26 July 2018
EMA/CHMP/398811/2018
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Vismodegib hard capsule 150 mg product-specific bioequivalence guidance' (EMA/CHMP/800794/2017)

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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1. General comments - oeverview

Stakeholder number	General comment (if any)	Outcome (if applicable)
1	Vismodegib demonstrates a unique single-dose pharmacokinetic (PK) profile, with sustained plasma concentration over several days contributing to a long terminal elimination half-life of 12 days; however, steady-state concentrations (Css) are typically achieved within only 7 days (Graham et al., Single and multiple dose intravenous and oral pharmacokinetics of the hedgehog pathway inhibitor vismodegib in healthy female subjects, Br J Clin Pharmacol 2012, 74:788–796). Furthermore, vismodegib displays nonlinear PK with respect to dose, with no increase in steady-state plasma concentrations when increasing the daily dose from 150 to 270 or 540 mg (LoRusso et al., Phase 1 trial of hedgehog pathway inhibitor vismodegib (GDC-0449) in patients with refractory, locally advanced or metastatic solid tumours, Clin Cancer Res 2011, 17:2502–2511). These unusual PK properties have been attributed to two distinct processes: (a) solubility-limited absorption related to the poor solubility of vismodegib and (b) high-affinity saturable plasma protein binding. In the single- and multiple-dose absolute bioavailability vismodegib PK study in healthy subjects, it was	Not accepted. It is agreed that the pharmacokinetics of vismodegib is complex. Vismodegib displays non-linear pharmacokinetics in total as well as unbound concentrations, with less than dose-proportional increases in exposure. This has been suggested to be due to two different mechanisms, saturable binding to AAG and solubility-limited absorption. Despite this, available data suggests that single-dose data, where protein binding is not saturated, is more relevant for evaluating differences between formulations. As described by LoRusso et al (2011), the single dose data indicate an increase in total as well as free concentrations between the 150 mg and 270 mg doses, but no further increase after the 540 mg dose. However, increasing daily doses of 150, 270 and 540 mg resulted in similar plasma concentrations at steady-state. Thus, small differences in bioavailability due to formulation related differences are not expected to be possible to identify at steady-state. A single-dose bioequivalence study with the 150 mg dose is recommended.

Stakeholder number	General comment (if any)	Outcome (if applicable)
	observed that the oral steady-state exposure (AUC_{0-24h}) after multiple dosing was approximately eight-fold lower when compared with the area under the plasma concentration-time curve from zero to infinity after a single dose (Graham et al., Single and multiple dose intravenous and oral pharmacokinetics of the hedgehog pathway inhibitor vismodegib in healthy female subjects, Br J Clin Pharmacol 2012, 74:788–796). However, the fact that the total clearance increased only by approximately two-fold (i.e., 81 %) suggests that the bioavailability is low for vismodegib and decreased considerably with multiple dosing. Moreover, in vitro vismodegib binds to both human serum albumin and human alpha-1-acid glycoprotein (AAG), with a higher affinity for AAG (Giannetti et al., Identification, characterization, and implications of species-dependent plasma protein binding for the oral Hedgehog pathway inhibitor vismodegib (GDC-0449), J Med Chem 2011, 54:2592–2601). Vismodegib Css and AAG plasma concentration are strongly correlated, with AAG levels explaining most (>70 %) of the PK variability observed in patients (Graham et al., Pharmacokinetics of hedgehog pathway inhibitor vismodegib (GDC0449) in patients with locally advanced or metastatic solid tumors: the role of alpha-1-acid glycoprotein binding, Clin Cancer Res 2011, 17:2512–2520).	

Stakeholder number	General comment (if any)	Outcome (if applicable)
	Given the unique PK of vismodegib and considerable differences between single dose and steady state PK characteristics, a multiple dose study with at least 7 days of daily dosing (with PK evaluation on Day 7 at steady state), is recommended for determination of bioequivalence.	

2. Specific comments on text

Line no.	Stakeholder no.r	Comment and rationale; proposed changes	Outcome
Table on line 17 Bioequivalence study design	1	Comment: The bioequivalence study should be a multiple dose evaluation given the nonlinear PK of vismodegib, therefore we recommend dosing once daily for 7 days. Proposed change (if any): Replace “Single dose” by ***Multiple dose (QD) with at least 7 days of dosing, with PK evaluation on Day 7 (steady-state).***	Not accepted (see above).
Table on line 17 fasting condition	1	Comment: Erivedge can be taken with or without food since the PK of vismodegib is not affected at steady-state (as reported in the SmPC Section 5.2). The bioequivalence study design has to reflect this aspect as no food effect is observed if the study uses multiple dosing (food effect is observed only with single dosing). Proposed change (if any): If study design is a multiple dose study then tick box ***“either fasting or fed”*** instead of “fasting” only.	Not agreed. Fasting is usually considered to be the most sensitive condition to detect a potential difference between formulations.
Table on line 17	1	Comment: Given the nonlinear PK of vismodegib, a single dose study is not recommended and multiple	Not accepted. A multiple-dose study is not recommended (see above).

Line no.	Stakeholder no.r	Comment and rationale; proposed changes	Outcome
AUC_{0-72h}		dose study would be needed, and hence primary PK parameter will be AUC_{0-24} at steady-state (if the bioequivalence study is a single dose study, then AUC_{0-72h} would not capture the elimination phase given the long half-life of vismodegib). Proposed change (if any): Replace "AUC_{0-72h}" by ***AUC_{0-24h} at steady-state***	In a single-dose study the absorption phase is expected to be covered by 72 h for immediate release formulations. A sampling period longer than 72 h is therefore not considered necessary for any immediate release formulation irrespective of the half-life of the drug.