07 April 2025
EMA/339228/2024
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Dabrafenib hard capsule 50 and 75 mg product-specific bioequivalence guidance' (EMA/CHMP/39771/2023)

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	Lotus Pharmaceuticals Limited
3	Midas Pharma GmbH
4	Synthon B.V.
5	Viatris Inc.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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 dabrafenib. In brief, considering the known properties of dabrafenib 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 are detailed in the comments below.	**Not accepted** While the risk of development of new malignancies seems to be associated with repeated and higher dosing, a threshold cannot be determined and the exact level of risk cannot be predicted. The risk of malignancy associated with a dabrafenib 75 mg single-dose cross-over study in healthy volunteers cannot be excluded based on the mechanism of action and available nonclinical and clinical data. Therefore, it is not accepted that a single-dose cross-over study can be conducted in healthy subjects
2	**Comment:** The 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	**Not accepted** See above; response to first general comment.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	on single dose of Dabrafenib have been conducted on healthy adult population and no safety concerns have been reported.3,4 As per the EMA guidance on bioequivalence, we would like to propose a single dose, two-way, crossover bioequivalence fasting study in adult, healthy male population.	
3	**Comment:** Midas Pharma welcomes the opportunity to comment on the dabrafenib 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 presently proposed in the draft. Dabrafenib is an immediate-release oral product with dose-proportional pharmacokinetics on single dosing. For such a product, 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 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.	**Not accepted** See above; response to first general comment.
4	**Comment:**	**Not accepted** See above; response to first general comment.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	The draft product-specific guidance for 50 and 75 mg dabrafenib hard capsules (EMA/CHMP/39771/2023, 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 dabrafenib two single-dose studies have been published in healthy male and female volunteers of non-childbearing potential with a dose of 100 mg (2 capsules of 50 mg) and a dose of 150 mg (2 capsules of 75 mg) (Novartis, 2019 and Tan et al., 2023). Based on publicly available information, these studies were performed without safety concerns. 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).	
5	**Comment:** Viatris is pleased to provide comments to EMA's draft product-specific bioequivalence guidance, which outlines the Agency's recommendations for	**Not accepted** See above; response to first general comment.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	multi-dose cross over studies 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 dabrafenib and a single dose PK study is more sensitive than multiple dose PK study for the demonstration of bioequivalence. Hence, in conclusion, single 75 mg dose PK study in healthy volunteers is recommended to demonstrate bioequivalence.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 16 Bioequivalence study design	1	**Comment:** 1. Dabrafenib hard capsules 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. Dabrafenib is a non-genotoxic, small-molecule drug that acts as a reversible, highly selective BRAF inhibitor. Because of this specificity, there is no prior reason to preclude healthy subjects from a single-dose cross-over investigation with dabrafenib, provided that caution is taken when selecting and monitoring trial participants. Indeed, while molecular-targeted, dabrafenib'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	**Not accepted** See above; response to first general comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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 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. Moreover, the Originator, who may be expected to have the best access to all safety-relevant data in this regard, selected healthy volunteers in different single-dose studies: i) Healthy volunteers were chosen as controls in single-dose studies analysing the pharmacokinetics and safety of dabrafenib in patients with renal (NCT02852239) or hepatic	

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		dysfunction (NCT02873650); ii) Healthy volunteers were enrolled in biopharmaceutical single-dose cross-over studies investigating novel formulations (tablets for suspension) and special food effects (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. 5. 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 dabrafenib. 2. For BE studies with the purpose of comparing a test and reference formulation, the highest strength (not the highest	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		clinical dose) is recommended to be used (e.g. EMA/CHMP/693923/2016 PSG on Panzopanib). Although the therapeutic unit dose is 2x75 mg, the study should be carried out with the highest strength, i.e. comparing single doses of 75 mg. **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: A study in patients is recommended due to safety reasons. Strength: INSERT: 75 mg. DELETE: The therapeutic dose should be administered (2 x 75 mg twice daily). Number of studies: DELETE: one multiple dose study INSERT: one single-dose study Other design aspects: INSERT: Subjects with BRAF-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 dabrafenib administration prior to PK sampling. DELETE: Co-	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		medication of medicines that could affect the pharmacokinetics of dabrafenib should be avoided, if possible, and if not, their use should be well documented. DELETE: A bioequivalence study for dabrafenib during combination therapy with trametinib is acceptable.	
Line 16 Bioequivalence assessment	1	**Comment:** See above (as applicable to a single-dose profile) **Proposed change:** Main pharmacokinetic variables: DELETE: AUC0-tau and Cmax,ss INSERT: AUC0-tlast and Cmax	**Not accepted** See above; response to first general comment.
Line 16	2	**Comment:** Strength: 75 mg. The therapeutic dose should be administered (2 x 75 mg twice daily). Rational: As Applicant proposing the single dose 75 mg study in healthy subjects. Background: Although the increase in exposure is less than dose-proportional after repeat twice daily dosing, probably due to induction of its own metabolism, the therapeutic dose is recommended in patients (two 75 mg capsules twice daily). Individuals on a lower dose can participate in the bioequivalence	**Not accepted** See above; response to first general comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		study as long as the same dose is administered to them throughout the study. Rational: Comment: Background: Although the increase in exposure is less than dose-proportional after repeat twice daily dosing, probably due to induction of its own metabolism, the therapeutic dose is recommended in patients (two 75 mg capsules twice daily). Individuals on a lower dose can participate in the bioequivalence study as long as the same dose is administered to them throughout the study. Rational: As Applicant proposing the single dose 75 mg study in healthy subjects. Above background information is not required. Other design aspects: Minimum 14 days of dabrafenib administration prior to PK sampling. Co-medication of medicines that could affect the pharmacokinetics of dabrafenib should be avoided, if possible, and if not, their use should be well documented. A bioequivalence study for dabrafenib during combination therapy with trametinib is acceptable. Rational: As Applicant proposing the single dose 75 mg study in healthy subjects. Above Other design aspects information is not required.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Number of studies: one multiple dose study. Rational: As Applicant proposing the one single dose study in healthy subjects. Main pharmacokinetic variables: AUC0-tau and Cmax,ss Rational: Comment: Main pharmacokinetic variables: AUC0-tau and Cmax,ss Rational: As Applicant proposing the one single dose 75 mg study in healthy subjects. The main pharmacokinetic variable is Cmax and AUC0-t. **Proposed change:** Strength: 75 mg single dose in healthy subjects. Background: Highest strength (75 mg) to be used for a drug with linear pharmacokinetics. Other design aspects: NA. Number of studies: one single dose study. Main pharmacokinetic variables: Cmax and AUC0-t.	
Line 16	2	**Comment:** The applicant believed that multiple dose study in patients (with melanoma or non-small cell lung carcinoma (NSCLC)) deemed	**Not accepted** See above; response to first general comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Bioequivalence study design		to be not necessary. The applicant proposed Bioequivalence study in 'Healthy Adult Human Male Subjects': We believe single dose bioequivalence study is feasible on normal healthy adult male subjects based on following facts: The risk of malignancy associated with Dabrafenib 75 mg Single dose in healthy volunteers is very limited. •In vitro tests in bacteria and cultured mammalian cells, and an in vivo rodent micronucleus assay are not mutagenic or clastogenic as a dabrafenib. The innovator has not been conducted the carcinogenicity studies with dabrafenib.1,2 It was proven that the dabrafenib is not carcinogenic in animals. •No dose-limiting toxicities were observed at the cumulative dose of 3.35mg/kg3. Dabrafenib safety profile does not significantly differ over the dose range given across a day. In addition, studies in animals that focused on overdosing did not reveal any organ toxicity and the originator has not conducted carcinogenicity studies. The maximum dose tested the dabrafenib 300 mg/day was administered to humans.[3] •During the Dabrafenib 150 mg as a monotherapy. The malignancies are reported in 10% of patients; 2% of cutaneous squamous cell carcinoma and 1% of non-cutaneous malignancies and uveitis were reported in the median time frame of 18–31 weeks treatment.[1,2] No new	

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		primary melanoma was reported from the NSCLC study.[2] Hence as per the provided information malignancy have been reported with the long term use of the drug and a single dose study with dermatological evaluation before dosing should minimize the risk of cutaneous malignancy. •The sum of healthy subject's literatures is available in public domain of Dabrafenib 150 mg Single dose. Summary of safety and pharmacokinetic profile related data described in below. •Relative bioavailability study of Dabrafenib on Healthy subject (Eugene Y. Tan et.al., 2023)4, The study was conducted in healthy subjects (N=26) and administered single dose of Dabrafenib 75mg capsule. Eligible participants included male and female adults aged 18–70 years with body weight of 50–150 kg and body mass index of 18–30 kg/m2. The most common AEs observed in both fast and fed with monotherapy are headache, myalgia, nausea, and blurred vision. None of the participants experienced an AE that led to permanent drug discontinuation in the dabrafenib arm. No serious AEs or deaths occurred during the study. Pharmacokinetic profile from Literature: Cmax: SmPC: 2100 ng/ml Literature: 2097 ng*hr/ml AUC: SmPC: 9570 ng/ml Literature: 9571 ng*hr/ml Tmax: SmPC: 2 hrs (1.0-4.0 hrs) Literature: 2 hrs (1.0-4.0 hrs) From the above data the	

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		pharmacokinetic parameters are comparable between the patients and healthy volunteers. •Age, Gender, weight and renal impairment does not have any clinically relevant effect on the pharmacokinetics of dabrafenib, as stated in the product label of Tafinlar and Literature. •The Innovator (Tafinlar) has done a relative bioavailability of two new oral suspension formulations of dabrafenib (10 x 10 mg dispersible tablets reconstituted in water) in comparison to dabrafenib HPMC capsules (2 x 50 mg) following a single oral dose of 100 mg in healthy adult volunteers (N=26). The healthy subjects received a dose of 100 mg and study has been completed. Considering that Dabrafenib single dose of 100 mg is safe in healthy subjects as there were no adverse events reported in the study. (Public Assessment Report of Finlee, Procedure No. EMEA/H/C/005885/0000).[5] •A single dose parallel study was conducted to evaluate the pharmacokinetic and safety of dabrafenib 100 mg in healthy subjects with normal renal function and subjects with impairment renal function. Total 22 subjects were enrolled and completed the study and there are no adverse events reported. The dabrafenib pharmacokinetic parameters are almost similar with healthy subjects and patients.[6] •Dabrafenib has not been reported as a Narrow Therapeutic Index drug by any of the	

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		regulatory agencies in the assessment and evaluation report and it is not considered a steep concentration-response product during any of the dose-finding, Phase-I to Phase-III study. •Dabrafenib as a monotherapy in patient and healthy subjects will have the common adverse events observed: hyperkeratosis, hypertension, blurred vision, headache, pyrexia, arthralgia, fatigue, nausea, papilloma, alopecia, rash, and vomiting. Based on available literature and SPC data, the pharmacokinetic profile will be same in both (patients and healthy) subjects. Due to potential of the drug to cause embryo -fetal toxicity we are proposing to conduct the study in healthy adult male volunteers who do not wish to procreate in the near future and agree to use condoms with spermicide during heterosexual intercourse from day 1 of this study and until 6 months after the last treatment. With the published clinical, toxicology and available safety data, it is evident that, Dabrafenib could be administered at single dose in healthy subjects by incorporating adequate safety measures during study conduct. The safety and PK profile of Dabrafenib will be considered for a single dose of 75 mg capsule and may not pose a safety concern in healthy male subjects.	

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		The safety parameters and the following precautions will be considered in the pre and post study. •12-lead ECG, 2D ECHO - to evaluate LVEF and subjects with < 50 % will be excluded from study, Ophthalmic examination with fundoscopy, Haematology including prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio, fibrinogen levels, Electrolytes, Glucose-6- phosphate Dehydrogenase (G6PD) test will be conducted at screening and those volunteers having reported deficiency will be excluded from participation in the study. Random glucose level, Biochemistry, Urine analysis and other safety parameters to be monitored prior and post study conduct. •History of skin and allergic reaction will be checked at the time of screening and subjects having any dermatological condition should be excluded from participation in the study. •Cardiologist should be available at the facility from dosing to completion of the study. •After 30 days, an ECG and 2D Echo should be performed to ensure the cardiac' safety of the subject.	

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		•At the time study conduct, principal investigator should take care for additional safety adverse events (Ex: Pyrexia, skin rashes etc…) Based on the above information, the applicant would like to propose a single dose, bioequivalence study in normal healthy adult male subjects for establishing the similarity between the two products. 1) EU Tafinlar 75 mg hard capsules® smpc 2) Tafinlar Capsules 75 mg, Novartis Pharma K.K. Report, the Deliberation Results - February 24, 2016. Pharmaceuticals and Medical Devices Agency 3) Tafinlar Capsules 50 mg, Novartis Pharma K.K. January 21, 2016 4) Eugene Y. Tan, 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). 5) Public Assessment Report of Finlee. Procedure No. EMEA/H/C/005885	

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		/0000 Published on 14 September 2023 (EMA/443504/2023). 6) Novartis (protocol number – CDRB436A2106), A single dose parallel study was conducted to evaluate the pharmacokinetic and safety of dabrafenib 100 mg (Phase I). **Proposed change:** Single dose cross-over Healthy Volunteers.	
Line 16 Bioequivalence study design	3	**Comment:** 1. Dabrafenib is a selective BRAF inhibitor, i.e. a molecular targeted non-genotoxic small-molecule drug with specific pharmacological action 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 dabrafenib, provided that caution is taken when 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 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.	**Not accepted** See above; response to first general comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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 different single-dose studies: - Healthy volunteers were chosen as controls in single-dose studies analysing the pharmacokinetics and safety of dabrafenib in patients with renal (NCT02852239) or hepatic dysfunction (NCT02873650). - Healthy volunteers were enrolled in biopharmaceutical single-dose cross-over studies investigating novel formulations (tablets for suspension) and special food effects (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 there are no safety concerns that should prevent the inclusion of healthy subjects from enrollment in a single-dose cross-over BE investigation. For some kinase inhibitors, EMA guidance might consider BE studies to be conducted in patients for precautionary matters; this approach was adopted for lapatinib which carries a well-established risk of hepatotoxicity. No such risk was established for dabrafenib	

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		and thus, 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),	

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		Pazopanib (2017), Sorafenib (2021), Sunitinib (2015), Vandetanib (2017). **Proposed change:** Single dose Cross-over Healthy volunteers.	
Line 16 Bioequivalence study design (strength, number of studies, other aspects)	3	**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 (e.g. EMA/CHMP/693923/2016 PSG on Panzopanib). Although the therapeutic unit dose is 2x75 mg, the study should be carried out with the highest strength, i.e. comparing single doses of 75 mg. **Proposed change:** Strength: 75 mg. Number of studies: one single-dose study. Other design aspects: Subjects with BRAF-mutations or any sign or history of malignancy or premalignancy will be excluded from	**Not accepted** See above; response to first general comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		enrollment. Follow-up to be extended up to 1 month after last dosing.	
Line 16 Bioequivalence assessment	3	**Comment:** See above (as applicable to a single-dose profile). **Proposed change:** Main pharmacokinetic variables AUC0-tlast and Cmax.	**Not accepted** See above; response to first general comment.
Line 16 Bioequivalence study design	5	**Comment:** "a study in patients is recommended due to safety reasons." The current safety profile of dabrafenib is based on repeated administration in indicated malignancies with a BRAF V600 mutation; as a monotherapy or in combination with trametinib for the treatment of adult patients with unresectable or metastatic melanoma; in combination with trametinib for the adjuvant treatment of adult patients with Stage III melanoma, following complete resection; in combination with trametinib for the treatment of adult patients with advanced non-small cell lung cancer. In all the above indications, dabrafenib is administered at a higher dose of 300mg/day [150mg (2x75mg) twice daily], until the patient no longer derives benefit or	**Not accepted** See above; response to first general comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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 had acceptable safety and tolerability profile, when dabrafenib was administered at 100-150mg, as single dose: • The results from a randomized, open-label, 2-part study conducted to evaluate the effect of a low fat, low-calorie meal on the relative bioavailability of trametinib and dabrafenib in healthy volunteers showed that, the most common AEs reported in the dabrafenib arm were headache, myalgia, nausea, and blurred vision. None of the participants experienced an AE that led to permanent drug discontinuation. No serious AEs or deaths occurred during the study. [Tan EY et al., 2023] • In a Phase I, open label, multi centre, single dose study, the pharmacokinetics (PK) of dabrafenib in healthy volunteers with normal renal function and with impaired renal function was evaluated and, all healthy volunteers completed the study without any significant safety issues. [CDRB436A2106, Clinical Trial Phase 1 Results, Novartis] Results of the above-mentioned studies show that there is no significant safety concern after administration of single dose of dabrafenib to healthy volunteers. Appropriate risk mitigation	

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		strategies [e.g., including participants without any pre existing illness and, regular monitoring) 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 events and appropriate management can be provided if any adverse event occurs. Hence, study in healthy volunteers is recommended to establish bioequivalence. Furthermore, as summarized in Table 01, there is no significant difference in the PK profile between healthy volunteers versus patient population (Puszkiel A. et al., 2019 and Tan EY et al., 2023). Table 01: Single dose pharmacokinetic parameters of dabrafenib 150 mg observed in healthy vs patient population. Single dose PK Parameters Healthy Volunteers (Arithmetic Mean) Patients (Arithmetic Mean) Cmax (ng/mL) 2310 2160 AUC0-t (ng.hr/mL) 10300 11843 AUC0-inf (ng.hr/mL) 10300 12120 Tmax (hrs) (Range) 2.03 (1.02–4.08) 2.0 (1.0–4.0) T half (hrs) 9.5 8.4 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.	

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		Conducting a large PK BE study at multiple clinical sites in patients 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 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. 2. Clinical Trial Results, CDRB436A2106, Clinical Trial Phase 1, Novartis. 3. Puszkiel A. et al., Clinical Pharmacokinetics and Pharmacodynamics of Dabrafenib. Clin Pharmacokinet 2019 Apr;58(4):451-467. doi: 10.1007/s40262-018-0703-0. **Proposed change:** "a study in healthy adult volunteers is recommended."	
Line 16	5	**Comment:** "number of studies: one multiple dose study."	**Not accepted** See above; response to first general comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Bioequivalence study design		Dabrafenib exposure (Cmax and AUC) increased in a dose proportional manner between 12 mg and 300 mg following single-dose administration, but the increase was less than dose-proportional after repeated twice daily dosing (a decrease in exposure was observed with repeat dosing, likely due to induction of its own metabolism) [SmPC-2023: Tafinlar 50mg, 75 mg hard capsules]. Thus, a single dose PK study (at a dose of 75mg) is considered to be more sensitive than a multiple dose PK study for establishing bioequivalence. References 1. Tafinlar 50mg, 75 mg hard capsules SmPC-2023. **Proposed change:** "number of studies: one single dose study."	