15 September 2016
EMA/CHMP/641527/2016
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Erivedge

International non-proprietary name: vismodegib

Procedure No. EMEA/H/C/002602/II/0025/G

## Note

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

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## Assessment Timetable / Steps taken for the assessment

| Timetable | Planned dates | Actual dates |
|---|---|---|
| Start of procedure | 25 April 2016 | 25 April 2016 |
| CHMP Rapporteur Assessment Report | 27 May 2016 | 31 May 2016 |
| PRAC Rapporteur Assessment Report | 27 May 2016 | 31 May 2016 |
| PRAC members comments | 1 June 2016 | 1 June 2016 |
| Updated PRAC Rapporteur Assessment Report | 2 June 2016 | 3 June 2016 |
| PRAC Outcome | 9 June 2016 | 9 June 2016 |
| CHMP members comments | 13 June 2016 | 13 June 2016 |
| Updated CHMP Rapporteur Assessment Report | 16 June 2016 | n/a |
| Request for supplementary information | 23 June 2016 | 23 June 2016 |
| Submission of MAH's responses | 16 August 2016 | 11 August 2016 |
| Re-start of procedure | 17 August 2016 | 17 August 2016 |
| CHMP Rapporteur Assessment Report | 31 August 2016 | 2 September 2016 |
| PRAC Rapporteur Assessment Report | 22 August 2016 | 22 August 2016 |
| PRAC members comments | 24 August 2016 | 24 August 2016 |
| Updated PRAC Rapporteur Assessment Report | 25 August 2016 | n/a |
| PRAC Outcome | 2 September 2016 | 2 September 2016 |
| CHMP members comments | 5 September 2016 | 5 September 2016 |
| Updated CHMP Rapporteur Assessment Report | 8 September 2016 | n/a |
| Opinion | 15 September 2016 | 15 September 2016 |

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# 1. Background information on the procedure

## *1.1. Requested group of variations*

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Roche Registration Limited submitted to the European Medicines Agency on 23 March 2016 an application for a group of variations.

The following changes were proposed:

| **Variations requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.4 | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | Type II | I, II and IIIB |
| C.I.11.z | C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation | Type IB | None |
| C.I.11.z | C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation | Type IB | I |

Update of sections 4.4, 4.6, 4.8 and 5.1 of the SmPC in order to update safety and efficacy information in the product information after finalisation of study MO25616 (SOB013). Considering the fulfilment of the SOB the MAH is also proposing the switch of the conditional MA to a marketing authorisation not subject to specific obligations. Data from the same study also fulfilled the analysis required in MEA 005 regarding evaluation of the time for washout of vismodegib after treatment discontinuation and in MEA 008 regarding reporting of adverse events. The Package Leaflet and the RMP are updated accordingly. Furthermore the Marketing authorisation holder (MAH) has taken the opportunity to update the RMP based on the results from nonclinical studies assessed within variation EMEA/H/C/002602/II/21 and to propose deletion of hyponatraemia as an important potential risk in the RMP and as an ADR in the EU Product Information as discussed in previous PSUR (EMEA/H/C/PSUSA/00010140/201407).

The requested group of variations proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

## *1.2. Rationale for the proposed changes*

The submitted application concerns a Type II variation (Category C.I.4) to submit a Specific Obligation (SOB) and two post-approval measures (MEA) for Erivedge (vismodegib), (see Table 1 and Table 2 below). The SOB completes the post-authorisation measures for the Conditional Marketing Authorisation of Erivedge (vismodegib), as outlined in Annex II.E of the EU product information.

The variation is presented as a single variation since both the SOB and the MEAs are being addressed by providing data from the MO25616 (STEVIE) study primary analysis to assess the safety and efficacy of vismodegib in patients with advanced BCC.

**Specific Obligations (Table 1)**

| Area | Description | Due Date | Key conclusions of the data presented in this application |
|---|---|---|---|
| Clinical | SOB 013<br>Further data on safety and efficacy in patients with symptomatic mBCC from the primary analysis of Study MO25616. | 31/03/2016 | Safety profile and efficacy results from this study were consistent with those previously reported in other vismodegib studies, and vismodegib continues to demonstrate a clinically meaningful benefit in patients with mBCC that is balanced with a tolerable and manageable safety profile. |

**Follow-up Measures (Table 2)**

| Area | Description | Due Date | Key conclusions of the data presented in this application |
|---|---|---|---|
| Pharmaco-vigilance | MEA 005<br>PK substudy (within the safety study) to further evaluate the time for washout of vismodegib after treatment discontinuation | 31/03/2016 | MAH has changed their recommended time for washout of vismodegib for pregnancy prevention from 24 months to 9 months based on a new PK model that includes samples from Study MO25616. |
| Pharmaco-vigilance | MEA 008<br>Reporting of adverse events | 31/03/2016 | MAH believes the potential risks of sudden death, SPM, SCC of the skin, fractures, keratitis, and VTEs are unrelated to vismodegib.<br>Results from Study MO25616 suggest that amenorrhea may be reversible once vismodegib treatment is discontinued. |

With SOB 013, the MAH is submitting all requested data to fulfill the last remaining specific obligation for Erivedge. Therefore the MAH is requesting the CHMP to consider, in accordance with Article 7 of Commission Regulation (EC) No 507/2006, to adopt an opinion recommending the granting of a marketing authorization in accordance with Article 14(1) of Regulation (EC) No 726/2004 ('marketing authorization not subject to specific obligations'). The updated product information deleting all information referring to the conditional approval/specific obligations is provided as part of this submission as well as a clinical expert statement, in support of the possible granting of a 'marketing authorization not subject to specific obligations'.

The MAH also requests the closure of MEA 5 and MEA 8 within this application as the requested data are provided.

Moreover, the MAH has provided an updated RMP so as include results from the GLP-compliant nonclinical fertility study 12-2793 to further characterise the risk of impairment of fertility (assessed within procedure EMEA/H/C/002602/II/21; MEA 002) (first type IB variation).

Furthermore, the MAH takes this opportunity to remove hyponatraemia as an important potential risk in the enclosed EU RMP version 10 and as an ADR in the EU Product Information. The signal of hyponatraemia was refuted with the third PSUR (reporting interval 30 January 2014 – 29 July 2014) and accepted by the PRAC as stated in the final PRAC PSUR assessment report dated 12 February 2015 (Procedure No. EMEA/H/C/PSUSA/00010140/201407, second type IB variation).

# 2. Overall conclusion and impact on the benefit / risk balance

A primary clinical study report for MO25616 (STEVIE) - a single-arm, open-label, phase II, multicentre study to assess the safety of vismodegib in patients with locally advanced or metastatic basal cell carcinoma with (data cutoff 16 March 2015), is submitted in this type II variation. A pharmacokinetics sub-study of MO25616 is also included. The safety, efficacy, and pharmacokinetics data submitted allow the following conclusions:

- SOB 013:

  Efficacy, in terms of overall response rate, duration of response, and PFS is largely consistent with the pivotal study SHH4476g, and the interim analysis of MO25616. A request for supplementary information, made with regards to an apparent improvement in PFS in MO25616, has been answered by the MAH indicating that censoring inequalities, not study population or frequency/method of tumour assessments, explains the difference in PFS. Different sample sizes affect uncertainty in PFS estimates, but not the point estimate in a certain direction; the conclusion that sample size contributes to the observed difference is not understood. The MAH has not proposed any changes to the SPC reflecting PFS findings in MO25616, which is supported.

  As regards safety, there is an increase in mortality in the final analysis compared to the interim analysis of MO25616 (5.8 to 9.1%). In the context of a full marketing authorization on the basis of two single-arm clinical studies, the MAH has provided requested analyses and data aimed at contextualising fatal treatment-emergent adverse events in MO25616. No findings indicate a significant excess mortality caused by vismodegib. Further pursuing a reliable control population for the MO25616 patients is not considered meaningful.

  An analysis of reversibility of muscle spasms after treatment discontinuation includes 621 safety-evaluable patients who signed protocol version 3 or higher. Only 266 patients are reported. The seemingly low number of patients assessed for reversibility of muscle spasms (266) is mostly explained by ongoing treatment (41%) and less than 12 months of follow-up (39%). Fourteen percent were lost to follow-up.

  A conspicuous difference in grade 1 and 2 hypokalemia between November 2013 and March 2015 presumably reflects a change in classification. Different versions of CTCAE were used (4.0 November 2013, 4.03 March 2015), but this did not cause the observed difference. In the current report, all patients fulfilling the "< lower limit normal to 3.0 mmol/L" hypokalemia were assumed to be symptomatic or require treatment (considered a conservative assumption by the MAH), thereby qualifying for a grade 2 assignment. For the November 2013 analysis, this assumption was not made, and corresponding instances of hypokalemia were graded 1.

  The apparent increase in post-baseline grade 1 creatinine elevations reflected a difference in classification. A limited number of patients (11.5%) did not revert to < ULN before data cut off. Findings in the current report are consistent with those of November 2013. Based on results presented from the larger number of patients with biochemistry data available for CPK and creatinine (n □ 482), the MA
  increased CPK and creatinine elevation. This is agreed.

- MEA005:

  For the proposed new threshold, it is not considered sufficiently justified why to base the threshold on mouse anti-tumour data rather than on data from the embryofetal toxicity study. Furthermore, the PK data are felt to be too limited to exclude the possibility of unsafe exposure levels between 12 and 24 months. It does not seem appropriate to decrease the waiting time from 24 months post last dose. For this reasons after discussion as reported in the AR the MAH has backed away from their proposal to increase the threshold for concern for teratogenicity, based on the discussion presented in the CHMP AR and data from another hedgehog inhibitor, sonidegib. This is agreed

- MEA008:

  Reporting of adverse events. Completed.

In this Assessment Report, including the MAH's responses to outstanding issues, as specified in the RSI section 5 and summarised and assessed in section 6. The SOB 013, MEA005 and MEA08 can be considered fulfilled.

Furthermore, the submission of the final clinical study report for MO25616 (STEVIE) study satisfactorily fulfils the specific obligation imposed to the product, leads to comprehensive data being now available for this product and does not affect the benefit-risk balance of the product, which remains positive. The request of the MAH to receive a marketing authorisation no longer subject to Specific Obligations is therefore endorsed by the CHMP.

The benefit-risk balance of Erivedge remains positive.

# 3. Recommendations

Based on the review of the submitted data, this application regarding the following changes:

| **Variations accepted** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.4 | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | Type II | I, II and IIIB |
| C.I.11.z | C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation | Type IB | None |
| C.I.11.z | C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation | Type IB | I |

Update of sections 4.4, 4.6, 4.8 and 5.1 of the SmPC in order to update safety and efficacy information in the product information after finalisation of study MO25616 (SOB013). Considering the fulfilment of the specific obligations a marketing authorisation not subject to specific obligations is recommended to be granted instead of the conditional MA. Data from the same study also fulfilled the analysis required in MEA 005 regarding evaluation of the time for washout of vismodegib after treatment discontinuation and in MEA008 regarding reporting of adverse events. The Package Leaflet and the RMP (Version 10.1) are updated accordingly.
Furthermore the Marketing authorisation holder (MAH) has taken the opportunity to update the RMP (version 10.1) based on the results from nonclinical studies assessed within variation EMEA/H/C/002602/II/21 and to propose deletion of hyponatraemia as an important potential risk in the RMP (version 10.1) and as an ADR in the EU Product Information as discussed in previous PSUR (EMEA/H/C/PSUSA/00010140/201407).

is recommended for approval.

The group of variations leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP) (version 10.1).

### Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Erivedge (vismodegib) is maintained in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU, and five years have not yet passed since the authorisation of the product in EU.

Therefore the summary of product characteristics and the package leaflet continue to include a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

# 4. Scientific discussion

## *4.1. Introduction*

Vismodegib is a small-molecule inhibitor of the Hh signalling pathway.

The Hedgehog (Hh) gene has a role in pattern formation in limb bud and ventral neural tube, but also other processes in embryonal development. It is also associated with cell proliferation and migration, stem cell renewal and tissue regeneration and repair.

The signalling cascade in humans is initiated in the target cell by the Hh ligand binding to the PTCH protein. When the Hh ligand is absent, the PTCH protein inhibits the activity of the protein SMO by localising it to the cell surface. When the Hh ligand binds to PTCH the inactivation of SMO is lost and the Hh signal is transduced to the cytoplasm. Vismodegib binds to and inhibits SMO. Specific mutations within SMO have been identified that alter the ability of vismodegib to bind and to inhibit the activity of SMO, directly linking the action of vismodegib to SMO.

There is a rare hereditary syndrome associated to Hh signalling; Gorlin syndrome, also known as nevoid basal cell carcinoma syndrome (NBCCS). Hh signalling has also been identified as an important signalling pathway in human cancers.

Erivedge (vismodegib) is indicated for the treatment of adult patients with:

• symptomatic metastatic basal cell carcinoma

• locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy

## *4.2. Nonclinical aspects*

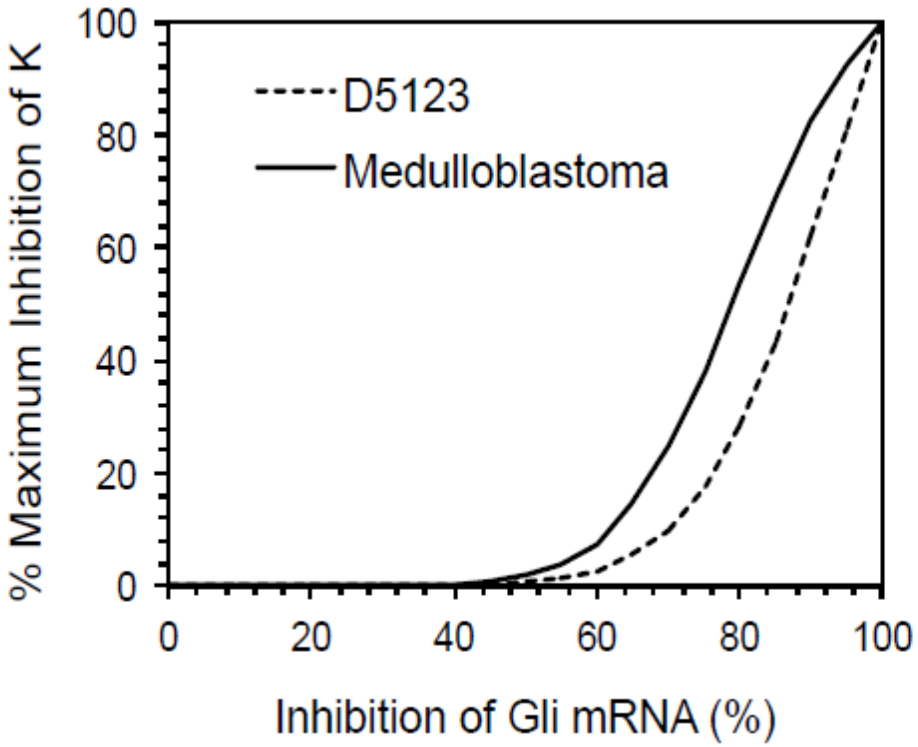
This variation II-25 includes a proposed change in the SmPC section 4.4 Special warnings and precautions for use. The Applicant suggests decreasing the mandated waiting time 24 months after discontinuation of Erivedge treatment when women of childbearing potential need to avoid getting pregnant. One basis for this proposal is a revision of the threshold of concern for teratogenicity.

The original exposure threshold for teratogenic risk was based on exposure data from a dose finding embryo-fetal development study in rats (Morinello et al. 2014) At the time of the original Marketing Authorisation Application, 1/10th of the Cmin of the lowest observable effect level was used to establish the exposure threshold in the pregnancy prevention recommendation for vismodegib (0.0037 µM, total plasma concentration).

The MAH considers this threshold highly conservative for the following reasons:

- The PK profile in rats is very distinct from the human PK profile. More rapid elimination in rats leads to a Cmin that is 463 fold lower than the Cmax whend dosed QD. In contrast, minimal elimination occurs in humans over 24 hours. A higher threshold would be derived using AUC.
- There is a species difference in plasma protein binding that was not taken into consideration. The free fraction of vismodegib in rat is higher relative to human: 1.3% to 2% vs 0.2%, respectively.
- There is a lack of pharmacological activity associated with the originally calculated exposure threshold concentration of 0.0037 µM.

A new threshold is proposed based on preclinical efficacy data (mouse cancer models). The manifestation of teratogenicity of vismodigib is presumed to correlate with inhibition of the Hh pathway and thus is an on-target effect. Therefore, anti-tumor activity is proposed to be used as a surrogate measure of potential of teratogenic risk. The anti-tumor effect in models of medulloblastoma and colorectal cancer (D5123) is shown in the following figure where the anti-tumour activity is presented in relation to inhibition of Gli mRNA as a pharmacodynamic marker of hedgehog inhibition:




Based on these data it is proposed to set a threshold at a free concentration of vismodegib resulting in 40% inhibition of the Hh pathway, 1.47 nM.

| Assessor's comment |
| --- |
| As evident from pharmacological considerations, and the study on embryofetal toxicity in rats, vismodegib is a potent teratogen. It is of utmost importance to take any step to avoid the occurrence of malformations in a child to patient having undergone treatment. The considerations leading to the current recommendation- 24 months contraception following cessation of treatment –included a number of uncertainties which hade be dealt with in a balanced way. |

The company considers the current threshold highly conservative based on several statements. In a case llike this, recommendations should be based on a conservatism but is not agreed that the current threshold is overly conservative. Some issues:

In the rat embyofetal toxicity study, no NOEL was determined. Severe malformations were observed at the lowest dose level. The threshold was defined by including a safey factor of 10 to the LOEL. This approach can be acceptable, but it does not represent any conservatism.

The threshold was defined from Cmin value in rats. It is true that human and rat differs with a much more rapid elimination in rats. From a scientific standpoint, it is however considered important to allow for the not unlikely situation that a persistent inhibition of hedgehog is of importance for the pharmacologically driven malformations.

Protein binding differs with a higher free fraction in rats. This is true and could have an impact on the threshold. However, it is not considered possible to use in vitro derived values for protein binding for extrapolation to the in vivo situation.

In conclusion, the current threshold is built on a reasonable conservative ground, and with the remaining uncertainties on the PK behavior in patients, the current recommendation of 24 months should be maintained.

For the proposed new threshold, it is not sufficiently justified why to base the threshold on mouse anti-tumor data rather than on data from the embryofetal toxicity study. There are many uncertainties in the extrapolation from anti-tumour activity in mice to embryofetal toxicity in humans. Importantly, this proposal does not deal with these uncertainties to any extent. The MAH proposal a level based on 40% inhibition of hedgehog. This is exactly the cutoff for pharmacological activity, based on the data submitted. Any minor difference in terms of species differences, distribution to placenta vs tumor etc. could result in that the proposed threshold level would in fact result in embryofetal toxicity. As a threshold to protect against such events, the proposal is not acceptable.

## *4.3. Clinical Pharmacology aspects*

This variation II-25 includes a proposed change in the SmPC section 4.4 Special warnings and precautions for use. The Applicant suggests decreasing the mandated waiting time 24 months after discontinuation of Erivedge treatment when women of childbearing potential need to avoid getting pregnant.

Assessor's comment:

The PK of vismodegib is characterized by a long half-life (12 days) and extensive binding to alpha-acidic glycoprotein (AAG).

The current SmPC for Erivedge clearly states that Women of Childbearing Potential (WCBP) must use effective contraceptives up until 24 months after the last dose of Erivedge has been taken. This is due to the teratogenic potential of the drug. The threshold for safe exposure was originally set to 0.0037 µM for total concentration. It was derived from an embryo-fetal development study in the Rat where malformations were seen in the lowest dose group (10 mg/kg/day). The threshold corresponds to 1/10 of the observed Cmin following 10 days dosing of 10 mg/kg/day to the Rat.

The time needed to reach safe exposure in humans following administration of the last dose of vismodegib was discussed during the original MAA procedure. A population PK model was used to simulate the concentration time profile during wash-out. The model predictions were considered uncertain and additional PK data from the wash-out phase was requested by the CHMP.

The current EPAR states that "*Due to limitations of the pharmacokinetic model, it is not considered possible to base predictions of the time needed to reach plasma levels below 0.0037 µM in all patients using this model. Nevertheless, the simulation raises concern that the previously proposed 7 month period is too short and it was finally considered that the duration of pregnancy prevention should be 24 months post-treatment for female patients of child bearing potential. Additional pharmacokinetic observed data from patients who have discontinued vismodegib is necessary to clearly establish the time period needed for vismodegib washout*."

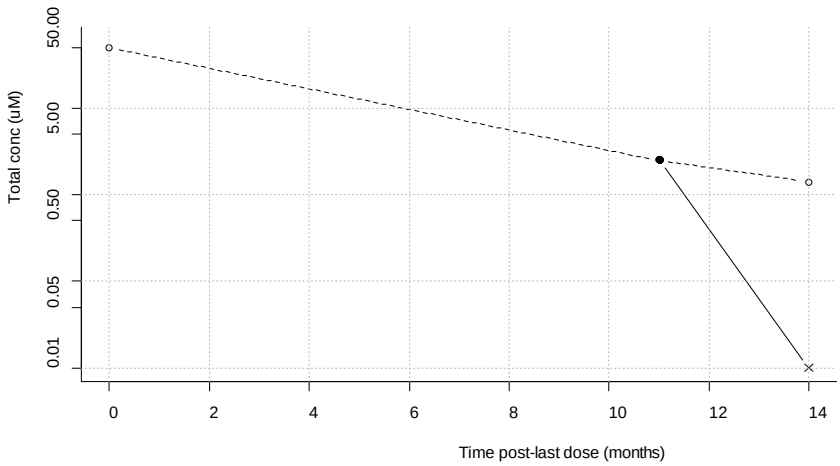
The current variation includes observed PK data to characterize the wash-out phase.

As described in the Rapporteurs' Fourth Joint Response Assessment Report from the original submission (EMEA/H/C/2602), a single event of higher than expected plasma concentration of vismodegib at 11-months post vismodegib discontinuation was observed in a patient treated on a US investigator sponsored trial SHH4685s, entitled "A Phase II Randomized, Double-Blind, Vehicle Controlled, Clinical Trial of GDC-0449 and Placebo Each Taken Once-Daily for 18 Months in Subjects with Basal Cell Nevus Syndrome".

The plasma concentration from the 11-month post study discontinuation sample was 1060 ng/mL or approximately 2.5 µM. The Applicant initiated an investigation to confirm the finding and to collect more detailed information about the patient. The patient agreed to provide a blood sample 14 months after treatment discontinuation. The results revealed that the total concentration of vismodegib was below the limit of quantification (LLOQ) in the LC-MS/MS assay (LLOQ is 5 ng/mL or approximately 0.01 µM). In addition, the Applicant conducted a PK trial simulation based on a Population PK (PopPK) model (Population Pharmacokinetics Report 11-2188) to predict the plasma concentrations at 11 and 14 months post treatment. A virtual female patient with a vismodegib plasma concentration of approximately 2.5 µM at 11-months after the last dose was simulated. This virtual patient would have had an expected on-treatment steady-state vismodegib concentration of approximately 50 µM. Notably, the typical steady-state concentration is 22.8 µM (7.6-53 µM, 5th-95th percentile). The simulation also suggested that the plasma concentration of vismodegib 14-months after the last dose is expected to be approximately 1.4 µM.

Assessor's comment

For this particular case, the Applicant used the original PopPK model to back calculate the total concentration at discontinuation of treatment. The result, a total plasma concentration of 50 uM at steady state would be unusually high but still plausible since it is within the 95th percentile of the distribution of steady state total concentration values. The observed total plasma concentration at 14 months after the last dose was below the LLOQ and thus far below the forward calculated value of 1.4 uM. The observed and predicted PK is illustrated in the graph below. Open circles and the dashed line represent predicted PK for this subject while the solid circle is the observed PK. The PK sample below the LLOQ is denoted with a cross. The y-axis is on the natural log-scale to facilitate comparison.

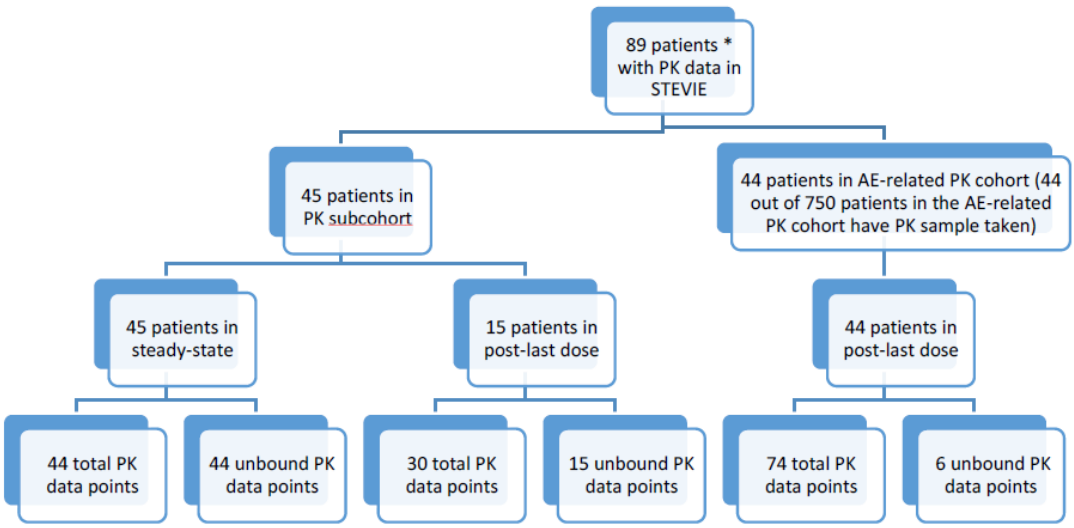



The observations made in this particular patient are not consistent with what is known about vismodegib half-life. A clear discordance is seen between the expected and observed value at 14 months post last dose. In the light of this patient case it appears even more important to characterize the PK during the wash-out phase.

### 4.3.1. Methods – analysis of data submitted

New PK data have been obtained during wash-out in Study MO25616 (STEVIE), an open-label, non-comparative, multicenter, Phase II study of vismodegib in patients with locally advanced basal cell carcinoma (laBCC) or metastatic basal cell carcinoma (mBCC). The trial consisted of a Treatment Phase, an End of Treatment Visit (when patient receives the last dose of vismodegib and thereafter discontinues vismodegib), and five safety follow-up visits.

Vismodegib plasma concentration data were collected for two subsets of patients from the study, an AE-related PK cohort and the PK subcohort (Figure below).




The AE-related PK cohort included patients who had vismodegib-related AEs based on investigator assessment that continued for at least 6 months after the last dose of vismodegib (750 patients) and who had PK samples collected (44 patients). Blood samples for PK analysis were collected to determine

whether vismodegib was present and whether it could be associated with the persistent AE at 6, 9, and 12 months after the last dose of vismodegib. In addition to the AE-related PK cohort, PK samples were collected in a PK subcohort (45 patients) to characterize the elimination of vismodegib from steady-state to 3, 6, 9, and 12 months after the last dose of vismodegib.

Standard statistics was used for summarizing data.

A Population PK analysis was performed using non-linear mixed effects modeling in NONMEM 7. A likelihood-based method usually referred to as the M3 method (Beal 2001), was used to model data below the lower limit of quantification.

### 4.3.2. Results

In total there were 44 patients with PK samples at steady state and 59 patients with PK samples after treatment discontinuation. All the 44 PK samples at steady-state (one sample per patient) were above the LLOQs for both total and unbound concentrations. The majority of the post last dose samples from the 59 subjects were below LLOQs (BLQ) (80% for total concentrations; 67% for unbound concentrations) (Figure 1 and Table 2). Unbound concentration was measured only when total concentration was above the LLOQ. The minimum quantifiable concentrations (lower limit of quantification; LLOQ) of the assay for total and unbound plasma vismodegib are 5.0 ng/mL (0.012 uM) and 0.2 ng/mL (0.47 nM), respectively.

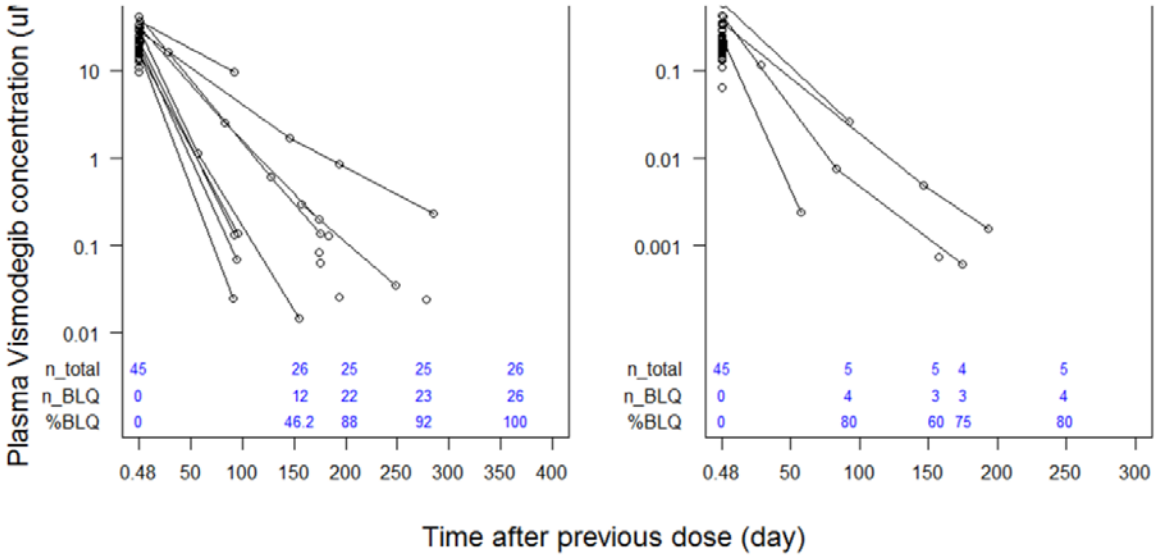
Summary statistics of total and unbound vismodegib plasma concentration and the level of alpha-acidic glycoprotein (AAG) by post-last dose visit is provided in the table below.

**Geometric Mean (%CV) total and unbound vismodegib plasma concentration and AAG concentration by post-last dose visit**

| | Steady State | 3 Months | 6 Months | 9 Months | 12 Months |
|---|---|---|---|---|---|
| Total Vismodegib (nM) | 21400 (35.6) | 459 (637.3) | 138 (NE) | NE | NE |
| Unbound Vismodegib (nM) | 219 (47.5) | 6.93 (131.6) | NE | NE | NE |
| AAG (µM) | 19.3 (49.4) | 20.7 (42.4) | 18 (31.5) | 16 (15.5) | 18.2 (NE) |

Values less than reportable (LTR) were treated as missing. NE = not estimated.

In the graph below, the individual observations of total (left) and unbound (right) vismodegib plasma concentration vs time post-last dose is shown. The percentage of PK observations below the LLOQ is shown at the bottom of the graph.



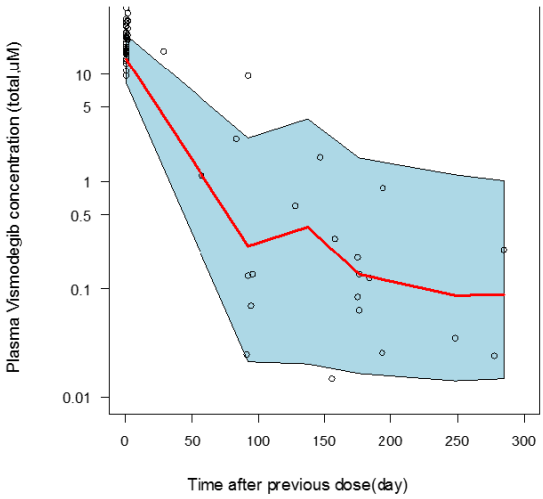

Assessor's comment:

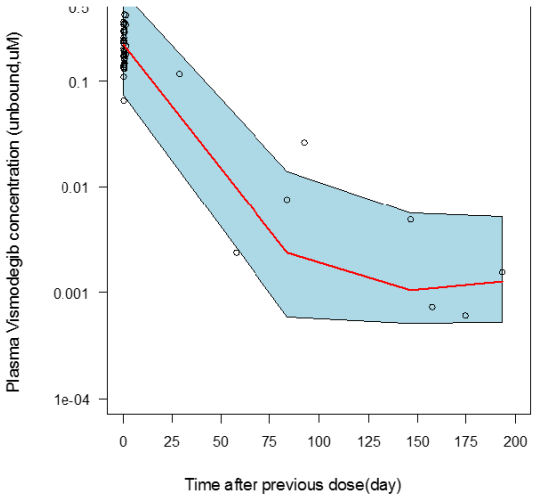
Very few patients had more than two observations of PK above the LLOQ which limits the possibility to draw conclusions about the wash-out phase. Assuming that the PK of vismodegib approximately follows exponential decay, it can be seen that half-life is highly variable between individuals.

**Population PK analysis**

The popPK model previously described for Erivedge (Lu et al. 2015) was updated based on additional PK data from Study MO25616, including those below LLOQ (BLQ). After including the BLQ data from study MO25616, the Model Development Dataset had a total of 5153 plasma vismodegib concentration data points from 313 subjects and was comprised of 2884 total concentrations (2801 non-BLQ data points and 83 BLQ data points) and 2269 unbound concentrations (2255 non-BLQ data points and 14 BLQ data points). In total, 211 new data points (147 total and 64 unbound) from 89 subjects were added to the previous Model Development Dataset (4942 data points) with only less than 5% new data added. Overall, 104 total drug and 21 unbound drug concentrations were collected from MO25616 2 month post-last dose, with 80% and 67% of the samples below LLOQ, respectively.

A graph comparing the model predicted total and unbound plasma concentration to observed data, respectively, is shown below. Open circles are the observed plasma concentrations, solid red lines represent the median observed value, and blue shaded areas represent the spread of the predicted values (5th percentile and 95th percentile). BLQ data points in the simulated VPC datasets were excluded.




Assessor's comment:

The model can describe most, but not all, of the new data. For instance, the prediction band does not cover the higher total concentration values at time zero (left figure above). Further, the subject with the highest total plasma concentration at 3 months seems to be outside the prediction band. It is of concern that the model is not fully qualified to describe the new PK data. In order to use the model for purpose of simulation, these issues need to be addressed.

**Simulation of wash-out of vismodegib after discontinuation of treatment**

Using the final updated model (M3 model), the popPK trial simulations without considering parameter uncertainty were conducted for the virtual population of 760,000 WOCBP (100 sets of population mean parameter * 100 replicated trials per set * 76 individuals per trial) to derive the 90% confidence interval for the pregnancy prevention duration for WOCBP after treatment discontinuation. To address parameter uncertainty, the same simulation methodology was applied to the 100 sets of population mean parameters that were randomly generated from the variance-covariance uncertainty matrix. In total, 100 values of the pregnancy prevention duration were derived. based on the updated PopPK simulation in WOCBP, and the threshold of concern for teratogenicity (Gli IC40,unbound, 1.47 nM), the median (90% CI) time required for unbound vismodegib plasma concentration to fall below the threshold of concern in 97.5% of the simulated population is 7.4 months (6 months to 9 months) after treatment discontinuation.

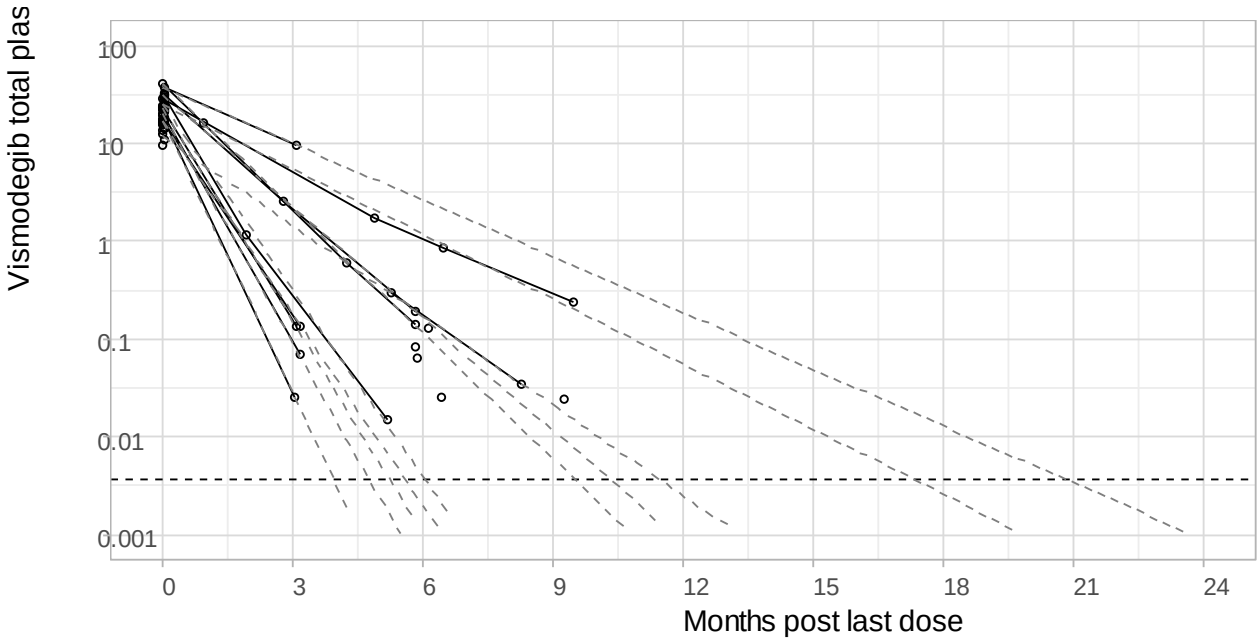
Assessor's comment:

The threshold of concern is discussed in the Nonclinical section of this report.

## 4.3.3. Discussion

There is a real concern that vismodegib may harm the developing fetus and safety measures are in place to avoid women of childbearing potential (WCBP) getting pregnant while being exposed to vismodegib. According to the current SmPC, women of childbearing potential must use effective contraceptives up until 24 months of treatment end. The MAH has provided new pharmacokinetic data that cover the wash out phase up until 12 months after discontinuation of treatment. Based on these data and an alternative definition of the concentration threshold of concern, the MAH claims that a shorter waiting period is possible. The alternative definition of threshold of concern is discussed in the Nonclinical section of this report.

The data are fairly limited and individual observed PK profiles are incomplete making determination of terminal half-life difficult. The Applicants presentation of the Population PK model raises some concerns about predictive performance. As a more simple approach, the individual log-transformed observed total concentrations of vismodegib were analyzed by linear regression in the R software (function lm). Observations below the lower limit of quantification were disregarded. The individual regression lines were extrapolated to see when a total concentration level of 0.0037 µM was reached. The result is illustrated in the graph below.




Open circles denote individual observed total concentration of vismodegib. Repeated observations in a patient are connected with solid lines. The non-horizontal dashed lines represent extrapolated individual total plasma concentration. The dashed horizontal line denotes a total concentration level of 0.0037 uM which is the current threshold with respect to teratogenicity. It can be seen that the intersection between individual extrapolated total concentration and the dashed horizontal line ranges from approximately 4 months to 21 months.

In conclusion, under the assumption of a total concentration threshold value of 0.0037 µM it does not seem appropriate to decrease the waiting time from 24 months post last dose.

**References**

Beal, Stuart L. "Ways to fit a PK model with some data below the quantification limit." Journal of pharmacokinetics and pharmacodynamics 28, no. 5 (2001): 481-504.

Lu, T., B. Wang, Y. Gao, M. Dresser, R. A. Graham, and J. Y. Jin. "Semi-Mechanism-Based Population Pharmacokinetic Modeling of the Hedgehog Pathway Inhibitor Vismodegib." CPT: pharmacometrics & systems pharmacology 4, no. 11 (2015): 680-689.

## *4.4. Clinical Efficacy aspects*

### 4.4.1. Methods – analysis of data submitted

The conditional marketing approval was based on the single arm pivotal study SHH476g, with 104 patients included, 33 with metastatic BCC and 71 with locally advanced BCC. In the approval procedure efficacy data was updated as of 28 Nov 2011 (12 month update).

Updated efficacy data was submitted (30 May 2013, 30 month update) in a type II variation (EMEA/H/C/002602/II/0008), together with interim safety data for another single arm study – MO25616 (STEVIE).

In the current procedure secondary objective efficacy data is submitted for MO25616 - a single-arm, open-label, phase II, multicentre study to assess the safety of vismodegib (GDC-0449) in patients with locally advanced or metastatic basal cell carcinoma - with data cutoff 16 March 2015.

## 4.4.2. Results

Overview of efficacy parameters

**Table 1. Efficacy of vismodegib in two single arm trials.**

| | **SHH4476g** | | | | **MO25616** | | | |
|---|---|---|---|---|---|---|---|---|
| | 12-month update (28 Nov 2011) | | 30-month update (30 May 2013) | | Efficacy-evaluable population | | 8-weekly tumour assessment population | |
| Efficacy parameter | Locally advanced (n= 63) | Meta-static (n= 33) | Locally advanced (n= 63) | Meta-static (n= 33) | Locally advanced (n=1103) | Meta-static (n= 89) | Locally advanced (n= 244) | Meta-static (n=24) |
| **Complete response** per IRF | 22% | 0 | - | - | - | - | - | - |
| **Complete response** per inv | 32% | 0 | 32% | 0 | 33% | 4.8% | 44% | 4.2% |
| **ORR** per IRF | 48% | 33% | - | - | - | - | - | - |
| **ORR** per inv | 60% | 49% | 60% | 49% | 69% | 37% | 83% | 50% |
| **DOR** per IRF | 9.5 months | 7.6 months | - | - | - | - | - | - |
| **DOR** per inv | NE | 14.7 months | 26.2 months | 14.8 months | 23 months | 13.9 months | 23 months | 8.3 months |
| **PFS** per IRF | 9.5 months | 9.5 months | - | - | - | - | - | - |
| **PFS** per inv | 12.9 months | 9.3 months | 12.9 months | 9.3 months | 23.2 months | 13.1 months | 25.1 months | 12.2 months |
| Median **OS** | NE | 24.1 months | NE | 33.4 months | NE | NE | NE | 18.1 months |

per IRF= by independent review facility assessment, per inv= by investigator assessment, efficacy-evaluable population= combination of clinical and radiological (when required; radiology every 8-16

weeks) assessments, 8-weekly tumour assessment population= after protocol amendment, patients with metastatic disease had to be radiologically assessed every 8 weeks.

### 4.4.3. Discussion

Efficacy results are largely consistent with the pivotal study, with the exception of progression-free survival.

**Assessor's comment**: the MAH is asked to discuss possible reasons for discordant PFS results in SHH4476g and MO25616.

## *4.5. Clinical Safety aspects*

### 4.5.1. Methods – analysis of data submitted

Interim safety data for MO25616 (STEVIE) - a single-arm, open-label, phase II, multicentre study to assess the safety of vismodegib (GDC-0449) in patients with locally advanced or metastatic basal cell carcinoma - was previously submitted in a type II variation (EMEA/H/C/002602/II/0008), with data cutoff 6 November 2013.

In the current procedure, the MAH has submitted an update, a 'primary clinical safety report' for MO25616, with data cutoff 16 March 2015.

### 4.5.2. Results

**Table 2. Patient disposition, MO25616**

| **Total** | **6 Nov 2013** | **16 March 2015** |
|---|---|---|
| | N= 500 | N= 1215 |
| **Dead,**<br>**cause:** | 29 (5.8%) | 110 (9.1%) |
| Disease progression | 4 (0.8%) | 27 (2.2%) |
| Adverse event | 20 (4%) | 71 (5.8%) |
| Treatment emergent | 16 (3.2%) | 46 (3.8%) |
| Treatment emergent and related | 2 (0.4%) | 7 (0.6%) |
| Other | 5 (1%) | 12 (1.0%) |
| **Discontinued treatment,**<br>**cause:** | 400 (80%) | 1068 (88%) |
| Death | 10 (2%) | 37 (3.0%) |
| Progression of disease | 70 (14%) | 189 (16%) |

| | | |
|---|---|---|
| Adverse event | 178 (36%) | 349 (29%) |
| Patient request/ withdrawal by subject | 62 (12%) | 237 (20%) |
| Investigator request/ physician decision | 14 (2.8%) | 76 (6.3%) |
| Lost to follow-up | 4 (0.8%) | 21 (1.7%) |
| Other | 62 (12%) | 159 (13%) |

Patient exposure

Median exposure to vismodegib in MO25616 was 8.3 months 6 November 2013, and 8.6 months 16 March 2015. Median exposure in the pivotal study SHH4476g was longer, about 13 months. Median dose intensity was 98% for MO25616 (16 March 2015), compared to 97-99% (metastatic and locally advanced patients, respectively) for SHH4476g.

Discontinuations due to AEs

In the current update, 88% of patients have discontinued treatment in MO25616, in 16% due to disease progression, and 29% due to adverse events. Of note, a total of about 55% of patients discontinued for adverse event, patient request/withdrawal by subject, or investigator request/physician decision.

**Assessor's comment**: in the approval process, "patient decision" and "physician decision" reasons for discontinuing treatment in SHH4476g were further explored in site interviews, the most common underlying reasons were "prolonged AEs are intolerable" (37%), "other" (27%), and "logistic challenges with travel and treatment" (20%). In MO25616 less than 20% of patients discontinued treatment due to death or disease progression, which may be a reflection of the tolerability of vismodegib.

Adverse events

**Table 3. Adverse events in MO25616/STEVIE (selected)**

| **Data cutoff** | 6 Nov 2013 | 16 March 2015 |
|---|---|---|
| **Number of patients** | 500 | 1215 |
| **Median exposure to vismodegib** | 8.3 months | 8.6 months |
| **Metabolism and nutrition disorders** | | |
| Decreased appetite | 127 (25%) | 303 (25%) |
| Dehydration | 8 (1.6%) | 10 (0.8%) |
| **Nervous system disorder** | | |
| Dysgeusia | 269 (54%) | 663 (55%) |
| Ageusia | 112 (22%) | 213 (18%) |
| Hypogeusia | 9 (1.8%) | 35 (2.9%) |

| | | |
|---|---|---|
| **Gastrointestinal disorders** | | |
| Nausea | 79 (16%) | 218 (18%) |
| Diarrhoea | 87 (17%) | 197 (16%) |
| Constipation | 43 (8.6%) | 116 (9.5%) |
| Vomiting | 39 (7.8%) | 102 (8.4%) |
| Dyspepsia | 15 (3.0%) | 34 (2.8%) |
| Upper abdominal pain | 34 (6.8%) | 67 (5.5%) |
| Abdominal pain | 27 (5.4%) | 84 (6.9%) |
| **Skin and subcutaneous tissue disorders** | | |
| Alopecia | 305 (61%) | 747 (62%) |
| Pruritus | 34 (6.8%) | 68 (5.6%) |
| Rash | 19 (3.8%) | 55 (4.5%) |
| Madarosis | 2 (0.4%) | 6 (0.5%) |
| Abnormal hair growth | 6 (1.2%) | 19 (1.6%) |
| **Musculoskeletal and connective tissue disorders** | | |
| Muscle spasms | 316 (63%) | 807 (66%) |
| Arthralgia | 45 (9%) | 124 (10%) |
| Pain in extremity | 19 (3.8%) | 53 (4.4%) |
| Back pain | 27 (5.4%) | 60 (4.9%) |
| Musculoskeletal chest pain | 3 (0.6%) | 8 (0.7%) |
| Myalgia | 38 (7.6%) | 81 (6.7%) |
| Musculoskeletal pain | 10 (2.0%) | 37 (3.0%) |
| **Neoplasms** | | |
| Squamous cell carcinoma (and skin SCC) | 21 (4.2%) | 51 (4.2%) |
| Other second malignancies | 10 (2%) | 31 (2.6%) |
| **Vascular disorders** | | |
| Deep vein thrombosis | 2 (0.4%) | 4 (0.3%) |
| Pulmonary embolism | 1 (0.2%) | 3 (0.2%) |
| Thrombosis | 2 (0.4%) | 2 (0.2%) |
| Venous thrombosis | 1 (0.2%) | 1 (<0.1%) |

| | | |
|---|---|---|
| **Reproductive system and breast disorders** | | |
| Amenorrhoea | 7 (1.4%) | 11 (0.9%) |
| Menstruation irregular | 1 (0.2%) | 9 (0.7%) |
| **General disorders and administration site conditions** | | |
| Fatigue | 79 (16%) | 201 (17%) |
| Pain | 7 (1.4%) | 27 (2.2%) |
| Asthenia | 141 (28%) | 291 (24%) |
| **Investigation** | | |
| Weight decreased | 162 (32%) | 493 (41%) |
| **Eye disorders** | | |
| Keratitis | 3 (0.6%) | 8 (0.7%) |
| Ulcerative keratitis | 2 (0.4%) | 2 (0.2%) |
| Ophthalmic herpes simplex | 1 (0.2%) | 1 (<0.1%) |

Serious adverse events

As of 16 March 2015, treatment emergent SAEs were reported in 289 patients (24%). Most frequent events (≥4) included pneumonia (18), squamous cell carcinoma of skin (12), general physical health deterioration (12), fall (9), myocardial infarction (9), gastroenteritis (6), hip fracture (6), syncope (6), dehydration (5), bronchitis (5), anaemia (5), hepatic enzyme increased (5), squamous cell carcinoma (5), pyelonephritis (4), chronic obstructive pulmonary disease (4), renal failure (4), asthenia (4).

In the previous report, for 6 Nov 2013, SAEs were reported in 107 patients (21%). Most frequent events (≥2) included pneumonia (9), general physical health deterioration (7), dehydration (5), myocardial infarction (4), squamous cell carcinoma (4), squamous cell carcinoma of skin (3), hip fracture (2), syncope (2), bronchitis (2), hepatic enzyme increased (2), pyelonephritis (2), chronic obstructive pulmonary disease (2), asthenia (2), cerebrovascular accident (2), dizziness (2).

Deaths

As of 16 March 2015, 110 patients (9.1%) had died while on study or in follow-up, 92 patients with locally advanced BCC (8.2%) and 18 with metastatic BCC (19%). Seventy-one deaths (5.8%) were due to adverse events, 27 (2.2%) were due to disease progression, and 12 (1%) had other causes. This represents an increase in deaths caused by AEs compared to 5 November 2013 (from 4% to 5.8%, table 2).

Fifty-three grade 5 treatment emergent adverse events occurred in 46 patients. The most common grade 5 TEAEs included myocardial infarction (n=6; 54-92 years old, all had a history of cardiovascular disease), general physical health deterioration (n=4; 84-88 years old), sepsis (n=3), and squamous cell carcinoma of the skin (n=3). Of note, grade 5 cardiac disorders were reported in an additional 5 patients (including acute left ventricular failure, cardiac arrest, cardiac failure, cardiac failure congestive, cardio-respiratory arrest, cardiopulmonary failure), and sudden death in 2 patients. Other malignancies reported as grade 5 TEAEs were: 1 metastasis to central nervous system, 1 NSCLC, 2 rectal cancers.

Seven of the 53 grade 5 TEAEs were considered by the investigator to be related to vismodegib; 2 myocardial infarctions, 1 pancreatitis, 1 pulmonary embolism, 1 ischemic stroke, 1 cardiopulmonary arrest, and 1 renal failure.

Selected adverse events

Teratogenicity

As of 16 March 2016, no pregnancies had been reported on study.

Irregular menses and amenorrhea

Sixty-four patients had menses at baseline. Eleven patients had AEs of amenorrhea, and 9 had irregular menses (together 31%). The corresponding proportion at the cutoff 6 November 2013 was 8 in 29 women (28%). Of these adverse events, 13 resolved following discontinuation of study drug, 2 resolved with sequelae, and 10 were unresolved at data cutoff. Patient ages for unresolved cases where 18, 25, 36, 43, 44, 45, 46, 49, 50 and 50 years. The 18 year old patient had a history of hypopituitarism, hypothyroidism, hyposomia, and Gorlin syndrome. She developed G1 irregular menstruation on treatment day 466, withdrew consent and did not participate in safety follow up. The 25 year old patient had a history of ovarian dermoid cyst, endometritis and Gorlin syndrome; she developed amenorrhea on treatment day 353, and the investigator assessment of relatedness is unknown. The 36 year old patient developed metrorrhagia on study day 31, the AE may have preceded vismodegib treatment, and follow-up was limited to 1 month (due to protocol version).

**Assessor's comment**: the frequency of irregular menses and amenorrhea is in line with previous data, and events often resolved with discontinuation of vismodegib. Patients with unresolved irregular menses and amenorrhea were in several cases approaching perimenopause. For a small number of younger patients information is limited.

Muscle spasms

Frequencies of muscle spasms and potentially related AEs are given in table 3. About 63% - 167 of 266 patients –report muscle spasms at treatment discontinuation, and 9 had muscle spasms at a 12 month follow-up visit.

**Assessor's comment**: an analysis of AE reversibility after treatment discontinuation includes 621 safety-evaluable patients who signed protocol version 3 or higher. Only 266 patients are reported. The MAH is asked to provide a table for all 621 patients describing reasons for not including remaining 355 patients in the table of TEAEs ongoing 12 months after treatment discontinuation.

Squamous cell carcinoma of the skin

Sixty occurrences of skin squamous cell carcinoma (SCC; including "squamous cell carcinoma," "squamous cell carcinoma of skin," "lip squamous cell carcinoma," "metastatic squamous cell carcinoma," "keratoacanthoma," and "Bowen's Disease") are reported in 51 patients (4.2%).

Eighteen of 51 patients had a history of SCC. Median SCC onset is about 200 days, with a distribution centred about the median.

Three patients had grade 5 events. A causal role for vismodegib cannot be ruled out based on narratives (available for 2 patients).

**Assessor's comment**: the frequency of second primary malignancies is consistent with previous findings.

Second primary malignancies

As of 16 March 2015 a total of 37 second primary malignancies are reported in 31 patients (excluding skin squamous cell carcinomas). Types with more than one occurrence included lung cancer (5), malignant melanoma and metastatic malignant melanoma (5), rectal cancer (3), b-cell lymphoma (2), colon cancer (2), breast cancer (2).

**Assessor's comment**: the frequency of second primary malignancies is consistent with previous findings.

Keratitis

Ten patents had treatment emergent events of keratitis or ulcerative keratitis, 2 of which were grade 3, the others grade 1 or 2. Seven of 10 events resolved , 1 resolved with sequelae, 2 were unresolved. The 2 unresolved events both had eye involvement of BCC.

**Assessor's comment**: the frequency of keratitis/ulcerative keratitis is consistent with previous findings.

Fractures

As of 16 March 2015, 36 patients (3.0%) had reported 39 fractures compared to 14 (2.8%) patients with 16 fractures 6 November 2013.

**Assessor's comment**: the frequency of fracture events is consistent with previous findings.

Venous thromboembolic events

Ten patients (0.8%) reported 12 treatment emergent thromboembolic events in the current update; deep vein thrombosis in 4 patients, pulmonary embolism in 3, thrombosis in 2, venous thrombosis in 1. Two were considered related, one of which was a grade 5 event.

In the previous report five (1.0%) patients reported 6 events of VTE.

**Assessor's comment**: the frequency of thromboembolic events is consistent with previous findings.

Laboratory findings

Alkaline phosphatase, SPGT/ALT, SGOT/AST, total bilirubin

**Table 3. Liver function tests, worst NCI-CTC grade during treatment**

| | 6 Nov 2013 | | | | 16 March 2015 | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Alkaline phosphatase | 19% | 2.8% | 0.6% | 0 | 21% | 3.2% | 0.7% | 0 |
| SPGT/ALT | 24% | 3.0% | 2.1% | 0.4% | 24% | 3.0% | 2.1% | 0.2% |
| SGOT/AST | 29% | 1.1% | 1.3% | 0.2% | 29% | 1.6% | 1.4% | 0.2% |
| Total bilirubin | 6.8% | 2.5% | 0.2% | 0 | 5.7% | 1.9% | 0.3% | <0.1% |

Sodium

Worst grade of hyponatremia was grade 1 (<LLN – 130 mmol/L) in 21% of patients, grade 3 (<130 – 120 mmol/L) in 2.4% of patients, grade 4 (<120 mmol/L) in 0.2% of patients. In the previous report corresponding numbers were 22 % grade 1, 0.8% grade 3 and 0.4% grade 4.

Potassium

**Table 4. Hypokalemia, worst NCI-CTC grade during treatment**

| | **Grade 0** | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
|---|---|---|---|---|---|
| **16 March 2015** | 88% | 0 | 8.2% | 0.6% | 0.2% |
| **6 Nov 2013** | 92% | 6.9% | 0 | 0.6% | 0.2% |

**Assessor's comment**: presumably the difference reflects a change in classification, an explanation is warranted. CTCAE version 4.03 vs 4.0?

Creatinine

As of 16 March 2015, worst grade elevated creatinine during treatment was grade 0 for 7.8% of patients, grade 1 (>ULN – 1.5 x ULN) for 75% of patients, grade 2 (>1.5 – 3 x ULN) for 14%, grade 3 (>3 – 6 x ULN) for 0.8%, and grade 4 (> 6 x ULN) for 0.5%. Baseline grade was 0 for 80%, grade 1 for 14%, grade 2 for 2.9%, grade 3 for 0.5%, and grade 4 for <0.1%.

For 6 November 2013, worst grade elevated creatinine during treatment was grade 0 for 67% of patients, grade 1 for 22% of patients, grade 2 for 7.9%, grade 3 for 1.3%, and grade 4 for 1.0%, the baseline distribution was grade 0 for 84%, grade 1 for 12%, grade 2 for 3.8% and grade 3 for 0.6%.

**Assessor's comment**: there is a significant increase in grade 1 creatinine elevations in the current compared to the previous report: in November 2013, 318 of 479 patients (66%) had a grade 0 baseline creatinine elevation without worsening during treatment; in March 2015, only 87 of patients (7.3%) were graded 0 at baseline without worsening, whereas 795 (65%) patients shifted from 0 to grade 1 as worst grade.

Creatine kinase

Of 29 patients with creatine kinase assessments for both baseline and follow-up (assessed only in patients who entered the study under protocol version 4 or later, n= 36), 18 (62%) remained at

baseline, 10 (35%) had shifts to grade 1 or 2, and 1 patient had a shift to grade 3. All were grade 0 at baseline.

For 453 patients without a baseline measurement, 181 (40%) had grade 1 or 2 elevations and 11 (2.4%) had grade 3 or 4 elevations.

In an exploratory analysis, no relationship between muscle spasm and creatine kinase could be demonstrated:

**Table 5. Creatine kinase and muscle spasms**

| | **Creatine kinase, max elevation** | | | | |
|---|---|---|---|---|---|
| | **Grade 0** | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
| **No muscle spasm, n = 121** | 64% | 30% | 3.3% | 2.5% | 0.8% |
| **Any muscle spasm during treatment, n= 59** | 66% | 24% | 6.8% | 3.4% | 0 |

A medical review of adverse events related to renal insufficiency or elevated creatinine, displaying a temporal relationship to events of increased creatine kinase, yielded a limited number of patients (7) and incomplete insight.

**Assessor's comment**: "blood creatine phosphokinase increased" has been added to the table of adverse reactions, as "common", in section 4.8 of the SPC, which is accepted.

A smaller number of patients with renal-related adverse events are reported compared to biochemistry test results (e.g 36 patients have AEs of "blood creatinine increased" compared to 795 patients with grade 1 "creatinine high"). Therefore, an analysis of biochemistry test results should be more sensitive in detecting a relationship between creatine kinase and creatinine increases.

### 4.5.3. Discussion

The main safety concern is uncertainty related to study design: no randomized control arm is available for comparison. There is an apparent increase in mortality in the final compared to the interim analysis of MO25616 (5.8 to 9.1%), that may well be within expectations for the studied population. Further reassurance could be provided by an external control population, and a more thorough analysis of relatedness in grade 5 treatment emergent events. Further clarifications regarding the reversibility of muscle spasms, possible differences in classification of hypokalemia, moderate creatinine elevations and a conceivable association between creatine kinase and creatinine increases, are wanted.

## 4.6. Risk management plan

The MAH submitted RMP version with this application. The main proposed RMP changes were the following:

***Safety concerns***

**Table 6: Summary of Ongoing Concerns**

| | |
|---|---|
| Important Identified Risks | Teratogenicity<br>Muscle spasms |
| Important Potential Risk | Post-natal developmental defects<br>Impairment of fertility<br>Second primary malignancies~~malignancy~~<br>Squamous cell carcinoma<br>Death / sudden death / ~~/~~cardiac death<br>Off-label use in pediatric medulloblastoma<br>Off-label use in BCC appropriate for treatment with surgery or radiotherapy<br>Off-label use in other cancers<br>Keratitis / ulcerative keratitis<br>Fracture<br>Venous thromboembolic events<br>Syncope<br>~~Hyponatremia~~ |
| Missing information | Nonclinical carcinogenicity studies<br>~~Long-term use of vismodegib in patients with advanced BCC (locally advanced and metastatic BCC)~~<br>~~Vismodegib exposure after discontinuation of treatment~~<br>Use in patients with severe renal impairment<br>Interaction with CYP inducers and OATP1B1 substrates<br>Interaction with oral contraceptives |

**Assessor's comment**: removal of hyponatremia as an important potential risk is accepted, in accordance with a PSUR previously accepted by PRAC (EMEA/H/C/PSUSA/00010140/201407).

Removal of "long-term use of vismodegib in patients with advanced BCC (locally advanced and metastatic BCC)" is accepted.

Removal of "vismodegib exposure after discontinuation of treatment" is accepted.

***Pharmacovigilance plan***

**Table 7: Summary of Safety Concerns and Planned Pharmacovigilance Actions**

| Safety Concern | Proposed routine and additional PhV activities | Objectives |
|---|---|---|
| **Important Identified Risks** | | |
| Teratogenicity | Routine pharmacovigilance<br>• Expedited reporting of all pregnancies as a serious event<br>• Global centralized data collection (safety database) and reporting of pregnancies by Pregnancy report forms in HCP educational brochure.<br>• Follow-up of all pregnancies until outcome and until final diagnosis for cases of congenital malformation<br>• Review in PBRERs/PSURs (periodic and cumulative).<br>Additional pharmacovigilance<br>• Central data collection<br>• Monitoring of implementation of Erivedge Pregnancy Prevention Programme on a country-specific basis in accordance with the local legal framework.<br>• Monitoring of the effectiveness and compliance of the PPP<br>– Compliance and effectiveness~~Effectiveness is to be monitored by the use~~ of the Erivedge PPP<br>– Market Research has been conducted twice in 2014 and 2015 via Health Care Professional Survey done in ~~market surveys of~~ the EU. The latest research survey concluded that the majority of prescribers are aware~~HCPs for awareness~~ of the PPP. For the prescribers who are aware of the PPP, the majority of them are providing precaution in their patients when prescribing Erivedge~~EU PPP~~.<br>– Compliance is to be monitored by the use of a global web-based tool point of access for HCPs.<br>– The EU PPP web portal survery completed in October 2014 on 27 EU countaries showed that more than 90% responders were directly involved in the implementation of the PPP. | Erivedge Pregnancy Pharmacovigilance Programme<br>• Provide a centralized database (ARISg) of all Erivedge pregnancy reports<br>• Determine the Erivedge exposure status for each reported pregnancy<br>• Monitor the compliance and effectiveness of the PPP in the EU<br>• Document the outcome of each Erivedge pregnancy<br>• Document abnormal fetal outcomes for Erivedge pregnancy reports<br>• Obtain pregnancy documentation to assist in the Root Cause Analysis of each pregnancy<br>• Provide pregnancy data to worldwide Regulatory Authorities where the product is marketed or investigated as per local regulations and guidelines. |

| Safety Concern | Proposed routine and additional PhV activities | Objectives |
|---|---|---|
| Muscle spasms | Routine pharmacovigilance<br>• Reporting of cases of muscle spasms<br>• Review in PBRERs/PSURs (periodic and cumulative). | Detection, collection and reporting of adverse events of muscle spasms. |

| Safety Concern | Proposed routine and additional PhV activities | Objectives |
|---|---|---|
| **Important Potential Risks** | | |
| Post-natal developmental defects | Routine pharmacovigilance<br>• Reporting of cases of post-natal developmental defects<br>• Review in PBRERs/PSURs (periodic and cumulative). | Detection, collection and reporting of pediatric adverse events and adverse reactions, including developmental defects. |
| Impairment of fertility | Routine pharmacovigilance<br>• Reporting of cases of impairment of fertility<br>• Review in PBRERs/PSURs (periodic and cumulative).<br>Additional pharmacovigilance<br>• Monitoring and follow-up of amenorrhea cases in clinical trials and spontaneous cases.<br>~~• Adjudication of events by an internal expert group for independent opinion.~~<br>~~• Clinical investigations within MO25616 (STEVIE) for evaluation of patients with irregular menses or amenorrhea including abdominal ultrasound and serum hormone evaluation, when possible.~~<br>• Reporting of all events of amenorrhea in the RegiSONIC study. | Detection, collection and reporting of impairment of fertility as adverse events and adverse reactions, including amenorrhea events. |
| Second primary malignancies | Routine pharmacovigilance<br>• Reporting of cases of second primary cancer<br>• Review in PBRERs/PSURs (periodic and cumulative)<br>Additional pharmacovigilance<br>• Nonclinical carcinogenicity studies ~~are ongoing~~ to further characterize the risk: GLP Study 13-0322 (completed; a summary is provided~~.~~<br>• ~~Adjudication of events of second primary cancer reported~~ in Section III.3) and GLP Study 13-0323 (ongoing). The two study reports will be submitted together when the results from GLP Study 13-0323 become available~~MO25616 (STEVIE) by an expert group for independent opinion~~.<br>• Reporting from the RegiSONIC study of second primary cancers that have been identified by the investigator as serious adverse events. | Detection, collection and reporting of second primary cancer events. |
| Squamous Cell Carcinoma | Routine pharmacovigilance<br>• Reporting of cases of squamous cell carcinoma<br>• Review in PBRERs/PSURs (periodic and cumulative)<br>Additional pharmacovigilance<br>• Nonclinical carcinogenicity studies ~~are~~ | Detection, collection and reporting of SCC events. |

| Safety Concern | Proposed routine and additional PhV activities | Objectives |
|---|---|---|
| | ongoing to further characterize the risk: GLP Study 13-0322 (completed; a summary is provided.<br>• Adjudication of events by an internal expert group for independent opinion.<br>• Adjudication of events of squamous cell carcinoma reported in Section III.3) and GLP Study 13-0323 (ongoing). The two study reports will be submitted together when the results from GLP Study 13-0323 become availableMO25616 (STEVIE) by an expert group for independent opinion.<br>• Reporting from the RegiSONIC study of squamous cell carcinomas that have been identified by the investigator as serious adverse events. | |
| Death/Sudden death/Cardiac death | Routine pharmacovigilance<br>• Reporting of cases of death/sudden death, cardiac death.<br>• Review in PBRERs/PSURs (periodic and cumulative).<br>Additional pharmacovigilance<br>• Adjudication of events of death/sudden death/cardiac death by an internal expert group for independent review<br>• Adjudication of events of death/sudden death/cardiac death reported in MO25616 (STEVIE) by an expert group for independent opinion<br>• Reporting of all events of death/sudden death/cardiac death as serious adverse events in the RegiSONIC study. | • Detection, collection and reporting of sudden cardiac death/death NOS events<br>• Risk evaluation by independent reviewer |
| Off-label use in pediatric medulloblastoma | Routine pharmacovigilance:<br>• Reporting of all adverse events associated with off-label use in pediatric medulloblastoma.<br>• Review in PBRERs/PSURs (periodic and cumulative). | Detection, collection and reporting of off-label use in pediatric medulloblastoma. |
| Off-label use in BCC that is appropriate for treatment with surgery or radiotherapy | Routine pharmacovigilance:<br>• Reporting of all safety reports from the setting of BCC that is appropriate for treatment with surgery or radiotherapy<br>• Review in PBRERs/PSURs (periodic and cumulative). | Detection, collection and reporting of off-label use in BCC appropriate for treatment with surgery or radiotherapy |

| Safety Concern | Proposed routine and additional PhV activities | Objectives |
|---|---|---|
| Off-label use in other cancers | Routine pharmacovigilance:<br>• Reporting of all safety reports from patients with other cancers<br>• Review in PBRERs/PSURs (periodic and cumulative). | Detection, collection and reporting of off-label use in cancers other than aBCC. |
| Keratitis / ulcerative keratitis | Routine pharmacovigilance:<br>• Reporting of cases of keratitis<br>• Review in PBRERs/PSURs (periodic and cumulative).<br><br>Additional pharmacovigilance<br>~~• Adjudication of events of keratitis/ulcerative keratitis reported in MO25616 (STEVIE) by an expert group for independent opinion.~~<br>• Reporting of events of keratitis/ulcerative keratitis that qualify as serious adverse events in the RegiSONIC study. | Detection, collection and reporting of cases of keratitis and ulcerative keratitis in patients receiving treatment with Erivedge |
| Fracture | Routine pharmacovigilance<br>• Reporting of cases of fracture.<br>• Review in PBRERs/PSURs (periodic and cumulative).<br>Additional pharmacovigilance<br>~~• Adjudication of events of fracture reported in MO25616 (STEVIE) by an expert group for independent opinion.~~<br>• Reporting of events of fracture that qualify as serious adverse events in the RegiSONIC study. | Detection, collection and reporting of fracture events |
| Venous thromboembolic events | Routine pharmacovigilance<br>• Reporting of cases of venous thromboembolic events<br>• Review in PBRERs/PSURs (periodic and cumulative).<br>Additional pharmacovigilance<br>• Reporting of all venous thromboembolic events (specifically DVT and PE) in the RegiSONIC study. | Detection, collection and reporting of venous thromboembolic events. |

| Safety Concern | Proposed routine and additional PhV activities | Objectives |
|---|---|---|
| Syncope | Routine pharmacovigilance<br>• Reporting of cases of syncope<br>• Review in PBRERs/PSURs (periodic and cumulative).<br>Additional pharmacovigilance<br>• Reporting of events of syncope that qualify as serious adverse events in the RegiSONIC study. | Detection, collection and reporting of cases of syncope in patients receiving treatment with Erivedge. |
| ~~Hyponatremia~~ | ~~Routine pharmacovigilance:~~<br>~~• Reporting of cases of hyponatremia~~<br>~~• Review in PBRERs/PSURs (periodic and cumulative)~~<br>~~Additional pharmacovigilance~~<br>~~• Monitoring of laboratory result changes, including hyponatremia, in Study MO25616 (STEVIE).~~ | ~~Detection, collection and reporting of adverse events of hyponatremia.~~ |
| **Missing information** | | |
| Nonclincal carcinogenicity studies | Routine pharmacovigilance:<br>Not applicable<br><br>Additional pharmacovigilance:<br>Nonclinical carcinogenicity studies: GLP Study 13-0322 (completed; a summary is provided in Section III.3) and GLP Study 13-0323 (~~are~~ ongoing). The two study reports will be submitted together when the results from GLP Study 13-0323 become available. | Characterize carcinogenicity of vismodegib in nonclinical settings. |
| ~~Long-term use of vismodegib in patients with advanced BCC (locally advanced and metastatic BCC)~~ | ~~Routine pharmacovigilance:~~<br>~~• Specific analysis in PBRERs/PSURs of adverse events that occur in patients who have long-term (over one year) usage of vismodegib.~~<br>~~Additional pharmacovigilance:~~<br>~~• MO25616 (STEVIE) CSR will include:~~<br>~~-Resolution of adverse events after treatment discontinuation~~<br>~~-PK obtained in patients with persistent adverse event~~ | ~~• Detection, collection and reporting of adverse events in the setting of long-term use of vismodegib~~<br>~~• On-going safety evaluation of the benefit/risk ratio of vismodegib~~ |
| ~~Vismodegib Exposure after discontinuation of treatment~~ | ~~Additional pharmacovigilance:~~<br>~~PK cohort in MO25616 (STEVIE).~~ | ~~Characterization of vismodegib of PK profile upto 1 year post treatment.~~ |
| Use in patients with severe renal impairment | Routine pharmacovigilance:<br>• Review in PBRERs/PSURs. | Detection, collection and reporting of events in patients with severe renal impairment |

| Safety Concern | Proposed routine and additional PhV activities | Objectives |
|---|---|---|
| Interaction with CYP inducers and OATP1B1 substrates | Routine pharmacovigilance:<br>• Review in PBRERs/PSURs. | Detection, collection, and reporting of events due to Drug-Drug interactions (DDI) |
| Interaction with oral contraceptives | Routine pharmacovigilance:<br>• Review in PBRERs/PSURs. | Detection, collection and reporting of events due to interaction with oral contraceptives |

**Assessor's comments**:

Changes reflecting a survey of PPP awareness are accepted.

Under important potential risks/impairment of fertility, removal of "adjudication of events by an internal expert group for independent opinion" and removal of "Clinical investigations within MO25616 (STEVIE) for evaluation of patients with irregular menses or amenorrhea including abdominal ultrasound and serum hormone evaluation, when possible", is removed, which is accepted.

References to the GLP Study 13-0322 and 13-0323 are made under important potential risks/second primary malignancies and important potential risks/squamous cell carcinoma, and further under missing information/nonclinical carcinogenicity studies, which is accepted. This will be reviewed in a future procedure.

Removal of "Adjudication of events of secondary primary cancer/squamous cell carcinoma/death-sudden death-cardiac death/keratitis-ulcerative keratitis/fracture/ reported in MO25616 (STEVIE) by an expert group for independent opinion" in corresponding sections is accepted.

Hyponatremia with pharmacovigilance activities and objectives is removed in accordance with a PSUR previously accepted by PRAC (EMEA/H/C/PSUSA/00010140/201407).

Removal of "long-term use of vismodegib in patients with advanced BCC (locally advanced and metastatic BCC)". Accepted.

Removal of "vismodegib exposure after discontinuation of treatment" with pharmacovigilance activities and objectives is accepted.

**Risk minimisation measures**

**Table 8: Summary table of Risk Minimisation Measures**

| Safety Concern | Routine RMM | Additional RM Activities. |
|---|---|---|
| **Identified Risks** | | |
| Teratogenicity | **Routine activity (SmPC and Package Leaflet)**<br>SmPC<br>Sections 4.3, Contraindications; 4.4, Special warnings and precautions for use; 4.6, Fertility, pregnancy and lactation; and 5.3, Preclinical safety data.<br><br>The SmPC states that the use of Erivedge is contraindicated in women who are pregnant and in women of childbearing potential who do not comply with the Erivedge Pregnancy Prevention Programme; that women taking Erivedge must not be pregnant or become pregnant during treatment and for 9~~2~~4 months after the final dose; that Erivedge may cause embryo-fetal death or severe birth defects when administered to a pregnant woman; that a patient must stop treatment and notify her treating physician immediately if she suspects that she is pregnant, or if she has missed an expected menstrual period; or if she stops using contraception unless she commits to not having sexual intercourse (abstinence) or if she needs to change contraception ; and that in case of pregnancy in a woman treated with Erivedge, treatment must be stopped immediately. Guidelines are provided for counseling of male and female patients as well as for contraceptive use and pregnancy testing.<br><br>Package Leaflet<br>The package leaflet provides information to the user consistent with the SmPC. | Erivedge Pregnancy Prevention Programme |
| Muscle spasms | **Routine activity (SmPC and Package Leaflet)**<br>SmPC<br>Section 4.8, Undesirable effects | None |
| **Important Potential Risks** | | |
| Post-Natal Developmental Defects | **Routine activity (SmPC and Package Leaflet)**<br>SmPC<br>Erivedge is contraindicated in breastfeeding women. Women must not breastfeed while taking Erivedge and for 9~~2~~4 months after the last dose due to its potential to cause serious developmental defects. The safety and efficacy of Erivedge in children and adolescents aged below 18 years have not been established. Due to safety concerns, Erivedge should not be used in children and adolescents aged below 18 years, and there are insufficient PK data in pediatric patients (Sections 4.2, Posology and | None |

| Safety Concern | Routine RMM | Additional RM Activities. |
|---|---|---|
| | method of administration; 4.3, Contraindications; 4.4, Special warnings and precautions for use; 4.6, Fertility, pregnancy and lactation; 5.1, Pharmacodynamic properties; 5.2, Pharmacokinetic properties; and 5.3, Preclinical safety data).<br><br>Package Leaflet<br>This document reports the currently-known risks associated with vismodegib use, and any actions to be taken by the patient. | |
| Impairment of fertility | **Routine activity (SmPC and Package Leaflet)**<br>SmPC<br>*Section 4.6 Impairment of fertility*<br>Human~~Dedicated studies to assess the potential of Erivedge to affect fertility have not been performed. However, data from studies in rats and dogs indicate that male and~~ female fertility may be ~~irreversibly~~ compromised by treatment with Erivedge (see section 5.3.). Reversibilty of fertility impairment is unknown. Additionally, amenorrhea has been observed in clinical trials in women of child-bearing potential (see section 4.8). Fertility preservation strategies should be discussed with women of child-bearing potential prior to starting treatment with Erivedge.<br>Fertility impairment in human males is not expected (see Section 5.3).<br><br>Package Leaflet<br>*Section 2 Fertility*<br>Erivedge may affect a woman's~~your~~ ability to have children~~, which applies to both men and women~~. Some women taking Erivedge have stopped having periods. If this happened to you, it is not known whether your periods would come back. Talk to your doctor if you wish to have children in the future. | None |
| Second primary malignancies | **Routine activity (SmPC and Package Leaflet)**<br>These documents highlight the risks associated with the use of Erivedge. Erivedge labeling documents will be updated with information specific to this risk as appropriate on the basis of data obtained from pharmacovigilance activities. | None |

| Safety Concern | Routine RMM | Additional RM Activities. |
|---|---|---|
| Squamous cell carcinoma | **Routine activity (SmPC and Package Leaflet)**<br>SmPC<br>Highlights the risks associated with the use of Erivedge.<br><br>*Section 4.4 Special warnings and precautions for use*<br>*Cutaneous squamous cell carcinoma (cuSCC)*<br>Patients with advanced BCC have an increased risk of developing cuSCC. Cases of cuSCC have been reported in advanced BCC patients treated with Erivedge. It has not been determined whether cuSCC is related to Erivedge treatment. Therefore, all patients should be monitored routinely while taking Erivedge, and cuSCC should be treated according standard of care. | None |
| Death/sudden death/cardiac death | **Routine activity (SmPC and Package Leaflet)**<br>These documents highlight the risks associated with the use of Erivedge. Erivedge labeling documents will be updated with information specific to this risk as appropriate on the basis of data obtained from pharmacovigilance activities. | None |
| Off-label use (pediatric medulloblastoma , BCC appropriate for treatment with surgery or radiotherapy, and other cancers) | **Routine activity (SmPC and Package Leaflet)**<br>SmPC<br>This document states that Erivedge is indicated for the treatment of adult patients with metastatic BCC or laBCC that is inappropriate for surgery or radiotherapy (see Section 4.1), and that Erivedge should only be prescribed by or under the supervision of a specialist physician experienced in the management of the approved indication (see section 4.2)<br><br>Package Leaflet<br>This document reports the currently-known risks associated with vismodegib use and the potential for post-natal developmental defects in pediatric patients.<br><br>Appropriate information regarding the use of vismodegib in aBCC is addressed in the SmPC. Vismodegib is currently used on an investigational basis for a number of indications. Information on off-label use as well as demographic data will be obtained post-launch. | None |

| Safety Concern | Routine RMM | Additional RM Activities. |
|---|---|---|
| Keratitis / ulcerative keratitis | **Routine activity (SmPC and Package Leaflet)**<br>These documents highlight the risks associated with the use of Erivedge. Erivedge labeling documents will be updated with information specific to this risk as appropriate on the basis of data obtained from pharmacovigilance activities. | None |
| Fracture | **Routine activity (SmPC and Package Leaflet)**<br>These documents highlight the risks associated with the use of Erivedge. Erivedge labeling documents will be updated with information specific to this risk as appropriate on the basis of data obtained from pharmacovigilance activities. | None |
| Venous thromboembolic events | **Routine activity (SmPC and Package Leaflet)**<br>These documents highlight the risks associated with the use of Erivedge. Erivedge labeling documents will be updated with information specific to this risk as appropriate on the basis of data obtained from pharmacovigilance activities. | None |

| Safety Concern | Routine RMM | Additional RM Activities. |
|---|---|---|
| Syncope | **Routine activity (SmPC and Package Leaflet)**<br>These documents highlight the risks associated with the use of Erivedge. Erivedge labeling documents will be updated with information specific to this risk as appropriate on the basis of data obtained from pharmacovigilance activities. | None |
| ~~Hyponatremia~~ | ~~**Routine activity (SmPC and Package Leaflet)**~~<br>~~Hyponatremia and increase of liver transaminases have been observed in some patients treated with Erivedge, however, the relationship to Erivedge is unknown (SmPC Section 4.8, Undesirable effects).~~ | ~~None~~ |
| **Missing Information** | | |
| Nonclinical carcinogenicity studies | Nonclinical carcinogenicity studies are ongoing to further characterize carcinogenicity of vismodegib in nonclinical settings. | None |
| ~~Long-term use of vismodegib in patients with advanced BCC (locally advanced and metastatic BCC)~~ | ~~**Routine activity (SmPC and Package Leaflet)**~~<br>~~These documents highlight the risks associated with the use of Erivedge. Erivedge labeling documents will be updated with information specific to this safety concern as appropriate on the basis of data obtained from pharmacovigilance activities.~~ | ~~None~~ |
| ~~Vismodegib Exposure after Discontinuation of Treatment~~ | ~~**Routine activity (SmPC and Package Leaflet)**~~<br>~~Provisionally extended pregnancy prevention recommendations to 24 months for WCBP~~ | ~~None~~ |
| Use in patients with severe renal impairment | **Routine activity (SmPC and Package Leaflet)**<br>These documents highlight the risks associated with the use of Erivedge. Erivedge labeling documents will be updated with information specific to this safety concern as appropriate on the basis of data obtained from pharmacovigilance activities. | None |
| Interaction with CYP inducers and OATP1B1 substrates | **Routine activity (SmPC and Package Leaflet)**<br>These documents highlight the risks associated with the use of Erivedge. Erivedge labeling documents will be updated with information specific to this safety concern as appropriate on the basis of data obtained from pharmacovigilance activities. | None |
| Interaction with oral contraceptives | **Routine activity (SmPC and Package Leaflet)**<br>These documents highlight the risks associated with the use of Erivedge. Erivedge labeling documents will be updated with information specific to this safety concern as appropriate on the basis of data obtained from pharmacovigilance activities. | None |

**Assessor's comment:**

Changing 24 to 9 months is not accepted under the following paragraphs: Identified Risks/Teratogenicity/Routine activity; Important Potential Risks/Post-Natal Development Defects/ Routine activity.

Changes under Important Potential Risks/Impairment of fertility/Routine activity are in accordance with procedure EMEA/H/C/002602/II/0021 and accepted.

Removal of hyponatremia from Important Potential Risks is in accordance with a PSUR previously accepted by PRAC (EMEA/H/C/PSUSA/00010140/201407).

Removal of "long-term use of vismodegib in patients with advanced BCC (locally advanced and metastatic BCC)" from Missing Information is accepted.

Removal of "vismodegib exposure after discontinuation of treatment" from Missing Information is accepted.

***Overall conclusion on the RMP***

The changes to the RMP and the changes to the conditions and obligations of MA are acceptable.

## *4.7. Changes to the Product Information*

- *Hyponatremia* is removed from the adverse effects table, section 4.8, in accordance with a PSUR previously accepted by PRAC (EMEA/H/C/PSUSA/00010140/201407). Accepted.
- *Blood creatine phosphokinase increased* is added as a common adverse reaction in the adverse effects table, section 4.8 and package leaflet. Accepted.
- Recommended time for washout: change from 24 to 9 months. Changes made with reference to pregnancy, contraception, breast feeding, blood donation (4.4, 4.6, and package leaflet) and health care professional and patient educational materials and reminder card (annex II D). Not accepted.
- Efficacy results from MO25616 are added to 5.1. Accepted.
- Removal of annex II E: specific obligation to complete post authorization measures for the conditional marketing authorisation. Accepted.

# 5. Request for supplementary information

## 5.1. Other concerns

***Nonclinical aspects***

1. The MAH proposes an increased threshold of concern for teratogenicity, based on pharmacodynamic considerations. This approach is not endorsed based on the following:

   The embryofetal toxicity study in rats is considered the most important data set for evaluation of teratogenic risk. In absence of a NOAEL, it is not considered overly conservative to base the threshold on 1/10 of Cmin at the LOEL. Differences in protein binding are acknowledged but the experimentally determined values on free fraction cannot be directly extrapolated to the in vivo situation.

   For the proposed new threshold, it is not sufficiently justified why to base the threshold on mouse anti-tumour data rather than on data from the embryofetal toxicity study. There are many uncertainties in the extrapolation from anti-tumour activity in mice to embryofetal toxicity in humans. Importantly, this proposal does not deal with these uncertainties to any extent. The MAH proposes a level based on 40% inhibition of hedgehog, which is exactly the cutoff for pharmacological activity, based on the data submitted. Any minor difference in terms of species differences, distribution to placenta vs tumour etc. could result in that the proposed threshold level would in fact result in embryofetal toxicity. As a threshold to protect against such events, the proposal is not acceptable.

   In order to consider a change in the threshold of concern for teratogenicity, a novel justification which addresses the concerns raised in this assessment should be submitted.

***Clinical aspects***

Clinical Pharmacology:

2. The submitted PK data are too limited to exclude the possibility of unsafe exposure levels (see Nonclinical aspects) between 12 and 24 months post discontinuation. It does not seem appropriate to decrease the waiting time from 24 months post last dose. The MAH is asked to comment.

Efficacy:

3. The MAH is asked to discuss possible reasons for discordant PFS results in SHH4476g and MO25616 in the presence of similar findings for overall response.

Safety:

4. In MO25616, there is an increase in mortality between 6 November 2013 and 16 March 2015 - from 5.8 to 9.1%. The dominating cause of death seems to be adverse events (5.8%) rather than disease progression (2.2%), which is obviously unusual for a cancer disease entity, and a likely reflection of the indolent nature of basal cell carcinoma. A more in-depth analysis reveals that a smaller fraction of the adverse events are in fact treatment emergent (3.8% in March 2015 compared to 3.2% in November 2013), and an even smaller proportion considered related by the investigator - 0.6% in March 2015 and 0.4% in November 2013. Although this

may seem reassuring, the absence of a control arm precludes further assessment of a mortality contribution from vismodegib. The MAH is asked:

- to provide the best available comparator for expected numbers and causes of deaths (database, historical or other), in the absence of a randomized control arm, the regulatory norm.
- to provide an in-depth analysis of possible relatedness for all 46 patients who died with TEAEs.

5. An analysis of reversibility of muscle spasms after treatment discontinuation includes 621 safety-evaluable patients who signed protocol version 3 or higher. Only 266 patients are reported. The MAH is asked to provide a table for all 621 patients describing reasons for not including remaining 355 patients in the table of TEAEs ongoing 12 months after treatment discontinuation.
6. A conspicuous difference in grade 1 and 2 hypokalemia between November 2013 and March 2015 presumably reflects a change in classification, an explanation is warranted. CTCAE version 4.03 vs 4.0?
7. There is a significant increase in grade 1 creatinine elevations in the current compared to the previous report: in November 2013, 318 of 479 patients (66%) had a grade 0 baseline creatinine elevation without worsening during treatment; in March 2015, only 87 of patients (7.3%) were graded 0 at baseline without worsening, whereas 795 (65%) patients shifted from 0 to grade 1 as worst grade. What percentage of creatinine elevations normalised on treatment? After treatment? At all? Or has classification changed?
8. A medical review of adverse events related to renal insufficiency/elevated creatinine, displaying a temporal relationship to events of increased creatine kinase, yielded a limited number of patients (7).

   An analysis of biochemistry test results should be more sensitive in detecting a relationship between creatine kinase and creatinine increases.

   Please provide a contingency table of worst NCI-CTC grade creatinine (high) during treatment and worst grade CPK increase (the latter available for 453 patients when not limiting to patients with baseline measurements), *based on biochemistry test results - not reported adverse events*. This should be available for several hundreds of patients.

Product information:

9. In the adverse effects table, section 4.8, “hepatic enzymes increased” and “blood creatine phosphokinase increased” should be presented under appropriate system organ class in accordance with the EU guideline on summary of product characteristics.

***Risk management plan***

10. The concerns raised in Q1 and Q2 are also relevant for the RMP; shortening of wash-out time from 24 to 9 months can currently not be supported.

# 6. Assessment of the responses to the request for supplementary information

***Other concerns***

**Non-clinical aspects**

**Question 1**
The MAH proposes an increased threshold of concern for teratogenicity, based on pharmacodynamic considerations. This approach is not endorsed based on the following:

The embryofetal toxicity study in rats is considered the most important data set for evaluation of teratogenic risk. In absence of a NOAEL, it is not considered overly conservative to base the threshold on 1/10 of Cmin at the LOEL. Differences in protein binding are acknowledged but the experimentally determined values on free fraction cannot be directly extrapolated to the in vivo situation.

For the proposed new threshold, it is not sufficiently justified why to base the threshold on mouse anti-tumour data rather than on data from the embryofetal toxicity study. There are many uncertainties in the extrapolation from anti-tumour activity in mice to embryofetal toxicity in humans. Importantly, this proposal does not deal with these uncertainties to any extent. The MAH proposes a level based on 40% inhibition of hedgehog, which is exactly the cutoff for pharmacological activity, based on the data submitted. Any minor difference in terms of species differences, distribution to placenta vs tumour etc. could result in that the proposed threshold level would in fact result in embryofetal toxicity. As a threshold to protect against such events, the proposal is not acceptable.

In order to consider a change in the threshold of concern for teratogenicity, a novel justification which addresses the concerns raised in this assessment should be submitted.

**Summary of the MAH's response**
The MAH discusses data available from regulatory documents on sonidegib (Odomzo). These data indicate that the minimal dose to reveal malformation in rabbit fetuses occurs at exposures approximately 14 -fold (15,400/1080 $AUC_{0-24}$ ng•h/mL) to 36-fold (38,400/1080 $AUC_{0-24}$ ng•h/mL) lower than the minimally toxic exposure in juvenile rats.

The nonclinical safety data on sonidegib adds additional uncertainties to our proposed approach (*Gli1*-$IC_{40}$) to selecting a teratogenic threshold for vismodegib. Notably, while the toxicity of vismodegib was assessed in a rat EFD study, a NOAEL was not established in this study and vismodegib was not evaluated in rabbits. Therefore, the MAH cannot conclude definitively that vismodegib will demonstrate a similar increase in sensitivity in fetal tissues as observed with sonidegib, despite the identical mechanism of action of both drugs.

On the basis of this added uncertainty revealed by the sonidegib data, the MAH agrees to maintain the teratogenic threshold established at the time of the original Marketing Authorization Application (0.0037 µM, total plasma concentration). This threshold was $1/10^{th}$ of the $C_{min}$ of the LOEL from the rat EFD study with vismodegib. The MAH acknowledges that extrapolating a teratogenic threshold from $C_{min}$ values obtained in rat toxicity studies to humans may lead to conservative values, as $C_{min}$ is unlikely to be a PK driver of vismodegib activity in these studies due to the 463-fold variation in plasma $C_{max}$ and $C_{min}$ values in rats and flat steady state PK profile in humans.

**Assessment of the MAH's response**

The MAH has backed away from their proposal to increase the threshold for concern for teratogenicity, based on the discussion presented in the CHMP AR and data from another hedgehog inhibitor, sonidegib. By agreeing to the current threshold, this issue **is resolved**.

**Conclusion**

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

**Clinical aspects**

**Question 2**
The submitted PK data are too limited to exclude the possibility of unsafe exposure levels (see Nonclinical aspects) between 12 and 24 months post discontinuation. It does not seem appropriate to decrease the waiting time from 24 months post last dose. The MAH is asked to comment.

**Summary of the MAH's response**
The Marketing Authorization Holder (MAH) acknowledges that the measured pharmacokinetic (PK) data cannot exclude exposure above 0.0037 mM between 12 and 24 months post-discontinuation. However the MAH wants to highlight that this limited data is not due to lack of sample collection, but rather because the concentration in these plasma samples is below the lower limit of quantification (LLOQ). The MAH considers the cumulative PK data collected after treatment discontinuation sufficient to characterize the elimination phase of vismodegib and to determine exposures at various timepoints after treatment discontinuation, based on the accumulated data to date. Based on observed vismodegib PK data, and the submitted population PK (popPK) model (Population Pharmacokinetic Report [Report 16-0421]), total plasma concentration of vismodegib, in 95% of women of child-bearing potential (WOCBP), is expected to fall below the threshold of exposure for teratogenicity (0.0037 mM; see response to Question No. 1) within 24 months of treatment discontinuation (median: 17.6 months; 90% CI: 14.6, 22.1 months). Therefore, the MAH agrees to maintain the current waiting period at 24 months after the last dose (see response to Question 10).

*PK data collected after treatment discontinuation in Study MO25616*

Vismodegib plasma concentration data were collected after treatment discontinuation in two subcohorts of Study MO25616. Plasma samples were collected in subjects who experienced a vismodegib-related adverse event (AE) at 6, 9 and 12 months after treatment discontinuation (AE-related PK cohort), and in subjects selected for PK sampling at steady state and 3, 6, 9, and 12 months after treatment discontinuation (PK subcohort). A total of 104 PK samples were collected from 59 subjects after treatment discontinuation (post last dose) across these two subcohorts (Figure 1, Population Pharmacokinetic Report [Report 16-0421]). The threshold of exposure for teratogenicity is based on total vismodegib concentration (see response to Question 1).

*Fraction of PK data below LLOQ after treatment discontinuation in Study MO25616*

Total vismodegib plasma concentration was below LLOQ (11.9 nM) in 80% (83/104) of all post-last-dose PK samples (Table 3, Population Pharmacokinetic Report [Report 16-0421]). Total vismodegib plasma concentration was below total LLOQ in all subjects within 12 months of treatment discontinuation (Figure 2, Population Pharmacokinetic Report [Report 16-0421]).

*Incorporation of LLOQ samples in the popPK model*

All available PK data was utilized for the popPK modeling of vismodegib (Population Pharmacokinetic Report [Report 16-0421]), including those which were below LLOQ (M3 method). The final popPK model adequately described all measurable PK data as well as the proportion of samples which were below LLOQ (based on visual predictive check [VPC]). Model simulations reasonably described the observed total drug for previous studies and Study MO25616.

Although the predicted total drug concentration at steady-state was slightly lower than the observed data in Study MO25616, the model was able to capture the long elimination phase of total drug (assessed by VPC), which was essential for the exposure prediction after vismodegib treatment. The VPC was conducted to capture 90% of data, which means that 10% of data will not be covered by the prediction band with 5% above and 5% below the median. Therefore, it is expected that some data points will lie outside the prediction band. Taken together, the final popPK model can be used for the purpose of exposure prediction long after drug treatment has been discontinued.

The submitted popPK model (Population Pharmacokinetic Report [Report 16-0421]) was used to predict the time required for total vismodegib plasma concentration to fall below the threshold of exposure for teratogenicity (pregnancy prevention duration). The pregnancy prevention duration for WOCBP, after treatment discontinuation, was defined based on when the simulated PK profiles for 95% of the virtual WOCBP population (7600 individuals) fell below the threshold of exposure for teratogenicity (hereinafter referred to as 95% coverage). A 90% confidence interval was generated based on 100 pregnancy prevention duration estimates to represent the uncertainty around this value. The median pregnancy prevention duration for 95% coverage was 17.6 months (90% CI: 14.6, 22.1 months).

In conclusion, PK data were collected up to 12 months after treatment discontinuation in Study MO25616. Additional PK assessment between 12 and 24 months is not expected to provide additional information about the elimination of vismodegib after treatment discontinuation because all later data points are expected to be below the LLOQ. Based on the observed vismodegib PK data, and the submitted popPK model, exposure levels are not predicted to be above the threshold of exposure for teratogenicity 24 months after treatment discontinuation. Therefore, the MAH agrees to maintain the currently recommended waiting period for pregnancy prevention at 24 months after treatment discontinuation.

**Assessment of the MAH's response**

The MAH has summarized the available pharmacokinetic information during the wash-out phase after stop of treatment. Total vismodegib plasma concentration falls below the lower limit of quantification (11.9 nM or 0.0119 µM) within 12 months of treatment discontinuation. The time to reach the threshold level that is based on preclinical toxicity (0.0037 µM) is uncertain. Based simulations from a Population PK model the total plasma concentration of vismodegib is expected to fall below the threshold of exposure for teratogenicity within 24 months of treatment discontinuation (median: 17.6 months; 90% CI: 14.6, 22.1 months) in 95% of women of child-bearing potential (WOCBP). The MAH agrees to maintain the current waiting period at 24 months after the last dose. This is acceptable.

**Conclusion**

The MAH agrees to maintain the current waiting period at 24 months after the last dose. **Issue resolved**.

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

**Question 3**

The MAH is asked to discuss possible reasons for discordant PFS results in SHH4476g and MO25616 in the presence of similar findings for overall response.

**Summary of the MAH's response**

Three principal reasons are considered in explaining this discordance:

- Patient selection and baseline characteristics of the treated population

  Both studies targeted similar populations, and demographic and baseline disease characteristics were broadly similar. The MAH considered identified minor differences in patient populations unlikely to have contributed to the differences in PFS between the two studies.

- Frequency and method of assessment for tumor response and disease progression (PD)

  In study SHH4476g tumor assessments were made every 8 weeks, whereas in MO25616, assessments were made every 4-8 weeks (for physically assessable tumors), or every 8-16 weeks (if imaging required). This difference in frequency of assessments was not considered a likely explanation for the PFS difference, as a subgroup of patients in MO25616 assessed every 8 weeks (enrolled under protocol amendment 4) displayed similar PFS (25.1 months for laBCC, 12.2 months for mBCC) to the MO25616 overall efficacy-evaluable population (23.2 months for laBCC, 13.1 months for mBCC). No other differences with potential to impact on PFS were identified. Overall, differences in frequency and methodology of assessing PD were not felt likely to have contributed to the PFS differences between the studies.

- Data maturity and impact of censoring on PFS estimates

**Treatment duration, discontinuation, and Investigator-assessed PFS in Study SHH4476g and Study MO25616**

| | SHH4476g (Clinical Cutoff: 30 May 2013) | | MO25616 (Clinical Cutoff: 16 March 2015) | |
|---|---|---|---|---|
| **Enrolled patients** | **laBCC (n=71)** | **mBCC (n=33)** | **laBCC (n=1119)** | **mBCC (n=96)** |
| Median treatment duration [a] | 12.7 months | 13.3 months | 256 days (8.4 months) | 319 days (10.5 months) |
| Patients who discontinued treatment | 64 (90.1%) | 32 (97.0%) | 988 (88.3%) | 80 (83.3%) |
| **Efficacy-evaluable patients** | **laBCC (n=63)** | **mBCC (n=33)** | **laBCC (n=1103)** | **mBCC (n=89)** |
| Overall response rate | 60.3% | 48.5% | 68.5% | 36.9% |
| Median PFS [b] | 12.9 months | 9.3 months | 23.2 months | 13.1 months |
| Median follow-up [b] | 25.0 months | 28.6 months | 11.1 months | 18.4 months |
| Patients with PD or death | 34 (54.0%) | 24 (72.7%) | 288 (26.1%) | 50 (56.2%) |
| Patients censored for PFS | 29 (46.0%) | 9 (27.3%) | 815 (73.9%) | 39 (43.8%) |

BCC = basal cell carcinoma; laBCC = locally advanced BCC; mBCC = metastatic BCC; PD = disease progression; PFS = progression-free survival
[a] arithmetic estimate;

[b] Kaplan-Meier estimate
Source: Table 5, Table 14, Table 16, Table 21, and Table 6e, 30-month Update SHH4476g CSR; Table 4, Table 10, Table 30, and Table 36, Primary MO25616 CSR; t_tte2_PFS_IT.out.

The majority of patients in both studies had discontinued treatment, primarily for a documented reason other than PD, such as adverse events (21.2% in SHH4476g and 28.7% in MO25616) or patient decision (26.0% in SHH4476g and 19.5% in MO25616) (Table 5, 30-month Update SHH4476g CSR and Table 4, Primary MO25616 CSR).

The proportion of laBCC patients censored in Study MO25616 was substantially higher than in study SHH4476g (46.0% vs. 73.9% in MO25616) and the median PFS follow-up time was shorter (25.0 months vs. 11.1 months in MO25616). The MAH acknowledged that the substantial proportion of patients discontinuing treatment prior to PD (in MO25616) may have resulted in some informative censoring and therefore a possibility of some inflation in the estimate of PFS.

The difference in size between the two studies is also pointed out as a potential source for the PFS difference. Study SHH4476g had a smaller sample size; therefore, a smaller number of patients were at risk for progression over time and at the median PFS time-point, resulting in each PFS event leading to a larger change (or "step") in the KM estimate and lower PFS estimates overall (Figure 9, 30-month Update SHH4476g CSR).

Overall, the MAH considers that the differing extent of censoring (higher proportion in Study MO25616) and the different sample sizes are likely to be contributing reasons for the observed differences in PFS estimates between Study SHH4476g and Study MO25616.

**Assessment of the MAH's response**

The MAH´s conclusion that censoring inequalities, not study population or frequency/method of tumour assessments, explains the difference in PFS is supported. Different sample sizes affect uncertainty in PFS estimates, but not the point estimate in a certain direction; the conclusion that sample size contributes to the observed difference is not understood. The MAH has not proposed any changes to the SPC reflecting PFS findings in MO25616, which is supported. **Issue resolved**.

**Conclusion**

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

**Question 4**

In MO25616, there is an increase in mortality between 6 November 2013 and 16 March 2015 - from 5.8 to 9.1%. The MAH is asked:

- to provide the best available comparator for expected numbers and causes of deaths (database, historical or other), in the absence of a randomized control arm, the regulatory norm.
- to provide an in-depth analysis of possible relatedness for all 46 patients who died with TEAEs.

**Summary of the MAH's response**

A best available comparator

In the absence of available published data on laBCC and mBCC populations without treatment, the on-treatment mortality rate in study MO25616 was compared to the mortality of the U.S. general population (Xu et al., Deaths: Final data for 2012. National vital statistics report; vol 63 no 9. Hyattsville, MD: National Center for Health Statistics. 2015.):

| Age groups (years) | Patient-years in MO25616 | Mortality per 1000 in U.S. general population | Expected cases [a] | Observed cases (on-treatment mortality in MO25616) |
|---|---|---|---|---|
| 45 – 54 | 144.53 | 4.06 | 0.59 | 2 |
| 55 – 64 | 216.51 | 8.6 | 1.86 | 6 |
| 65 – 74 | 238.39 | 18.02 | 4.30 | 9 |
| 75 – 84 | 229.82 | 46.48 | 10.68 | 5 |
| 85+ | 146.8 | 136 | 19.96 | 18 |
| **Total** | | | **37.39** | **40** |
| **SMR [b] (95% CI [c])** | | | **1.07 (0.74; 1.40)** | |

CI = confidence interval; SMR = standardized mortality ratio; U.S. = United States.

[a] Expected cases = Patient-years in MO25616 × Mortality rate in the US general population

[b] SMR = Observed number of cases / Expected number of cases

[c] 95% CI = SMR +/- 1.96 × [SQRT(Observed number of cases)/Expected number of cases]

Source: Study MO255616: t_dd_ptyrs_ONTRT_SE; US general population: Xu et al. 2015

An in-depth analysis of relatedness

In the MAH response to question 4, it was stated that all 46 patients who experienced TEAEs leading to death were independently reviewed by the Data Safety Monitoring Board (DSMB) for the study as part of its ongoing responsibilities. A table for all 46 patients, including age, disease status, performance status, medical history, a short narrative, and investigator's and the DSMB's assessment of relatedness was supplied. For 45 of the 46 cases, the DSMB concluded that the TEAEs leading to death were unrelated to study drug. In the one remaining case, the DSMB felt there was insufficient clinical data provided by the site to make a full assessment.

**Assessment of the MAH's response**

The MAH has provided an age matched control based on the U.S. general population, for patients treated in MO25616. The numbers of observed deaths in MO25616 are higher than expected < 75 years age, which may seem natural for a non-representative population of locally advanced and metastatic BCC patients. Speculatively, the fewer than expected deaths ≥ 75 years age might reflect a counteracting tendency to include healthier patients in clinical trials; a tendency that may increase with the age of the patient. It is not possible to conclude from these data, that vismodegib does not contribute to mortality in treated patients. The number of deaths does not however significantly exceed what is expected for the age-matched U.S. general population. To further pursue a reliable control (e.g. by attempting to match for comorbidity, or utilizing a European population) is not deemed meaningful.

A review of the supplied table of patients experiencing grade 5 TEAEs confirms the gravity of comorbidities as well as the advanced age (median 80) in this group.

The MAH has provided requested analyses and data aimed at contextualising fatal treatment-emergent adverse events in MO25616. No findings indicate a significant excess mortality caused by vismodegib. Further pursuing a reliable control population for the MO25616 patients is not considered meaningful.

**Issue resolved.**

**Conclusion**

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

**Question 5**

An analysis of reversibility of muscle spasms after treatment discontinuation includes 621 safety-evaluable patients who signed protocol version 3 or higher. Only 266 patients are reported. The MAH is asked to provide a table for all 621 patients describing reasons for not including remaining 355 patients in the table of TEAEs ongoing 12 months after treatment discontinuation.

**Summary of the MAH's response**

Reasons for non-completion of the 12-month safety follow-up visit for patients with ongoing TEAEs 12 months after treatment discontinuation:

| **Reasons for non-completion** | **N = 355<br>n (%)** |
|---|---|
| Ongoing on treatment | 147 (41.4%) |
| Safety follow-up ongoing | 140 (39.4%) |
| <=3 months of safety follow-up | 30 (8.5%) |
| 6 months of safety follow-up | 39 (11.0%) |
| 9 months of safety follow-up | 71 (20.0%) |
| Withdrew from study prior to 12-month assessment | 68 (19.2%) |
| Death | 18 (5.1%) |
| Lost to Follow-up | 50 (14.1%) |

**Assessment of the MAH's response**

The seemingly low number of patients assessed for reversibility of muscle spasms (266) is mostly explained by ongoing treatment (41%) and less than 12 months of follow-up (39%). Fourteen percent were lost to follow-up. **Issue resolved.**

**Conclusion**

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

**Question 6**
A conspicuous difference in grade 1 and 2 hypokalemia between November 2013 and March 2015 presumably reflects a change in classification, an explanation is warranted. CTCAE version 4.03 vs 4.0?

**Summary of the MAH's response**
Different versions of CTCAE were used (4.0 November 2013, 4.03 March 2015), but this did not cause the observed difference. In the current report, all patients fulfilling the "< lower limit normal to 3.0 mmol/L" hypokalemia were assumed to be symptomatic or require treatment (considered a conservative assumption by the MAH), thereby qualifying for a grade 2 assignment. For the November 2013 analysis, this assumption was not made, and corresponding instances of hypokalemia were graded 1.

**Assessment of the MAH's response**

An explanation has been provided. **Issue resolved.**

**Conclusion**

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

**Question 7**
There is a significant increase in grade 1 creatinine elevations in the current compared to the previous report. What percentage of creatinine elevations normalised on treatment? After treatment? At all? Or has classification changed?

**Summary of the MAH's response**
CTCAE criteria did not change between reports, but were applied differently: in the previous report, only the "> upper limit normal (ULN) to 1.5 times the ULN" was used, whereas in the current report the "> 1 – 1.5 x baseline" criterion was used as well. Applying both approaches to both reports yields:

| Clinical cutoff | Number of subjects (%) who met the Grade 1 criteria | |
|---|---|---|
| | >ULN - 1.5 × ULN | >1 - 1.5 × baseline; >ULN - 1.5 × ULN |
| November 2013 (n=479) | 75 (15.7%) | 322 (67.2%) |
| March 2015 (n=1185) | 213 (18.0%) | 795 (67.1%) |

With regards to creatinine normalization, outcomes of patients experiencing post-baseline shifts from grade 0 to grade 1 elevations was provided:

| Outcome of creatinine elevation | Number of subjects (%) (n = 795) |
|---|---|
| Normalized ~~at all~~ | 422 |
| Normalized on treatment | 358 (84.8%) |
| Normalized after treatment | 64 (15.2%) |
| Did not normalize | 373 |
| Never Above ULN | 289 (77.5%) |
| Reached >ULN, did not return to <ULN before data cut | 43 (11.5%) |
| Reached >ULN, returned to <ULN before data cut | 41 (11.0%) |

**Assessment of the MAH's response**

The apparent increase in post-baseline grade 1 creatinine elevations reflected a difference in classification. A limited number of patients (11.5%) did not revert to < ULN before data cut off. Findings in the current report are consistent with those of November 2013. **Issue resolved.**

**Conclusion**

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

**Question 8**

Please provide a contingency table of worst NCI-CTC grade creatinine (high) during treatment and worst grade CPK increase (the latter available for 453 patients when not limiting to patients with baseline measurements), *based on biochemistry test results - not reported adverse events*. This should be available for several hundreds of patients.

**Summary of the MAH's response**

| | Creatinine Elevated | | | | | |
|---|---|---|---|---|---|---|
| Creatine Kinase Increase | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Total |
| Total (N=482) | | | | | | |
| Grade 0 | 23 (4.8%) | 209 (43.4%) | 46 ( 9.5%) | 1 (0.2%) | 0 | 279 ( 57.9%) |
| Grade 1 | 9 (1.9%) | 112 (23.2%) | 27 ( 5.6%) | 2 (0.4%) | 3 (0.6%) | 153 ( 31.7%) |
| Grade 2 | 2 (0.4%) | 32 ( 6.6%) | 4 ( 0.8%) | 0 | 0 | 38 ( 7.9%) |
| Grade 3 | 0 | 7 ( 1.5%) | 1 ( 0.2%) | 0 | 0 | 8 ( 1.7%) |
| Grade 4 | 0 | 4 ( 0.8%) | 0 | 0 | 0 | 4 ( 0.8%) |
| Total | 34 (7.1%) | 364 (75.5%) | 78 (16.2%) | 3 (0.6%) | 3 (0.6%) | 482 (100.0%) |

Based on results presented in this table from the larger number of patients with biochemistry data available for CPK and creatinine (n = 482), the MAH concludes there is no evidence of an association between increased CPK and creatinine elevation.

**Assessment of the MAH's response**

Agreed. **Issue resolved.**

**Conclusion**

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

**Product information**

**Question 9**

In the adverse effects table, section 4.8, “hepatic enzymes increased” and “blood creatine phosphokinase increased” should be presented under appropriate system organ class in accordance with the EU guideline on summary of product characteristics.

**Summary of the MAH’s response**

The MAH agrees to follow the EU guideline on summary of product characteristics and assign any adverse reactions to the most relevant SOC related to the target organ.

Therefore, the MAH proposes to update the adverse effects table (Table 1), Section 4.8 as follows:

- “Hepatic enzymes increased” to be placed under the SOC “Hepatobiliary Disorders”.
- “Blood creatine phosphokinase increased” to be placed under the SOC “Musculoskeletal and Connective Tissue Disorders”.

The product information has been revised accordingly.

**Conclusion**

The response is satisfactory. **Issue resolved.**

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

**RMP aspects**

**Question 10**
**Summary of the MAH’s response**

As explained in responses to questions 1 and 2, the MAH proposes to maintain the 0.0037 µM teratogenicity threshold and the conservative 24-months wash-out period. An updated EU Risk Managemant Plan v10.1, incorporating this proposal has been submitted with this response.

**Assessment of the MAH’s response**

The 24 month wash-out period maintained.

**Conclusion**

This is accepted. **Issue resolved.**

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance