23 February 2017
EMA/CHMP/803499/2016
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Vemurafenib film-coated tablets 240 mg product-specific bioequivalence guidance' (EMA/CHMP/476248/2016)

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

Stakeholder no.	Name of organisation or individual
1	F. Hoffmann-La Roche Ltd

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	With reference to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 rev. 1/ corr) where it is mentioned that alternative designs for Bioequivalence study can be accepted under exceptional circumstances, the MAH would recommend the use of a multiple dose parallel design study as an alternative for the following reasons: **1- Vemurafenib's non stationary Pharmacokinetic profile:** The steady state exposure for vemurafenib cannot be predicted with single dose data as the pharmacokinetics (PK) of vemurafenib are not stationary. In study NP25163: *A Phase I, randomized, open-label, multi-center, multiple dose study to investigate the pharmacokinetics and pharmacodynamics of RO5185426 administered as 240 mg tablets to previously treated BRAF V600E positive metastatic melanoma patients*, the mean observed accumulation ratio (~23 fold, N=11) following 14 days of 960 mg bid dosing was much more than expected from the observed single dose half-life and the observed mean terminal half-life was **34 hours** (N=11) following 14 days of 960 mg bid dosing of vemurafenib. From population PK approach, the median of the individual elimination half-life estimate for vemurafenib is **57** hours (the 5th and 95th percentile range is 30 to 120 hours) following multiple doses. Both of these half-life values are longer than the observed half-life from the single-dose data. In a single dose study NP25396: *A Phase I, Randomized, Open-Label, Multi-Center, Two-Period, Crossover Study to Investigate the*	Partly accepted. 1) Vemurafenib exhibits time-dependent pharmacokinetics, however, if bioequivalence following single dose can be demonstrated for test and reference product, a similar time-dependency for test and reference product is expected and no steady-state study would be necessary for this reason. 2) It is acknowledged that the inter-subject variability in pharmacokinetics following single dose administration is high. This might be a challenge to get a sufficiently powered study requiring a large number of patients. Under steady-state conditions the inter-subject variability is lower and a cross-over study is feasible. 3) Zelboraf is an immediate release formulation. For an immediate release formulation, it is accepted that the absorption phase has been completed 72h after administration. The elimination phase can continue for a much longer period of time. For that reason a truncated AUC0-72h is considered an acceptable endpoint for absorption of substances with a long elimination half-life. (Guideline on the investigation

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	*Effect of Food on the Pharmacokinetics of a Single Oral Dose of RO5185426, Followed by Administration of 960 mg RO5185426 Twice Daily to BRAFV600E Positive Metastatic Melanoma Patient*s, the observed mean terminal half-life was 25-26 hr (N=16 for Fasted condition, N=15 for Fed condition, dose 960 mg). **2- High inter-subject variability from single dose study** Another consideration is the PK variability difference between single dose and multiple dose study for vemurafenib. For a single dose study (NP25396), the CV% was 59% for Cmax, and 93% for AUCt under fasted condition, and 27% for Cmax and 49% for AUCt under fed condition. In the multiple dose study NP25163, the CV% was 37% for Cmax, and 32% for AUC0-8 following 14 days of 960 mg bid dosing of vemurafenib, while the Day 1 value (first dose) was 70% for Cmax, and 70% for AUC0-8 in the same study. These results suggest that the variability associated with Cmax and AUC are higher in a single dose study, which will make a sufficiently powered study a challenge with the requirement of large number of patients. **3- Likely inadequate study evaluation period:** Although according to the guidance, AUC truncated at 72 h (AUC(0-72h)) may be used as an alternative to AUC(0-t) for comparison of extent of exposure as the absorption phase has been covered by 72 h for immediate release formulations. The 3-day period recommended for the single dose design is likely insufficient to fully characterize the extent of absorption for vemurafenib (AUC). From study NP25396, the median Tmax is 4-hr with a range of 2-12.58 hr under fasted conditions, and 8-hr with a range of 5-16 hr under fed condition. The wide range of Tmax	of bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). A 3-day delay in start of treatment is considerably shorter than the two-times 10-days wash-out period as was conducted in study NP25396. A pronounced food effect has been demonstrated for the absorption of vemurafenib following single dose administration of Zelboraf. A bioavailability study under steady-state conditions will not provide data on fasted/fed conditions as the peak-to-trough concentrations are close to 1, but the steady-state concentrations reached will be influenced by the administration of vemurafenib with regards to meal and type of meal during the period to reach steady-state. Thus, because of the pronounced food effect of Zelboraf, meal conditions should be controlled during the bioavailability study. In conclusion, a comparable bioavailability study of two formulations under single dose conditions is considered the most sensitive to detect differences in absorption of vemurafenib under fasted and fed conditions. However, it is acknowledged that delay of treatment even though only for 3 days may be a concern. Therefore, a comparative bioavailability study under steady-state conditions can be accepted. As there is a pronounced food effect for Zelboraf, administration with regard to food intake should be well controlled.

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	suggests the absorption process may be more complicated than what is generally observed in a simple immediate release formulation. The mean terminal half-life was 24.94 hr with a range of 6.39-61.51 hr under fasted condition, and 26.46 hr with a range of 8.72-65.75 hr under fed condition, These results suggest that 3-day period may represent less than 3-half -lives for the majority of patients, and just around 1-half-life for some individuals. Thus the AUC may not be accurately evaluated by the current recommended single dose design. In addition, the single dose study will delay the patient from active therapy, for at least 3-days based on the current recommendation. Therefore the MAH believes that multiple dose study seems more appropriate for BE evaluation for vemurafenib. The recommended design is a parallel design with ~20 days 960 mg BID dose in BRAFV600mutated patients and the PK variables will be AUCtau and Cmax on Day 20. Day 1 values will be collected, but not as endpoint parameters. Considering the feasibility of fasting or fed in cancer patients for ~20 days, the MAH would suggest a light meal.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Table in line 17		Comment: Please refer to general comments, paragraph 1 to 3 Proposed change (if any): ~~**Single dose**~~ **multiple doses** Comment: Please refer to general comments paragraph 1 and 3 Proposed change (if any): ☒ **fed** ☐ ~~**both**~~ **Background:** light meal ~~both fasting and fed are necessary due to specific formulation characteristics~~ Comment: Please refer to general comments paragraph 2 and 3 Proposed change (if any): **Strength:** 240 mg **Background:** 960 mg BID for 20 days. ~~240 mg is the only strength but the clinical dose of 960 mg could be~~	**Partly accepted (see text above)** **multiple-dose, cross-over** ☐ **fasting** ☒ **fed** ☐ **both** ☐ **either fasting or fed** **Background:** Bioequivalence study needs to be conducted in patients. There is a pronounced food effect for Zelboraf, administration with regard to food intake should be well controlled. **Strength:** 240 mg **Background:** 240 mg is the only strength but the clinical dose of 960 mg BID should be used.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~used~~ Comment: Please refer to general comments paragraph 2 and 3 Proposed change (if any): **Number of studies:** one multiple doses study (960 mg BID for 20 days). ~~two single dose studies (fasting and fed)~~ Comment: Please refer to general comments paragraph 3 Proposed change (if any): **Other critical aspects:** ~~cancer treatment with vemurafenib could be started at day 4.~~ Comment: Please refer to general comments paragraph 3 Proposed change (if any): **Main pharmacokinetic variables:** ~~AUC_{0-72}~~ AUC_{tau} and C_{max}	**Number of studies:** One multiple dose study (960 mg BID, administration with regard to food intake should be well controlled) **Other critical aspects:** Achievement of steady-state conditions should be demonstrated. Co-medication of medicines that could affect the pharmacokinetics of vemurafenib should be avoided, if possible, and should be documented well. **Main pharmacokinetic variables:** **Multiple dose:** $AUC_{0-\tau}$, $C_{max,ss}$ and $C_{\tau,ss}$