (https://www.ema.europa.eu/en/documents/product-information/mekinistepar-product-information_en.pdf)	

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		3. EMA Guideline on the investigation of bioequivalence, CHMP, Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr,20Jan2010 (https://www.ema.europa.eu/en/documents/scientific-guideline/guidelineinvestigation-bioequivalence-rev1_en.pdf) 4. Tan E.Y. et al. Comparative Bioavailability of a Single Dose of Trametinib (TMT212) Containing 9% vs 11% Dimethyl Sulfoxide in Randomized Healthy Volunteers to Assess Long-Term Storage at Room Temperature, Clinical Pharmacology in Drug Development 2022, 11(10) 1203–1210 5. Tan E.Y. et al. Evaluation of a Low-Fat Low-Calorie Meal on the Relative Bioavailability of Trametinib and Dabrafenib: Results From a Randomized, Open-Label, 2-Part Study in Healthy Participants. Clinical Pharmacology in Drug Development 2023, 12(3) 333–342 **Proposed change:** Bioequivalence study design: Single dose Cross-over Fasting Normal healthy subjects Background: Trametinib tablets 2mg upon single dose is safe and well tolerated by healthy subjects. Following precautions are recommended: -Male and female subjects with no childbearing potential are recommended. -Male subjects (including those who have had vasectomies) with female partners of reproductive potential should use condoms throughout the study and for at least 4 months after the last dose. -Subjects with a history of, or current evidence of, either central serous retinopathy or retinal vein thrombosis, or both, or any risk factors for these conditions, including uncontrolled	

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		glaucoma or a history of hyper viscosity or hyper coagulability syndromes, should be excluded from the bioequivalence study.	
Line 16	3	**Comment:** In January 2016, FDA issued a draft product-specific guidance for industry on generic trametinib dimethyl sulfoxide, suggesting clinical program to be conducted in patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. Being in effect for 6.5 years, FDA guideline was revised 2 years ago (May 2022) proposing Healthy males and females not of reproductive potential as suitable study population. This switch might indicate that experience was obtained during this period regarding product safety profile to support this change in the product specific guidance. It can be assumed that above revision was based on additional pharmacokinetic and pharmacodynamic data generated in the meantime along with data from post marketing studies and clinical experience. To the best of applicant's knowledge there are data available from two (2) clinical studies conducted from the Marketing Authorization Holder (i.e. Novartis Pharmaceuticals), where trametinib was successfully administered in healthy population (i.e. males and females not of reproductive potential). Although results of those studies became available for the public after revision of FDA guideline in May 2022 (i.e. 1st article by Tan and co-workers was published in October of 2022 while 2nd article was published in March 2023), both studies have been conducted few years earlier (i.e. between September 13, 2018, to December 2, 2018 and between March 11, 2020, to December	**Accepted that a single dose cross-over study can be conducted in healthy subjects (see above; first specific comment)**

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		24, 2020, respectively). In the first study (Tan et al., 2022), the bioavailability of a single 2-mg tablet of trametinib containing 9% DMSO (test formulation), was evaluated vs bioavailability of a 2-mg tablet containing 11% DMSO (reference formulation). In this open-label, phase 1, single-dose, randomized, 2-treatment, 2-period crossover study, 2mg of trametinib were administered in 60 (39 male and 21 female) healthy volunteers, of non-reproductive potential. Sixty-five percent of subjects were men, mean (SD) age was 45.6 (11.2) years, mean body mass index (SD) was 28.4 (2.6) kg/m2, and 83.3% were White. Even though 55% (33/60) of subjects experienced at least 1 AE of any grade, the majority of AEs were mild and only 11.7% (7/60) of subjects reported treatment-related AE (headache [6.7%, 4/60]; diarrhoea [5.0%, 3/60]; abdominal pain [3.3%, 2/60]; nausea [1.7%, 1/60]). One subject reported a grade 3 headache. The most commonly reported AEs irrespective of treatment relation (≥5%) were headache (13.3%; 8/60), constipation (10.0%; 6/60), abdominal pain, diarrhoea, upper respiratory tract infection (7%; 4/60 each), back pain, and dyspepsia (5.0%; 3/60 each;). One subject experienced grade 3 headache, and no grade 4 or grade 5 AEs were reported. No SAEs and no deaths were reported during the study. In the second study (Tan et al., 2023), the effect of a low-fat low-calorie (LFLC) meal on the relative bioavailability of a trametinib 2-mg film coated tablet was evaluated in healthy participants. In this randomized, open-label, single-centre, phase 1, 2 × 2 cross-over design study, 2mg of trametinib were administered in 30 (27 male and 3 female) healthy volunteers, of non-reproductive potential. The median age was 36.0 years, the	

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		majority of participants were men (90.0%) and either White (63.3%) or Black/African American (23.3%). Overall, 12 (40.0%) participants experienced at least 1 AE, however only 4 participants (13.3%) reported 6 AEs related to trametinib treatment. Permanent discontinuation due to an AE occurred in 2 participants. From these 2, only 1 participant experienced an AE (chorioretinopathy) on day 28, which was resolved on day 87 and was deemed to be related to the study drug. No SAEs and no deaths were reported during the study. Evaluating collectively the data available from the 2 studies, it is evident that 11 out of 90 participants experienced an AE deemed to be related to the study drug. The majority of AEs, were mild in nature and were resolved during the course of the study. Permanent discontinuation due to an AE was infrequent and primarily attributed to non-drug-related factors, further supporting the safety of the investigational drugs in healthy volunteers of non-reproductive potential. Concerning inclusion criteria and considering the single incident of severe adverse event recorded in the previously mentioned studies in healthy population, participants who have history of eye problems including blockage of the vein draining the eye (retinal vein occlusion) or swelling in the eye which may be caused by fluid blockage (chorioretinopathy), will be carefully excluded. Considering also that Trametinib may impair female fertility in humans (as described in section 5.3 of Mekinist SmPC), and even though female patients of reproductive potential advised to use effective methods of contraception for 16 weeks after stopping treatment, applicant is considering that only healthy	

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		volunteers of non-reproductive potential should be included in the clinical program. **Proposed change:** Bioequivalence study design: single dose cross-over Healthy: Healthy volunteers of non-reproductive potential Background: A study in healthy volunteers of non-reproductive potential is recommended. Strength: 2 mg Background: 2 mg once daily is the recommended in healthy males and females not of reproductive potential. Number of studies: One single dose study. Bioequivalence assessment: Main pharmacokinetic variables: AUC0-t and Cmax.	
Line 16 Bioequivalence study design	4	**Comment:** The applicant believed that multiple dose study in patients (stable patients with melanoma or non-small cell lung carcinoma (NSCLC)) deemed to be not necessary. The applicant proposed Bioequivalence study in 'Healthy Adult Human Subjects': We believe single dose bioequivalence study is feasible on normal healthy adult subjects based on following facts: •No new malignancy reported when Trametinib administered as monotherapy. The risk of malignancy associated with Trametinib monotherapy in single dose is very limited. New malignancies (Cutaneous and non-cutaneous) can occur when trametinib is used in combination with dabrafenib.[1] •Originator has conducted phase I dose-escalation study to investigate the safety, pharmacokinetics, and pharmacodynamics of the trametinib in subjects with solid tumours or lymphoma. In this study maximum tolerated dose	**Accepted that a single dose cross-over study can be conducted in healthy subjects (see above; first specific comment)**

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		was defined as 3 mg QD, during the study dose limiting toxicities (DLT) were observed as rash (grade 3), diarrhoea (grade 3) and chorioretinopathy (grade 2). The incidence of AEs ≥ grade 3 in the 2.0 mg QD dose group was considered acceptable (14%) when compared with the higher 2.5 and 3 mg QD dose groups (23 and 31% respectively). With the 2 mg QD no AE grade ≥ 4 was encountered. [2] •Trametinib was not genotoxic based on the studies evaluating reverse mutations in bacteria, mutagenicity and chromosomal aberrations in cultured mouse lymphoma cells, and micronuclei in the bone marrow of rats. [1] •Trametinib may impair female fertility in humans, as in repeat-dose studies, increases in cystic follicles and decreases in corpora lutea were observed in female rats at exposures below the human clinical exposure. However, toxicity studies (in rat & dog) with 13 weeks duration, there were no treatment effects observed in male reproductive tissues. [1] •The safety pharmacology studies suggest that, at the relevant low dose of 3 mg/kg, tolerated by rats and dogs, with the exception of diarrhoea and inhibition of body weight gain, no significant effects on general behaviour, physiologic function or acute neurotoxicity were observed. However, administration of trametinib to rats at the high dose of 100mg/kg (non GLP) resulted in decreased body weight gain, sporadic incidence of reduced spontaneous locomotion, prone position, blepharoptosis, diarrhoea, piloerection, and mydriasis, described in order of onset. Subsequent studies showed that this dose leads to morbidity and mortality. [2] •Efficacy and safety of Trametinib in combination with dabrafenib in East Asians was similar to global studies. No new safety findings were observed	

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		with Trametinib in combination with dabrafenib in East Asian patients.[3] •Trametinib has not been reported as a Narrow Therapeutic Index drug by any of the regulatory agencies in the assessment and evaluation report and it is not considered a steep concentration-response product during any of the dose-finding, clinical study. • Few literatures are available in the public domain where researcher has conducted study on normal healthy volunteers The summary of the literature as below. •The food effect study was conducted by innovator to evaluate the effect of low-fat, low-calorie meal on the relative bioavailability of drug product with sample size of 30 healthy adult subjects.[4] •During the study overall, 12 subjects had reported AE's. The most common AEs reported are, diarrhoea, and Headache. No serious adverse event reported. The AEs reported are mild to moderate in nature and resolved without sequel. [4] •The pharmacokinetic profile of trametinib from the literature. Cmax: SmPC: 22.2ng/mL Literature: 6.9ng/mL AUC: SmPC: 370 ng*hr/mL Literature: 314.00 ng*hr/mL Tmax: SmPC: 1.5 hrs. Literature: 1.29 hrs. From the above data the pharmacokinetic parameters are almost comparable. •With the published clinical, toxicology and available safety data, it is evident that, Trametinib could be administered at single dose in healthy subjects by incorporating adequate safety measures during study conduct. •Moreover, USFDA has recommended to conduct Trametinib product bioequivalence study on healthy adult population by adapting study design as either with two-way, crossover design or alternative approach as parallel bioequivalence study. [5] •Based on available literature, we are proposing to conduct the single dose, single-period, parallel,	

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		oral bioequivalence study in healthy, adult, human male subjects and female subjects of non-childbearing potential under fasting condition by ensuring adequate safety measures during screening study conduct and post study follow up procedures. Along with all the above facts we Lotus Pharmaceutical company has recently conducted one pilot bioequivalence study (single dose, open label, parallel design) on healthy, adult, human male subjects and female subjects of non-childbearing potential to evaluate the bioequivalence safety of the Trametinib Tablets subjects in comparison to Mekinist (Trametinib Tablets 2mg). In this study few adverse events were observed all of them are mild in nature and was resolved without any sequel. Out of all the adverse events only one participant has observed event of Bradycardia, and all other events were related to post study safety analysis (abnormal lab parameters). Please refer Attachment-1 for all the adverse events observed during the study. The brief study details are as follows. Drug product was administered to the healthy subjects as single dose, we request agency to consider the study design as single dose parallel single arm bioequivalence study in normal adult healthy volunteers under fasting condition. As per the Mekinist product SmPC Trametinib should be taken orally with a full glass of water. The tablets should not be chewed or crushed, and they should be taken without food. Hence as per EMA guidance requirement the bioequivalence study has been conducted on fasting condition.	

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		Additionally, based on the safety profile mentioned in the innovator SmPC, we have set the pre-defined inclusion and exclusion criteria for the subjects to be enrolled in the study as mentioned below. •Normal or clinically insignificant findings during screening for Ophthalmic examination, 12 lead ECG, 2D Echo and chest X-ray. •The participant was excluded from the enrolment if they had central serious retinopathy, retinal vein thrombosis, uncontrolled glaucoma, ocular hypertension, or history of hyper viscosity or hyper coagulability syndromes, blurred vision, decreased acuity etc. Please refer Attachment-2 for study report synopsis for more details on the inclusion and exclusion criteria and other safety measures taken during study. The applicant believed that multiple dose study in patients (stable patients with melanoma or non-small cell lung carcinoma (NSCLC)) deemed to be not necessary. The applicant proposed Bioequivalence study in 'Healthy Adult Human Subjects': We believe single dose bioequivalence study is feasible on normal healthy adult subjects based on following facts: • No new malignancy reported when Trametinib administered as monotherapy. The risk of malignancy associated with Trametinib monotherapy in single dose is very limited. New malignancies	

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		(Cutaneous and non-cutaneous) can occur when trametinib is used in combination with dabrafenib.[1] • Originator has conducted phase I dose-escalation study to investigate the safety, pharmacokinetics, and pharmacodynamics of the trametinib in subjects with solid tumours or lymphoma. In this study maximum tolerated dose was defined as 3 mg QD, during the study dose limiting toxicities (DLT) were observed as rash (grade 3), diarrhoea (grade 3) and chorioretinopathy (grade 2). The incidence of AEs ≥ grade 3 in the 2.0 mg QD dose group was considered acceptable (14%) when compared with the higher 2.5 and 3 mg QD dose groups (23 and 31% respectively). With the 2 mg QD no AE grade ≥ 4 was encountered. [2] • Trametinib was not genotoxic based on the studies evaluating reverse mutations in bacteria, mutagenicity and chromosomal aberrations in cultured mouse lymphoma cells, and micronuclei in the bone marrow of rats. [1] • Trametinib may impair female fertility in humans, as in repeat-dose studies, increases in cystic follicles and decreases in corpora lutea were observed in female rats at exposures below the human clinical exposure. However, toxicity studies (in rat & dog) with 13 weeks duration, there were no treatment effects observed in male reproductive tissues. [1] • The safety pharmacology studies suggest that, at the relevant low dose of 3 mg/kg, tolerated by rats and dogs, with the exception of diarrhoea and inhibition of body weight gain, no	

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		significant effects on general behaviour, physiologic function or acute neurotoxicity were observed. However, administration of trametinib to rats at the high dose of 100mg/kg (non GLP) resulted in decreased body weight gain, sporadic incidence of reduced spontaneous locomotion, prone position, blepharoptosis, diarrhoea, piloerection, and mydriasis, described in order of onset. Subsequent studies showed that this dose leads to morbidity and mortality. [2] • Efficacy and safety of Trametinib in combination with dabrafenib in East Asians was similar to global studies. No new safety findings were observed with Trametinib in combination with dabrafenib in East Asian patients.[3] Trametinib has not been reported as a Narrow Therapeutic Index drug by any of the regulatory agencies in the assessment and evaluation report and it is not considered a steep concentration-response product during any of the dose-finding, clinical study. • Few literatures are available in the public domain where researcher has conducted study on normal healthy volunteers The summary of the literature as below. • The food effect study was conducted by innovator to evaluate the effect of low-fat, low-calorie meal on the relative bioavailability of drug product with sample size of 30 healthy adult subjects.[4] • During the study overall, 12 subjects had reported AE's. The most common AEs reported are, diarrhoea, and Headache. No	

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		serious adverse event reported. The AEs reported are mild to moderate in nature and resolved without sequel. [4] • The pharmacokinetic profile of trametinib from the literature. Parameters (SmPC) Steady state Literature (Tan YE et.al., 2023) Two-way crossover Cmax 22.2 ng/ml 6.98 ng/ml AUCtau 370 ng*hr/ml AUCt 314.00 ng*hr/ml Tmax 1.5 hours 1.29 hours From the above data the pharmacokinetic parameters are almost comparable. • With the published clinical, toxicology and available safety data, it is evident that, Trametinib could be administered at single dose in healthy subjects by incorporating adequate safety measures during study conduct. • Moreover, USFDA has recommended to conduct Trametinib product bioequivalence study on healthy adult population by adapting study design as either with two-way, crossover design or alternative approach as parallel bioequivalence study. [5] •Based on available literature, we are proposing to conduct the single dose, single-period, parallel, oral bioequivalence study in healthy, adult, human male subjects and female subjects of	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		nonchildbearing potential under fasting condition by ensuring adequate safety measures during screening study conduct and post study follow up procedures. Along with all the above facts we Lotus Pharmaceutical company has recently conducted one pilot bioequivalence study (single dose, open label, parallel design) on healthy, adult, human male subjects and female subjects of non-childbearing potential to evaluate the bioequivalence safety of the Trametinib Tablets subjects in comparison to Mekinist (Trametinib Tablets 2mg). In this study few adverse events were observed all of them are mild in nature and was resolved without any sequel. Out of all the adverse events only one participant has observed event of Bradycardia, and all other events were related to post study safety analysis (abnormal lab parameters). Please refer Attachment-1 for all the adverse events observed during the study. The brief study details are as follows. Drug product was administered to the healthy subjects as single dose, we request agency to consider the study design as single dose parallel single arm bioequivalence study in normal adult healthy volunteers under fasting condition. As per the Mekinist product SmPC Trametinib should be taken orally with a full glass of water. The tablets should not be chewed or crushed, and they should be taken without food. Hence as per EMA guidance requirement the bioequivalence study has been conducted on fasting condition.	

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		Additionally, based on the safety profile mentioned in the innovator SmPC, we have set the pre-defined inclusion and exclusion criteria for the subjects to be enrolled in the study as mentioned below. •Normal or clinically insignificant findings during screening for Ophthalmic examination, 12 lead ECG, 2D Echo and chest X-ray. •The participant was excluded from the enrolment if they had central serious retinopathy, retinal vein thrombosis, uncontrolled glaucoma, ocular hypertension, or history of hyper viscosity or hyper coagulability syndromes, blurred vision, decreased acuity etc. Please refer Attachment-2 for study report synopsis for more details on the inclusion and exclusion criteria and other safety measures taken during study. References: [1] Summary of product characteristic for Mekinist [2] EMA Public Assessment Report for Mekinist [3] Lu Si et al., Open-label, phase IIa study of dabrafenib plus trametinib in East Asian patients with advanced BRAF V600-mutant cutaneous melanoma. European Journal of cancer 2020. [4] Tan YE et al., Evaluation of a Low-Fat Low-Calorie Meal on the Relative Bioavailability of Trametinib and Dabrafenib:	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Results from a Randomized, Open-Label, 2-Part Study in Healthy Participants. Clinical Pharmacology. 2023 [5] Product specific BE recommendation by USFDA **Proposed change:** Single dose cross-over truncated/ or parallel truncated Healthy Volunteers.	
Line 16 Bioequivalence assessment	4	**Comment:** The applicant is in opinion that, based on above fact the single dose, single-period, parallel, oral bioequivalence study in healthy, adult, human male subjects and female subjects of non-childbearing potential under fasting condition can be conducted. **Proposed change:** Main pharmacokinetic variables: Cmax and AUC0-72.	**Accepted**
Line 16 Bioequivalence study design	5	**Comment:** 1. Trametinib is a non-genotoxic, small-molecule drug type, reversible, highly selective inhibitor of mitogen-activated extracellular signal-regulated kinase 1 (MEK1) and MEK2. While molecular-targeted, trametinib's pharmacological action may be expected to be highly specific, resulting in less risk of damage to non-target tissues and functions. Given this specificity, there is no reason per se to preclude healthy subjects from a single-dose cross-over investigation with trametinib, provided that caution is taken when	**Accepted that a single dose cross-over study can be conducted in healthy subjects (see above; first specific comment)**

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		selecting and monitoring trial participants. This is in line with several state-of-the-art reviews on whether and how healthy volunteers can take part in early and/or later development studies of non-genotoxic, molecular-targeted small molecules in oncology. e.g. Iwamoto et al., 2012 [Clin Pharmacol Ther. 2012;92(5):571-4]; Karakunnel et al., 2018 [J Transl Med. 2018;16(1):336]; Ahmed et al., 2022 [Clin Transl Sci. 2020 Jan;13(1):31-40]. 2. Moreover, the Originator selected healthy volunteers in biopharmaceutical single-dose studies. Two late-stage, life-cycle management studies were undertaken by the Originator with single doses of 2 mg trametinib administered twice in cross-over to healthy volunteers to investigate the effects of a light meal on bioavailability (Tan et al., 2023; N: 26) or the effects of a lower DMSO content to permit less strict low-temperature storage (Tan et al., 2022; N: 65). In both studies, safety and tolerability were closely monitored and reported in detail. Overall, tolerability under these experimental conditions was excellent. see Tan et al., 2022. Clin Pharmacol Drug Dev. 2022;11(10):1203-1210 Tan et al., 2023. Clin Pharmacol Drug Dev. 2023;12(3):333-342 Although the database of healthy subjects is small, it is sufficiently explicit that no safety concerns ought to preclude healthy subjects from enrolment in a single-dose cross-over BE investigation. Note: For some kinase inhibitors, EMA guidance may recommend BE studies to be conducted in patients for precautionary matters; this approach was adopted for lapatinib, which carries a well-	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		established risk of hepatotoxicity. No such risk was established for trametinib and hence, there is no compelling reason for such precautionary measure. 3. With a single-dose cross-over study in healthy volunteers, the highest sensitivity for formulation effects is ensured without exposing trial subjects to undue risk. Also, irrespective of the type of volunteers, BE studies, like the present, demand strict standardisation; this generally poses no problem in healthy volunteers; in patients, especially in those with advanced, unresectable or metastatic cancer, this may conflict with the obvious medical priority to put the patient's individual interests first, focusing on his comfort and well-being, irrespective of possible group-ethical considerations (i.e. to contribute to the availability of a generic drug mainly to the benefit of others). 4. The proposal for revision is in line with the recommended single-dose cross-over study design in healthy volunteers adopted in several EU product-specific BE guidelines on similar drugs: e.g. Alectinib (2020), Bosutinib (2023), Cabozantinib (2019), Crizontinib hard capsules (2017), Dasatinib (2020), Gefitinib (2020), Ibrutinib (2022), Pazopanib (2017), Sorafenib (2021), Sunitinib (2015), Vandetanib (2017). 5. For trametinib, a first FDA PSG draft in 2016 proposed a randomised, open-label, once daily repeated dosing, 2x2 cross-over trial in patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations. Review	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		led to a substantially revised draft PSG (May 2022) favouring a randomised, open-label, single-dose, 2x2cross-over trial in healthy volunteers investigating the highest strength of 2 mg, i.e. a design that is agreement with our proposal here. **Proposed change:** Single dose Cross-over Healthy volunteers.	
Line 16 Bioequivalence study design	5	**Comment:** For BE studies with the purpose of comparing a test and reference formulation, the highest strength (not the highest clinical dose) is recommended to be used. **Proposed change:** Strength: 2 mg Number of studies: one single-dose study Other critical aspects: Subjects with pertinent mutations or any sign or history of malignancy or premalignancy will be excluded from enrolment. Follow-up to be extended up to 1 month after last dosing.	**Accepted that a single dose cross-over study can be conducted in healthy subjects (see above; first specific comment)**
Line 16 Bioequivalence assessment	5	**Comment:** See above (as applicable to a single-dose profile). **Proposed change:** Main pharmacokinetic variables: AUC0-72 and Cmax.	**Accepted**

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 16 Bioequivalence study design	7	**Comment:** "a study in patients is recommended due to safety reasons." The current safety profile of Trametinib is based on repeated administration in indicated malignancies with a BRAF V600 mutation; as a monotherapy or in combination with dabrafenib for the treatment of adult patients with unresectable or metastatic melanoma; in combination with dabrafenib for the adjuvant treatment of adult patients with Stage III melanoma, following complete resection; in combination with dabrafenib for the treatment of adult patients with advanced non-small cell lung cancer. In all the above indications, trametinib is administered at a dose of 2 mg/day, until the patient no longer derives benefit or develops unacceptable toxicity. Even in the adjuvant melanoma setting, patients are treated for a period of 12 months unless there is disease recurrence or unacceptable toxicity. However, recently reported healthy adult volunteers' studies demonstrate acceptable safety and tolerability profiles when Trametinib was administered at 2 mg, as a single dose: • An open-label, phase 1, single-dose, randomized, 2-treatment, 2-period crossover study (n=65) in healthy volunteers, was conducted to evaluate bioavailability of a single 2-mg tablet of trametinib containing 9% dimethyl sulfoxide (DMSO) (test formulation) vs bioavailability of a 2-mg tablet of trametinib containing 11% DMSO (reference formulation). Majority of the adverse events reported were mild in severity, with 1 participant experiencing grade 3 headache, and no grade 4 or grade 5 AEs. No new safety findings were observed. [Tan EY et al., 2023-1] • A randomized, open-label, 2-part, 2 × 2	**Accepted that a single dose cross-over study can be conducted in healthy subjects (see above; first specific comment)**

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		crossover, phase 1 study (n=30) was conducted to evaluate, the effect of a low-fat, low-calorie (LFLC) meal on the relative bioavailability of a trametinib 2-mg tablet or dabrafenib 150-mg capsule in healthy participants. The safety conclusions of the study were, as follows: Overall, 12 (40.0%) and 5 (19.2%) participants experienced at least 1 AE in the trametinib arm and the dabrafenib arm, respectively. The most common AEs were catheter site pain, diarrhoea, and headache (2 [6.7%] participants each) in the trametinib arm. Four participants (13.3%) reported 6 AEs related to trametinib treatment. Permanent discontinuation due to an AE occurred in 2 participants in the trametinib arm; One participant randomly assigned to receive trametinib under fed and fasted conditions tested positive for coronavirus disease 2019 on Day 28 that was reported to be resolved on day 51 and was not deemed to be related to the study drug. Another participant randomly assigned to receive trametinib under fed and fasted conditions experienced a severe AE of chorioretinopathy on Day 28, which was resolved on Day 87 and was deemed to be related to the study drug. No serious AEs or deaths occurred during the study. (Tan EY et al., 2023-2). Results of the above-mentioned studies show that there is no significant safety concern after administration of single dose of trametinib to healthy volunteers. Appropriate risk mitigation strategies [e.g., excluding participants with pre-existing ophthalmic conditions] (FDA Draft Guidance on Trametinib Dimethyl Sulfoxide May 2022) can be considered. More-over the healthy volunteers can be dosed under controlled conditions (by admitting in Phase I unit) and monitored for occurrence of any adverse event, and	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		appropriately managed, if any adverse event occurs. Furthermore, as summarized in Table 01, there is no significant difference in the PK profile between healthy volunteers versus patient population: Table 01 Single dose PK Parameters Healthy Volunteers (Arithmetic Mean) (Tan EY et al., 2023-2) Healthy Volunteers (Arithmetic Mean) (Tan EY et al., 2023-1) Patients (Arithmetic Mean) (Leonowens C et al., 2014) Cmax (ng/mL) 7.68 8.47 8.03 AUC0-t (ng.hr/mL) 332 339 248 AUC0-inf (ng.hr/mL) 431 580 525 Tmax (hrs) 1.29 (1.00–4.98) 1.50 (1.00; 4.00) 1.50 (1.00 to 1.58) T half (hrs) 218 141 264 In addition, healthy volunteers constitute a homogenous population without comorbidities, and concomitant medications, thus a healthy volunteer population is more sensitive to establishing bioequivalence than a patient population. Patients constitute a heterogenous population with potential comorbidities and use concomitant medications. Conducting a large PK BE study in patients at multiple clinical sites is not always a practical option given the operational challenges (e.g., multiple PK sampling). In summary, because a study in patients would not add significant scientific value and would potentially delay patient access to this important product by increasing the time necessary for recruitment, we suggest revising the study recommendation to healthy adult volunteers. References 1. Tan EY, Chiparus O, Choudhury S, Kim C, Lau M, Ziltener C, Ilankumaran P. Comparative Bioavailability of a Single Dose of Trametinib (TMT212) Containing 9% vs 11% Dimethyl Sulfoxide in Randomized Healthy Volunteers to Assess Long Term Storage at Room Temperature.	

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		Clin Pharmacol Drug Dev. 2022 Oct;11(10): 1203-1210. 2. Tan EY, Pazdirkova M, Taylor AJ, Singh N, Iyer GR. Evaluation of a Low-Fat Low-Calorie Meal on the Relative Bioavailability of Trametinib and Dabrafenib: Results from a Randomized, Open-Label, 2-Part Study in Healthy Participants. Clin Pharmacol Drug Dev. 2023 Mar;12(3):333-342 3. Leonowens C, Pendry C, Bauman J, Young GC, Ho M, Henriquez F, Fang L, Morrison RA, Orford K, Ouellet D. Concomitant oral and intravenous pharmacokinetics of trametinib, a MEK inhibitor, in subjects with solid tumours. Br J Clin Pharmacol. 2014 Sep;78(3):524-32. 4. Product Specific Guidance – EMATrametinib 5. FDA Draft Guidance on Trametinib Dimethyl Sulfoxide May 2022 **Proposed change:** "a study in healthy adult volunteers is recommended."	
Line 16 Bioequivalence study design	7	**Comment:** "number of studies: one multiple dose study." Dose linearity after single versus multiple dose: Following single dose administration, trametinib AUC0-24 increased in a greater than dose-proportional manner with a mean slope (90% CI) of the power model of 1.30 (1.08 - 1.52), while increases in Cmax were generally dose-proportional with a mean slope (90% CI) of	**Accepted that a single dose cross-over study can be conducted in healthy subjects (see above; first specific comment)**

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the power model of 1.08 (0.90-1.25). Increases in Day 15 (steady-state) AUC0-24 and Cmax were generally dose-proportional with once-daily doses of 0.125 to 4 mg of the product, and this was confirmed in another study for the 1 to 2 mg dose range. (SmPC-2024: Mekinist, 0.5mg and 2mg film coated tablets) Viatris thus considers a single dose PK study (with Cmax and AUC0-72hrs as endpoints) to be more sensitive than a multiple dose PK study for establishing bioequivalence. References 1. Summary of Product Characteristics-Mekinist-Mar 2024. **Proposed change:** "number of studies: one single dose study."	