EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 April 2013
EMA/297688/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Erivedge

International non-proprietary name: **vismodegib**

Procedure No. **EMEA/H/C/002602**

Note

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

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Product information

Name of the medicinal product:	Erivedge
Applicant:	Roche Registration Ltd. 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom
Active substance:	vismodegib
International Nonproprietary Name/Common Name:	vismodegib
Pharmaco-therapeutic group (ATC Code):	L01XX43, Antineoplastic agents
Therapeutic indication:	the treatment of adult patients with: - Symptomatic metastatic basal cell carcinoma - Locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy
Pharmaceutical form:	Capsule, hard
Strength:	150 mg
Route of administration:	Oral use
Packaging:	HDPE bottle
Package size:	28 capsules

List of abbreviations

Abbreviation	Definition
AAG	alpha-1-acid glycoprotein
BCC	basal cell carcinoma
BCS	Biopharmaceutics Classification System
CPP	Critical Process Parameter
CQA	critical quality attribute
CSR	Clinical Study Report
ECOG PS	Eastern Cooperative Oncology Group performance status
E–R	exposure–response
Hh	Hedgehog
HNSTD	highest non-severely toxic dose
INV	investigator
IRF	Independent Review Facility
IV	intravenous
GLI	Glioma-Associated Oncogene I
MED	Minimal effective dose
NC	not collected
NE	not estimable
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PGA	Physician's Global Assessment
PTCH1	Patched-1
QbD	Quality by Design
QD	once daily
QOL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
QTPP	Quality Target Product Profile
SBS	Summary of Biopharmaceutic Studies and Associated Analytical Methods
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology Studies
SF-36	Short Form 36
SLD	sum of the longest dimensions
SMO	Smoothened
STD_{10}	severely toxic dose to 10% of animals

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Roche Registration Ltd. submitted on 1 December 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Erivedge, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 June 2011.

The applicant applied for the following indication: treatment of advanced basal cell carcinoma.

The legal basis for this application refers to:

Article 8(3) of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMA/638789/2012 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance vismodegib contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 16 December 2010. The Scientific Advice pertained to pre-clinical and clinical development aspects of the dossier.

Licensing status

Erivedge has been given a Marketing Authorisation in United States of America on 30 January 2012.

Erivedge has since received approval in the following countries: Switzerland, Australia, Mexico, Israel, Korea and Ecuador.

A new application has also been filed in the Canada.

1.2. Manufacturers

Manufacturer responsible for batch release

Roche Pharma AG

Emil-Barell-Strasse 1

D-79639 Grenzach-Whylen

Germany

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP:

Rapporteur: **Kristina Dunder** Co-Rapporteur: **Pierre Demolis**

- The application was received by the EMA on 1 December 2011.
- The procedure started on 21 December 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 09 March 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 March 2012.
- During the meeting on 19 April 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 19 April 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 13 September 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 26 October 2012.
- During the CHMP meeting on 15 November 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 12 December 2012.
- During a meeting of a SAG-Oncology on 9 January 2013, experts were convened to address questions raised by the CHMP.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 22 January 2013.
- During the CHMP meeting on 21 February 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 15 March 2013.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 March 2013.
- During the CHMP meeting on 21 March 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 4 April 2013.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 19 April 2013.
- During the meeting on 25 April 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a conditional Marketing Authorisation to Erivedge on 25 April 2013.

2. Scientific discussion

2.1. Introduction

Basal Cell Cancer or Basal Cell Carcinoma (BCC) is a slow-growing, locally invasive, malignant epidermal skin tumour predominantly affecting Caucasians. Although it is the most common malignancy worldwide, it is very difficult to estimate the incidence and prevalence of BCC because cases typically have been designated as non-melanoma skin cancers (NMSCs), which include both basal cell and squamous cell skin cancers (SCCs), and these cases, unlike melanoma, are not required to be reported to cancer registries. Furthermore, there is no standardized staging system for BCC. As a result, the epidemiology and natural history of advanced BCC have been poorly described. Estimates suggest an annual incidence of 234 per 100,000 for Europe[1].

Most BCCs are small and are treated by dermatologists using various surgical methods, photodynamic therapy, and approved topical treatments. Treatment modalities of localised disease include imiquimod, photodynamic therapy, radiotherapy, surgery, including Moh's micrographic surgery, the latter normally reserved for high risk facial lesions[2]. Cure rates are generally high irrespective of modality if properly applied. A very small proportion of BCCs may progress to an advanced state that is no longer amenable to available treatments. In these cases progressive disease results in morbidity from local tissue invasion and destruction particularly on the face, head and neck. These lesions include both locally advanced BCCs, that are either inoperable or in patients who have medical contraindications to surgery and for whom radiotherapy was unsuccessful or contraindicated, or very rarely, metastatic BCC, in whom BCC has spread to distant sites [3, 4, 5]. There are no published data on prevalence and life expectancy for locally advanced BCC because of its absence from major registries and databases. Based on published data the incidence of metastatic BCC is believed to be significantly lower than 0.1% of cases of BCC. Radiation therapy and cisplatin-based chemotherapy have been used to treat it. Median survival has been reported to be about 8 to 10 months.

In the late 1990s it was shown that BCC appears to be driven by the activation of the Hedgehog (Hh) pathway. This gene was initially discovered in 1980 and 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 [6, 7].

In short, the signalling cascade in humans is initiated in the target cell by the Hh ligand binding to the Patched-1 (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. The signal is transmitted via the Glioma-Associated Oncogene (GLI) transcription factors. The expression of GLI1 is highly dependent upon active Hh signaling and often used as a read-out of pathway activation[8].
There is a rare hereditary syndrome associated with aberrant Hh signalling; Gorlin syndrome, also known as nevoid basal cell carcinoma syndrome (NBCCS). Gorlin syndrome is caused by germ-line mutations in the PTCH1 gene. The main clinical manifestations include multiple BCCs, odontogenic keratocysts of the jaws, hyperkeratosis of palms and soles, skeletal abnormalities, intracranial ectopic calcifications, and facial dysmorphism (macrocephaly, cleft lip/palate and severe eye anomalies)[9]. BCC

most often appear between puberty and 35 years of age, but cases have been reported in 3 or 4 year-old patients.

Hh signalling has also been identified as an important signalling pathway in human cancers. Mutations in components of the Hh pathway has been identified both in basal cell carcinoma and medulloblastoma, but are also implicated in the development of other cancer such as lung, breast and pancreas[6,8]. In basal cell carcinoma a high frequency (about 90%) of inactivating mutations in PTCH1 or to a lesser extent (about 10%) activating mutations in SMO is identified.

Vismodegib is a small molecule inhibitor of the Hh signalling pathway, which acts by binding to SMO[10,11]. 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.

This is an application for Erivedge (vismodegib) proposed for the treatment of adult patients with advanced basal cell carcinoma for whom surgery is inappropriate, as one 150 mg hard capsule taken once daily.

2.2. Quality aspects

2.2.1. Introduction

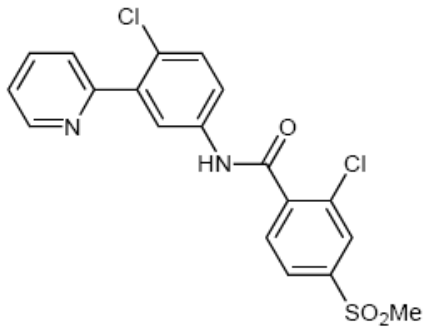
Erivedge is presented as hard gelatine capsules containing 150 mg of vismodegib as the active substance. The capsules consist of pink coloured opaque body marked “150 mg” and a grey opaque cap marked “VISMO” with black ink. The size of the capsule is ‘size 1’ (dimensions 19.0 x 6.6 mm).

Excipients used in the preparation of Erivedge are well known excipients, commonly used in oral solid dosage forms. The capsule content is composed of microcrystalline cellulose, lactose monohydrate, sodium lauryl sulfate, povidone, sodium starch glycolate (Type A), talc and magnesium stearate. Capsule shells are made of gelatine, iron oxide black (E172), iron oxide red (E172) and titanium dioxide (E171). The printing ink contains shellac, iron oxide black (E172) and solvents which are removed during imprinting.

The capsules are packed in high density polyethylene (HDPE) bottles fitted with white child resistant polypropylene (PP) screw cap.

2.2.2. Active Substance

Vismodegib (INN) is chemically designated as 2-Chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide (chemical name), and has the following structure:



Vismodegib is a crystalline free base, appearing as a white to tan solid. The substance is non-hygroscopic and achiral. It is practically insoluble in water, soluble in acetone, sparingly soluble in acetonitrile and slightly soluble in ethanol.

In Biopharmaceutics Classification System (BCS) vismodegib is classified as a Class 2 compound (expressing low solubility and high permeability).

Vismodegib primarily exists as polymorph B, the most thermodynamically stable polymorph observed to date. Formation of the desired polymorphic form during manufacture of vismodegib is assured by seeding with crystals of Polymorph B and by drying to ensure low solvate and thus low residual solvent levels. In addition, the crystal form is confirmed by an X-ray powder diffraction analysis on the final active substance. Form B of vismodegib is the only form that has been used in clinical development. Sufficient evidence was provided to demonstrate that Form B is obtained by the employed manufacturing process of the active substance.

Particle size was considered a critical quality attribute of the active substance as vismodegib is not dissolved in the dosage form. Therefore an appropriate test on particle size determination was included in the active substance specification.

Manufacture

A Quality by Design (QbD) approach was employed during the development. However, no design space has been claimed for the active substance. Consequently, the manufacturing processes of the active substance is expected to run in the set target values (within the approved ranges) and with traditional control strategy (including in-process controls).

During development, the critical quality attributes (CQAs) of the active substance were established based on the potential to impact the performance and manufacturability of the finished product and these include impurities (organic and inorganic impurities, residual solvents, water, and metals), polymorph form, and particle size. Process development efforts have focused on the identification and control of active substance CQAs and the Critical Process Parameters (CPPs) that impact them. The CQAs of the active substance requiring investigation have been determined and an appropriate control strategy for the manufacturing process has been employed.

The synthesis of vismodegib involves three steps which comprise formation and/or breaking of chemical bonds. The substance is produced from commercially available starting materials. Two intermediates are isolated.

The particle size of the dried vismodegib is reduced by milling to obtain the desired particle size distribution. The manufacturing process has been suitably described in flow charts and a narrative description. The length of the synthesis was justified in terms of control of purity profile of the starting materials.

Potential impurities have been well discussed in relation to their origin (raw material, manufacturing process and degradation products) and potential carry-over into the final active substance. Impurities derived from starting materials as well as process impurities formed in the manufacturing process have been demonstrated to be sufficiently controlled by the applied analytical methods, the specifications, and the manufacturing process.

The possibility of genotoxic impurities was also addressed during the development. A scientific rationale that it is not necessary to monitor genotoxic impurities in vismodegib due to their reactive nature and the purging power of the synthesis and evidence supporting such rationale have been provided. Satisfactory purging data for potential genotoxic impurities has been provided.

In general, sufficient information regarding the manufacturing process, starting materials, critical steps and intermediates, process validation and manufacturing process development have been provided. The synthesis and process parameters have been well characterised and described.

Confirmation of the chemical structure of vismodegib was provided by elemental analysis (confirmation of the determined elementary composition by evaluation of C, H, N, Cl, O and S content), spectroscopic methods as UV, FITR, ^{1}H-NMR, ^{13}C-NMR as well as by mass spectral (MS) analysis XRPD and single crystal X ray diffraction. The IR, NMR and MS spectrum assignations were consistent with the declared chemical structure.

The potential for polymorphism has been investigated to identify polymorphic forms of vismodegib. Many polymorphs of vismodegib were observed as part of extensive polymorph screening, however only two polymorphs (Form A and B) have been observed during manufacturing at any scale. Polymorph A was discovered as the initial crystalline form, but could not be reproduced. Polymorph B is the thermodynamically most stable polymorph observed to date and its formation is induced by seeding during crystallization. Other polymorphic forms of vismodegib (Forms C and E) are also known. Forms C and E were observed only in the extensive polymorph screening study with a low frequency of occurrence. The crystallization solvents and conditions to generate Forms C and E are drastically different from the conditions used in vismodegib processing. Form B is the most thermodynamically stable polymorph discovered, it is monotropically more stable than Forms A and C, and is enantiotropically more stable than Form E at lower temperature.

Specification

The active substance specification includes tests for appearance, identification (FTIR, HPLC and XRPD), assay (HPLC), chromatographic purity (HPLC), water content (Karl Fischer), residual solvents (GC), particle size (Light Scattering) heavy metals and residue on ignition.

A detailed description for all analytical methods was provided. Complete method validation data was provided for the non compendial (*in-house*) analytical methods.

In general specification limits and analytical methods proposed are suitable to control the quality of the active substance.

Batch analysis results for vismodegib have been presented. All batches were manufactured by the proposed commercial manufacturers according to the proposed process. Batches were used in preclinical and clinical studies during development, clinical scale-up, and process validation. In total 29 batches of vismodegib have been manufactured during the development phase. All batches showed comparable impurity profile. It can be concluded that the batch analysis results indicate that the manufacturing process is reproducible and under control.

Stability

Primary stability studies according to ICH guidelines have been initiated on pilot and commercial scale batches of the active substance stored in the commercial package.

Primary stability program involves testing on 3 commercial scale batches placed at long term conditions (30°C/65 % RH) and accelerated conditions (40°C/75% RH). Six months of accelerated data are available for all batches and up to 24 months of data have been reported for the 30°C/65% RH condition. The batches are monitored for appearance, water content, assay, and impurities and physical form. All results reported are within proposed specifications. No trends are seen in the primary and supportive studies.

The active substance has also been subjected to forced degradation with regards to acid, base, peroxide (oxidant), heat, humidity, and light stress conditions. Vismodegib is stable under light, heat, and humidity, with some degradation observed under acidic and basic stress conditions. Degradation was also observed when vismodegib was exposed to oxidative reagent (H_2O_2) for a longer period. In the photostability study the appearance of the substance was changed from white to light orange, no changes were seen for the other parameters.

The results of the forced-degradation study and of the long-term and accelerated primary stability studies, as presented in the dossier, show that vismodegib is chemically and physically stable under stress conditions.

Based on the available stability data, vismodegib showed to be a stable when packaged in the proposed container closure system.

2.2.3. Finished Medicinal Product

Pharmaceutical development

The aim of the pharmaceutical development was to obtain a solid, oral dosage form that would deliver the required dose of the active substance.

The development of the capsule formulation and manufacturing process was based on prior knowledge. It followed a classic development approach and adopted elements of QbD and risk-based methodology. An in-depth understanding of the effects of formula components, process intermediates and process parameters was obtained from design of experiment studies (DoEs), scale-up studies and analysis of batches manufactured for clinical studies. Based on these studies, appropriate control strategy has been implemented to mitigate the risks identified initially and to ensure that the characteristics specified in the Quality Target Product Profile (QTPP) will be met consistently. However, no design space has been claimed for the finished product. Consequently, the manufacturing processes of the finished product is expected to run in the set target values (within the approved ranges) and with traditional control strategy (including in-process controls).

During the development of the finished product risk assessment was performed with regards to formulation and manufacturing development to establish the critical quality attributes (CQA) and critical process parameters (CPP). The approach and the conclusions (in terms of CQA and CPP) were considered acceptable. The proposed process description is adequately detailed and includes all parameters that are needed to be monitored or controlled during the process to ensure the intended quality of the finished product.

Phase I clinical trial was conducted on a dry blend capsule formulation with 25 mg, 125 mg, and 270 mg of vismodegib whereas Phase II clinical trials was conducted on an earlier wet granulation capsule formulation of 150 mg. The same 150 mg hard capsule formulation as developed for the clinical studies will also be used for the commercial capsule.

In the risk assessment performed prior to the development of the wet granulated formulation focus was set on compendial capsule dosage form parameters (dissolution, content uniformity (UoC) and stability), active substance physical characteristics and the excipients sodium lauryl sulfate and magnesium stearate, since the drug substance was considered to be a BCS Class 2 compound. Factors not considered to be critical or having a significant effect were e.g. water content, stability of drug substance (stable), polymorphic form (since it was established that the B form was achieved in the manufacturing and it is thermodynamically stable) and level of disintegrant since the microcrystalline cellulose filler also act as disintegrant. The primary goal of the initial risk assessment was to prioritize optimization studies, where high risk factors were prioritized; factors that were assigned an uncertain effect were subject to further data collection and evaluation and low risk factors monitored and studied selectively.

A final risk assessment was conducted based on the knowledge gained from the development studies. Initial potential risks were reviewed and reduced due to proposed process parameter settings and control measures in place.

The manufacturing process development has been well documented. A wet-granulation process was selected after experimentally comparing it with a direct blending and a dry granulation process. The study showed that the high shear wet-granulation process produced granules with the best flow quality. Additionally, the granule particle size produced by high shear wet granulation was significantly smaller than that produced by the roller compaction process, which reduced capsule weight variation during encapsulation. The selection of the wet-granulation process also took into consideration the high process robustness, the availability of equipment at varying scales, and the stability of the active substance against heat and moisture. Choice of the process was considered justified and the critical process parameters and process equipment were generally satisfactorily identified. It has been shown that the manufacturing process was robust.

It can be concluded that the formulation development of the product was satisfactorily described. The key critical parameters were identified and successfully evaluated.

Adventitious agents

Among excipients used in the medicinal product gelatine (component of the capsule shell) and lactose (component of the capsule fill) are of animal origin.

Ph. Eur. TSE Certificates of Suitability were provided for gelatine.

It has been certified by the supplier that lactose is produced in compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products" (EMEA/410/01). Lactose is produced from milk obtained from healthy cattle under the same conditions as milk intended for human consumption.

Magnesium stearate is of vegetal origin and relevant certificates from manufacturers of this excipient have been provided.

Manufacture of the product

The manufacturing process is sufficiently described as well as a process flow diagram provided. The hard capsules are manufactured by a standard process comprising wet granulation in high-shear granulator where the active substance, microcrystalline cellulose, lactose monohydrate, sodium lauryl sulfate, and part of sodium starch glycollate is granulated with the granulation solution consisting of povidone and purified water. The granules are dried in a fluid-bed, milled and mixed with sodium starch glycollate and talc followed by mixing with magnesium stearate and filling.

Overall, description of manufacturing process is adequate and includes all the relevant critical and non-critical process parameters. Critical steps have been identified and properly evaluated at the commercial scale. The reproducibility of the process has been suitably demonstrated during the development of the manufacturing process. Formal validation will be performed post-approval on the first three consecutive commercial batches. An acceptable validation plan for this activity has been provided.

During manufacturing process development, process parameters settings have been optimized through the use of multivariate DoEs (full factorial and fractional factorial). Considering the limited extent of the ranges explored (normal operating ranges), it is considered that these studies demonstrate the robustness of the process. Although no formal validation has been performed yet, robustness of the process and consistency of the quality was further confirmed by the data collected from the verification batches manufactured at commercial scale.

Product specification

The finished product is controlled by testing attributes relevant for this dosage form. The finished product specification includes tests for appearance, identity of the active (HPLC and UV), uniformity of content, assay (HPLC), degradation products (HPLC), dissolution, water content (Karl Fischer). The capsules comply with Ph. Eur. criteria for microbiological quality.

The proposed specifications were justified based on the batch and stability results and are generally adequate for assuring the product quality and therefore were accepted.

A detailed description for all analytical methods was provided. Full method validation data was provided for the non compendial (in-house) analytical methods.

Batch results are provided for 19 batches produced from 2006 to the present and used in clinical studies, process development studies and primary stability studies. Batch analysis results demonstrated compliance with the proposed specifications and confirmed consistency and uniformity of the product. The results were consistent from batch to batch and proved that the product can be manufactured reproducibly according to the agreed specifications.

Stability of the product

Stability studies have been initiated according to ICH guidelines on production scale batches of the finished product packaged in its commercial HDPE bottle package. Data from six months of accelerated conditions (40°C/75% RH) and 24 months of long term conditions (30°C/65 % RH) are available for three batches. At both long term and accelerated conditions no significant changes or trends in any of the parameters monitored have been seen and all data are within proposed specifications.

Freeze/thaw studies and samples stored in an open container up to 12 months did not show trending, and a photostability study in ICH conditions shows that the finished product is not sensitive to light.

The overall stability data showed that Erivedge was stable under all tested conditions. The results generated during the stability studies support the proposed shelf life and storage conditions as defined in the SmPC.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The information provided about the active substance, vismodegib, was of acceptable quality. In general sufficient information regarding the manufacturing process, materials, critical steps and intermediates, process validation and manufacturing process development have been provided. The synthesis and process parameters have been well characterised and described.

Specification limits and analytical methods are suitable to control the quality of the active substance.

A retest period was supported by satisfactory stability studies which show that the active substance is stable.

The finished product is an immediate release hard capsule containing 150 mg of vismodegib. The development pharmaceutics has been satisfactorily described. The excipients are well established and used in acceptable quantities. Their function has been satisfactorily described. The formulation is considered satisfactorily justified.

The method of manufacture is considered standard and has been satisfactorily described, including in-process tests. The data shows consistent manufacture and is considered sufficient for this manufacturing process. A satisfactory validation protocol has been provided.

The proposed specifications were justified based on the batch and stability results, and are in general adequate for assuring the product quality and therefore were accepted.

The stability program is considered satisfactory. The batches placed on stability are considered representative of the product to be marketed. The results generated during the stability studies support the proposed shelf life and storage conditions as defined in the SmPC.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The active substance (vismodegib) and the finished product (hard capsules 150 mg) have been appropriately characterised and generally satisfactory documentation has been provided. The results indicate that vismodegib as well as the capsules can be reproducibly manufactured. Therefore the product should have a satisfactory and uniform performance in the clinic.

2.3. Non-clinical aspects

2.3.1. Introduction

Pivotal preclinical studies on safety pharmacology and toxicology were performed in accordance with GLP and EU guidelines.

The applicant received Scientific Advice on pre-clinical aspects from the CHMP on 16 December 2010. The Scientific Advice pertained to the preclinical toxicity studies package, the acceptability of carcinogenicity and early embryonic development studies.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Studies on primary pharmacodynamics are summarised in the following **table 1.**

Study No.	Study Title
In Vitro	
06-0636	Evaluation of GDC-0449 in Cellular GLI-Luciferase Reporter Assay
In Vivo	
04-0242 K	Response of Subcutaneous Patched Heterozygous Murine Medulloblastoma Xenografts to GDC-0449.23 Administered at 100 mg/kg Twice a Day
09-2968	Dose Escalation Study of GDC-0449.23 Versus Subcutaneous *Ptch* $^{+/-}$ *p53* $^{+/+}$ Murine Medulloblastoma (SRC 125826, Passage 6) Allografts in Female CD-1 Nude Mice
09-0633	Characterization of the PK/PD Dose Response of the Hedgehog Pathway Inhibitor GDC-0449 versus Subcutaneous *Ptch* $^{+/-}$ *p53* $^{+/+}$ Murine Medulloblastoma Allografts in Female CD-1 Nude Mice
D5123-05-04	Determination of the Minimum Effective Dose of GDC-0449.23 to Inhibit the Growth of Subcutaneous D5123 Primary Colorectal Carcinoma Xenografts
D5123-05-06	Pharmacokinetic/Pharmaco-dynamic Study of GDC-0449.23 Administration in Primary Human Colorectal Carcinoma Xenograft D5123
05-1039 D	Determination of the Minimum Efficacious Dose of GDC-0449.23 in LS180 Human Colorectal Carcinoma Xenograft Model: Efficacy and PK/PD
D5124-06-02	Effect of GDC-0449.23 at 69 mg/kg Twice a Day Alone or With Gemcitabine on Growth of Primary Human Pancreatic Adenocarcinoma Xenograft Model D5124

Vismodegib inhibited Hh signalling with an IC_{50} of 12.7 nM in a mouse 10T1/2 cell line and with an IC_{50} of 2.8 nM in the human embryonic palatal mesenchymal (HEPM) Hh responsive cell line. Vismodegib exerts this activity through binding to and inhibiting SMO.

Vismodegib was evaluated for its ability to inhibit the growth of subcutaneous (SC) murine medulloblastoma allografts that are driven by constitutive Hh pathway activation caused by mutation of the *Ptch1* gene. When dosed twice daily at 100 mg/kg, vismodegib caused regressions of established *Ptch1*$^{+/-}$ medulloblastoma tumor allografts. The PD effect of vismodegib on *Gli1* expression was determined following a single PO dose of 1, 10, or 50 mg/kg in this model. In general, the PD effect of vismodegib appeared to be dose and plasma concentration dependent. Expression of *Gli1* in tumours was maximally repressed at concentrations > 1 µM.

Vismodegib was evaluated for its ability to inhibit the growth of SC xenograft tumours through inhibition of paracrine Hh signalling between tumour and the surrounding stroma. Dosed twice a day (BID) significantly delayed growth in a patient-derived human colorectal xenograft model, D5123 in nude mice with a minimal effective dose (MED) of 69 mg/kg. The MED for anti-tumour activity correlated with the dose needed for maximum Hh signalling in tumours for 12-18 hours. A similar MED for vismodegib when dosed twice daily was also observed in a subcutaneous LS180 human CRC xenograft model.

Secondary pharmacodynamic studies

A PK/PD study was performed to validate the use of hair follicles and/or skin as surrogate tissues to monitor vismodegib activity. Oral administration of 100 mg/kg vismodegib BID for 5 total doses resulted in significant suppression of mouse *Gli1* (*mGli1*) RNA in hair follicles and skin biopsies during

anagen harvested 4 hours following the final dose. Pathway suppression was observed to a greater extent in skin than in hair follicles regardless of the phase of the hair cycle. A greater fold reduction in *Gli1* expression was detected in anagen (9.3-fold) vs telogen (3.6-fold) in skin whereas *Gli1* was repressed similarly during telogen and anagen in hair follicles (1.5-fold).

Safety pharmacology programme

Table 2

Study No	Study Title	Findings
04-1008-1791	Hit Profiling Screen with GDC-0449.1	Vismodegib was evaluated for its ability to inhibit radioligand binding to 43 receptors from recombinant and non-recombinant cells identified as potential mediators of unintended pharmacologic activity. At a concentration of 9.2 μM, vismodegib did not have a biologically significant effect on radioligand binding to any of the off-target receptors.
04-1278-1791	Lead Profiling Screen with GDC-0449.1	
05-0606	Effects of GDC-0449.1 on Cloned hERG Potassium Channels Expressed in Mammalian Cells	The in vitro effects of vismodegib on the hERG channel mediated ion current (I_{Kr}; rapidly activating, delayed rectifier cardiac potassium current) were evaluated in voltage-clamped HEK293 cells that stably express hERG potassium channels. At concentrations of 3 μM, 10 μM, 30 μM, and 80 μM, vismodegib inhibited hERG potassium current by (mean ± SEM) 4.9 ± 0.5%, 14.4 ± 0.3%, 40 ± 0.4%, and 77 ± 0.8%, respectively, compared to 0.2 ± 0.1% in vehicle-treated controls. The IC_{50} for the effect of vismodegib on hERG potassium current was 37.2 μM, which is approximately 340-fold greater than typical free plasma drug concentration in patients at steady state (0.11 μM based on a typical total drug plasma concentration of 22.3 μM).
05-1458	An Oral Gavage Cardiovascular Safety Pharmacology Study with GDC-0449.1 in Conscious Beagle Dogs	Administration of vismodegib at 600 or 2000 mg/kg had no toxicologically relevant effects on ECG results (RR interval, QT interval, or QT interval corrected for variations in heart rate), blood pressure measurements including heart rate, systolic, diastolic and mean arterial pressure and pulse pressure (systolic-diastolic), or on body temperatures. A complete scan of the lead II ECG waveforms after dose administration revealed no abnormalities. In a single-dose pilot dog toxicity study, the peak concentration of vismodegib in dogs given 2000 mg/kg is approximately 4-fold greater than the typical plasma drug concentration in patients at steady state (22.3 μM).

Pharmacodynamic drug interactions

No Pharmacodynamic drug interactions have been performed (see discussion on non-clinical aspects).

2.3.3. Pharmacokinetics

Methods of analysis

Vismodegib concentrations in GLP studies were quantitated using a liquid chromatographic-tandem mass spectrometric (LC/MS/MS) assay method that was developed and validated in both rat and dog plasma.

Absorption

Single-dose PK studies were performed in mice (Study 05-0547), rats (Study 05-0657), dogs (Study 05-1405), and monkeys (Study 04-0745). Animals were given single PO doses of vismodegib in 0.5% methylcellulose with 0.2% Tween-80 (MCT) at 2 (dog and monkey) or 5 mg/kg (mouse and rat) and single IV doses at 1 mg/kg. Vismodegib was administered as its free base in all PK studies except the *Cynomolgus* monkey PK study in which animals were given the hydrochloride salt. PK parameters are summarised in the following table.

Table 3

Parameter	CD-1 Mouse	Sprague-Dawley Rat	Beagle Dog	Cynomolgus Monkey [a]
IV administration				
No./Animals	27 (3/timepoint)	3	3	3
Sex	F	M	M	M
Dose (mg/kg)	1	1	1	1
CL (mL/min/kg)	23.0	4.65 ± 1.81	0.338 ± 0.203	19.3 ± 6.93
$t_{1/2}$ (hr)	0.976	1.32 ± 0.258	41.8 ± 19.8	0.581 ± 0.0922
MRT (hr)	1.22	1.89 ± 0.508	62.3 ± 30.0	0.855 ± 0.101
V_{ss} (L/kg)	1.68	0.490 ± 0.0653	1.03 ± 0.119	0.984 ± 0.342
PO administration				
No./Animals	27 (3/timepoint)	3	3	3
Sex	F	M	M	M
Dose (mg/kg)	5	5	2	2
C_{max} (ng/mL)	311	2760 ± 1020	591 ± 97.7	162 ± 121 (52.0 ± 46.6) [a]
t_{max} (hr)	1.00	0.667 ± 0.289	9.33 ± 12.7	2.00 ± 0.00 (2.00 ± 0.00) [a]
AUC_{inf} (ng • hr/mL)	696	10500 ± 3150	39400 ± 5800	256 ± 112
F (%) [b]	19.2	52.9	32.9	13.4 ± 2.07
Renal clearance (mL/min/kg)	NA [c]	0.00149 ± 0.00101 [d]	0.000464 ± 0.000435 [e]	NA [f]

AUC_{inf} = area under the concentration–time curve from zero to infinity; CL = plasma clearance; C_{max} = highest observed plasma concentration; F = bioavailability; IV = intravenous; MRT = mean residence time; NA = not available; PO = oral; $t_{1/2}$ = half-life; t_{max} = time at which C_{max} occurred; V_{ss} = volume of distribution at steady state.

[a] GDC-0449 was administered to monkeys orally in MCT or in 80% PEG400

(parameters from 80% PEG 400 administration are in parentheses when available).

[b] Oral vehicle was MCT for all estimates of bioavailability presented.

[c] No urine was collected from mice.

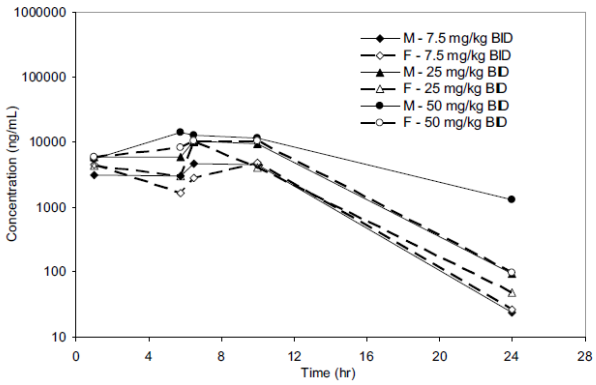
[d] Renal clearance was assessed for IV and PO groups.

[e] Renal clearance was assessed for the IV group only.

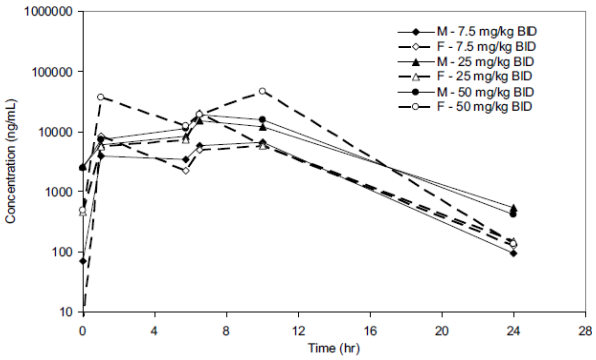
[f] GDC-0449 was not detected in urine.

Repeat dose pharmacokinetics was evaluated in the toxicokinetics studies. Time profiles on plasma exposure from the chronic toxicity studies in rats and dogs are presented below. Curves from other toxicity studies within the same species showed a similar pattern.

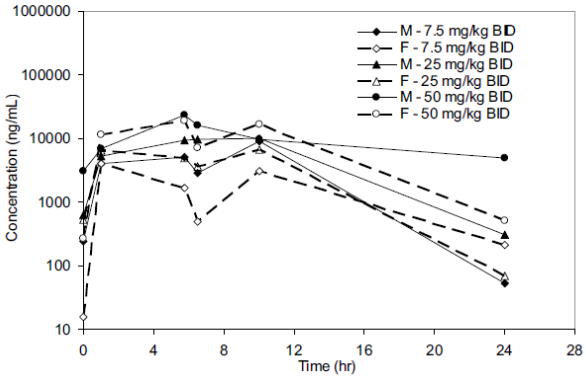
Day 1: Mean Plasma GDC-0449 Concentrations following Twice-Daily PO Doses of GDC-0449 in Male and Female Rats



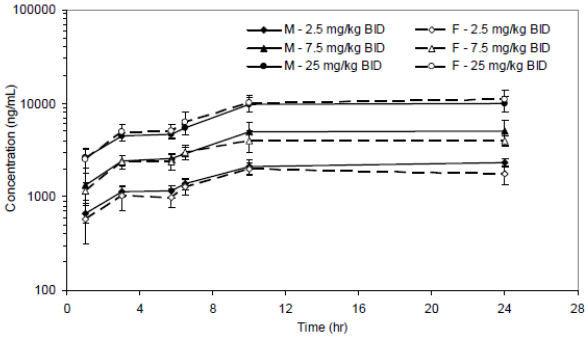
Day 91: Mean Plasma GDC-0449 Concentrations following Twice-Daily PO Doses of GDC-0449 in Male and Female Rats



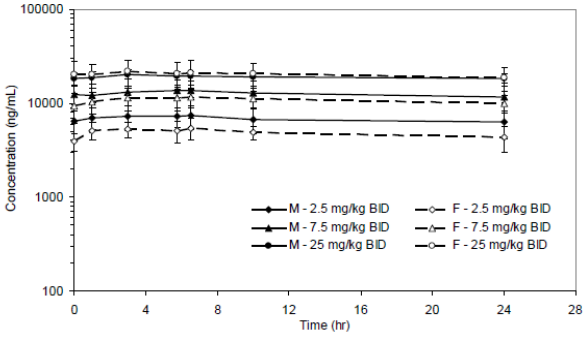
Day 182: Mean Plasma GDC-0449 Concentrations following Twice-Daily PO Doses of GDC-0449 in Male and Female Rats

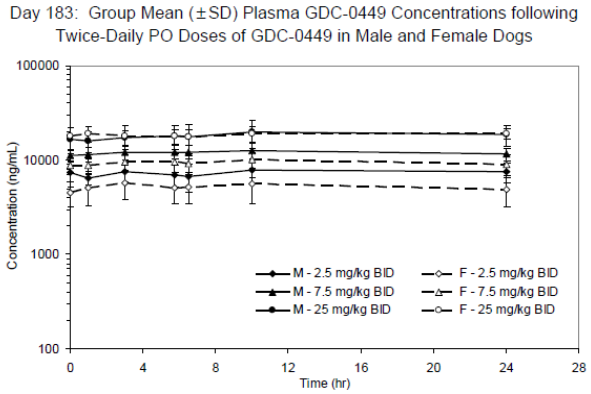


Day 1: Group Mean (±SD) Plasma GDC-0449 Concentrations following Twice-Daily PO Doses of GDC-0449 in Male and Female Dogs



Day 92: Group Mean (±SD) Plasma GDC-0449 Concentrations following Twice-Daily PO Doses of GDC-0449 in Male and Female Dogs





Distribution

The in vitro plasma protein binding of vismodegib was evaluated by equilibrium dialysis using [^{14}C]vismodegib (Study 06-0526). Protein binding was assessed at vismodegib concentrations of 1, 10, and 100 μM in mouse, rat, rabbit, dog, cynomolgus monkey, and human pooled plasma. Vismodegib appeared to be highly protein bound (> 95% in all species). Values were between 98.1 and 98.44% (rat), 95.8 to 95.9% (dog) and between 96.0 and 97.0% (human).

Vismodegib binds to alpha-1-acid glycoprotein in a concentration-dependent manner. In contrast, binding to human serum albumin was independent of drug concentration but dependent on protein concentrations (Study 10-2576).

Vismodegib did not appear to preferentially distribute to red blood cells, with blood-plasma partition ratios ranging from 0.608 to 0.881 in mouse, rat, dog, monkey, and human pooled whole blood (Study 06-0599).

[^{14}C]-vismodegib was widely distributed to tissues in a quantitative whole-body autoradiography study in rats (Study 08-0915). The highest concentrations of radioactivity in tissues at t_{max} were found in: liver, eye uvea, adrenal gland, white adipose, Harderian gland, kidney cortex and medulla, aorta, ovary, and small intestine. The highest concentration of drug-derived radioactivity at t_{max} was observed in the contents of the alimentary canal. Elimination was not complete at 144 hours post-dose from all tissues. However, as radioactivity was still declining, it was anticipated that drug would have been cleared if the study had been conducted over a longer period.

Metabolism

Major metabolic pathways of vismodegib identified from in vitro (rat, dog, and human liver microsomes or in vivo studies (rat and dog) involve primary oxidations followed by sequential glucuronidation or sulfation. No human specific metabolites were identified in vitro in the human mass balance study, parent compound represented > 98% of circulating drug-related material.

The metabolism of vismodegib was investigated in both in vitro and in vivo investigations. The major metabolic pathways involved oxidations of the 4-chloro-3-(pyridine-2-yl)-phenyl moiety followed by sequential glucuronidation or sulfation. Three additional metabolites were identified from in vivo studies that resulted from an uncommon pyridine ring opening. Two minor GSH conjugates were also identified in rat bile, but not in dog bile. A minor glucose conjugate was identified in dog bile.

Excretion

In mass balance studies in rat and dog, drug derived radioactivity was recovered largely in feces followed by bile.

Metabolic profiling (Study 07-1010 A) was performed on plasma, urine, feces, and bile from rats following a single PO dose of 50 mg/kg (100 μCi/kg) of [^{14}C]vismodegib. Unchanged vismodegib accounted for > 95% of radioactivity in rat plasma up to 24 hours post-dose. Approximately 90% of the dose was recovered in rat faeces in intact rats. Unchanged vismodegib accounted for 44.7% (male) and 40.2% (female) of the dose in rat faeces. The most abundant metabolite was M3, representing 15.9% (male) or 10.2% (female) of the dose. M9 was the second most abundant metabolite detected in rat faeces, accounting for 1.7% and 5.7% of the dose in male and female rats, respectively.

Metabolic profiling (Study 09-0830) was performed on plasma, urine, faeces, and bile from dogs following a single PO dose of approximately 5 mg/kg (17 μCi/kg) of [^{14}C]vismodegib. Vismodegib was the predominant radioactive component detected in dog plasma, accounting for > 94% of the circulating radioactivity exposure. An average of 62.9% (male) and 79.9% (female) of the dose was recovered in faeces during the 144-hour collection period. Unchanged vismodegib accounted for 23.0% (male) or 13.2% (female) of the dose in dog faeces. The most abundant faecal metabolite was M3, a mono-oxidation metabolite, accounting for 18.9% (male) or 28.0% (female) of the dose in dog faeces. Another predominant faecal metabolite was M13, accounting for 7.1% (male) and 12.1% (female) of the dose.

Radioactivity recovered in bile was mainly in the form of metabolites. Recovery of drug-derived radioactivity in urine from both species occurred to a lesser extent (<9% of dose).

Pharmacokinetic drug interactions

(See Clinical Pharmacokinetics section)

2.3.4. Toxicology

Table 4 Toxicity studies performed with vismodegib.

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day [a])	GLP Status	Study No.
Single-Dose Toxicity	Mouse, Crl:CD1(ICR)	PO	1 Day	0, 200, 600, 2000	Yes	05-1454
	Rat, Crl:CD(SD)	PO	1 Day	0, 200, 600, 2000	Yes	05-1455
	Dog, Beagle	PO	1 Day	0, 75, 225, 700, 1400, 2000	No	05-0598-1604
Repeat-Dose Toxicity	Rat, Crl:CD(SD)	PO	5 Days, QD	0, 300, 1000	No	05-0479
	Rat, Crl:CD(SD)	PO	14 Days, BID	0, 80, 250, 500	No	05-0943
	Rat, Crl:CD(SD)	PO	28 Days, BID	0, 50, 150, 500	Yes	05-1456
	Rat, Crl:CD(SD)	PO	13 Weeks, BID	0, 10, 50, 150, 500	Yes	06-1202
	Rat, Crl:CD(SD)	PO	26 Weeks, BID	0, 15, 50, 100	Yes	07-1224
	Dog, Beagle	PO	7 Days, BID	0, 150, 400, 1200	No	05-1061
	Dog, Beagle	PO	28 Days, BID	0, 50 [b], 150, 400	Yes	05-1457
	Dog, Beagle	PO	13 Weeks, BID	0, 15, 50, 150	Yes	06-1003
	Dog, Beagle	PO	26 Weeks, BID	0, 5, 15, 50	Yes	07-1047

Genotoxicity (Bacterial Reverse Mutation Assay)	*S. typhimurium* (TA98, TA100, TA1535, TA1537) *E.coli* (WP2*uvr*A)	In Vitro	52 ± 4 Hours (± S9)	0, 10 [c], 33.3, 100, 333, 1000, 2000, 5000 (µL/Plate)	Yes	05-1451
Genotoxicity (Chromosomal Aberrations Assay)	Primary Human Lymphocytes	In Vitro	3 Hours (-S9) 22 Hours (-S9) 3 Hours (+S9)	101 to 600 µg/mL 34.6 to 108 µg/mL 24.2 to 451 µg/mL	Yes	05-1452
Genotoxicity (Micronucleus Assay)	CD®(SD)IGS BR Rat Bone-Marrow Micronuclei	PO	1 Day, QD	0, 500, 1000, 2000	Yes	05-1453
Reproductive and Developmental Toxicity	Rat, WIST (Wistar)	PO	From Day of Gestation 6 to 17 Inclusive, QD	0, 10, 60, 300	Yes	09-2778 (3036R09)
Phototoxicity	Balb/c 3T3 fibroblasts	In Vitro	Not applicable	0.0054, 0.017, 0.054, 0.17, 0.54, 1.71, 5.41, 17.1 mg/L	Yes	12-1121

BID = twice daily; PO = oral gavage; QD = once per day.

[a] Unless otherwise specified. For Repeat-Dose Toxicity, the highest No-Observable-Adverse-Effect-Level (NOAEL) is underlined if determined.

[b] NOAEL 50 mg/kg/day in females. NOAEL not determined in males.

[c] 10 µL/plate not tested in *E. coli* strain.

Single dose toxicity

Vismodegib produced no evidence of adverse effects in mice, rats, or dogs following a single PO dose ≤ 2000 mg/kg in the single dose toxicity studies referenced in the above table.

Repeat dose toxicity

In all repeat dose toxicity studies, vismodegib dosing was by oral gavage. Dosing was either once daily (QD) or twice daily (BID), with doses separated by 6 hours.

Administration of repeated doses of vismodegib was associated with clinical observations of reversible tremors, jerking and/or ataxia in rats. Reversible decreases in platelet counts were observed in dogs given 150 mg/kg/day vismodegib, with clinical manifestations of platelet-related toxicity limited to 1 dog euthanized as moribund in association with thrombocytopenia in the 13-week toxicity study. Decreased hematocrit was observed in 1 dog (high-dose group, 50 mg/kg/day). Administration of vismodegib produced reversible increases in serum cholesterol in rats and dogs, with no corresponding effects on serum triglycerides.

Additional significant findings considered to be related to the pharmacologic mode of action included irreversible alteration/loss of incisors (erupting teeth) and closure of the femoral epiphysis (growth plate) in rats, alopecia in rats and dogs and follicular cysts in rats, reversible swelling of the paws in dogs with histopathologic correlates of follicular hyperkeratosis and dermal inflammation and reduced number of taste buds in rats.

Toxicokinetic analysis showed that systemic exposure in both rats and dogs reached the clinical exposure but no substantial (> 5-fold) exposure multiples were achieved in the pivotal repeat-dose toxicity studies.

Table 5

Study ID GLP status	**Species/ Sex/ Number/ Group/ Duration**	**Dose (mg/kg /day)**	**Main findings**
05-0479 Non-GLP	Rat 3M / 3F 5 days	0 300 1000 QD	Weight loss. Slight decrease in total white blood cell counts (HD F). Increase in serum cholesterol, decrease in serum triglycerides. In high dose animals, the stomach was enlarged and filled with food and white material. Ingestion and impaction of bedding or other material may have contributed to the observed effects on body weight and white blood cell counts. Similar observations were not seen in the 4 week toxicity study where wire-bottom cages were used.
05-0943 Non-GLP	Rat 4M /4 F 14 days + 14 days recovery, 4M /4F	0 80 250 500 BID	Body weight loss during first week of dosing (possibly related to ingestion of bedding as in 5 day study). Up to 2-fold increase in total serum cholesterol. Dose-dependent decreases in alkaline phosphatase.
05-1456 GLP	Rat 10M/10F 4 weeks + 4 weeks recovery, 5M/5F	0 50 150 500 BID	Mild body tremors (HD males + 1 M MD), reversed within first week of recovery phase. Thin and hunched appearance and rough haircoat (HD), persisted during recovery phase. Increased incidence of malocclusion during recovery phase (all doses). Reversible up to 2-fold increases in serum total cholesterol (MD, HD). Increased protein and decreased alkaline phosphatase (MD, HD). Microscopic findings were limited to effects on incisor teeth: degradation of dentin with scattered sequestrate and degeneration/necrosis of odontoblasts; secondary findings of fluid-filled cysts in dental pulp, hyperplasia of the periodontal ligament, ossification of the root canal, regeneration of the dental organ and scattered haemorrhage. Primary findings were generally dose responsive and persisted in recovery animals. No abnormalities were observed in the molar teeth, suggesting that these effects were related to the continuously growing nature of the rodent incisors.
06-1202 GLP	Rat 10M/10F 13 weeks + 8 weeks recovery, 5M/5F	0 10 50 150 500 BID	Dosing of animals given 500 mg/kg/day was discontinued on Study Day 44 due to a substantial body weight loss and associated clinical signs of hunched and thin appearance, clear oral discharge, and rough haircoat. At the 150 mg/kg dose level, 2 toxicity-study males were necropsied at an unscheduled interval (Study Days 67 and 71) due to general debilitation attributed to vismodegib. A dose-related increase in the incidence of malocclusion was present for males and females given 50 or 150 mg/kg/day. Missing incisors were noted for males and females given 150 or 500 mg/kg/day and females given 50 mg/kg/day. A dose-related increase in the incidence of leg-twitching and/or tremors (limb and body) was present for animals given 50 or 150 mg/kg/day during the dosing phase. Test article–related clinical signs that persisted through the completion of the recovery phase were limited to malocclusion and/or missing teeth in animals given ≥ 50 mg/kg/day. No test article–related clinical signs were present in the 10 mg/kg/day dose group during the dosing or recovery phases. Minimally to mildly higher total and HDL-cholesterol for animals given 500 mg/kg/day. Minimally to mildly lower alkaline phosphatase activity for animals given 500 mg/kg/day and males given 150 mg/kg/day may have been test article related.

			Histopathologic, dose response-related effects were seen in the upper incisor teeth of male and female rats given ≥ 50 mg/kg/day. Microscopic changes consisted of loss/atrophy of odontoblasts and ameloblasts, degradation of dentin with scattered sequestrae, formation of fluid-filled cysts in the dental pulp, hyperplasia of the periodontal ligament, ossification of the root canal, regeneration of the dental organ, occasional fibrometaplasia, and scattered haemorrhage and subacute inflammation. The majority of these changes persisted in recovery animals.
07-1224 GLP	Rat 10M/10F 26 weeks + 10M/10F 8 weeks recovery, 10M/10F	0 15 50 100 BID	A dose-related, reversible decrease in body weight gain observed during the dosing phase in males given 50 or 100 mg/kg/day was correlated with a decrease in food consumption. Clinical signs of malocclusion/missing incisors were observed at all dose levels with additional findings of red ocular discharge and red discoloration of the skin or haircoat. Additional test article–related effects in animals given 50 or 100 mg/kg/day included previously observed tremors as well as squinted or protruding eyes, alopecia, and rough or thinning haircoat. Clinical signs noted only in animals given 100 mg/kg/day included myoclonic jerking. Tremors and myoclonic jerking were rapidly reversible following the cessation of dosing, and the increased incidence of squinted or protruding eyes was reversible during the recovery phase. Test article–related findings in the functional observational battery were limited to animals given 100 mg/kg/day and included excessive lacrimation, low carriage, myoclonic jerking of the limbs, and reduced grip strength. These findings were reversible by the end of the recovery phase, and the reduced physical and nutritional status of animals given 100 mg/kg/day may have contributed to some of these observations. Test article–related effects on clinical pathology parameters were limited to minimally to mildly lower alkaline phosphatase activity and minimally to mildly higher total, LDL, and HDL-cholesterol in animals given ≥ 50 mg/kg/day and were reversible. Test article–related microscopic findings were noted in bone, teeth, skin/subcutis, taste buds, and ovaries. Alterations in the femoral epiphyseal plate were observed in animals given ≥ 50 mg/kg and were characterized by loss and disorganization of chondrocytes and cartilaginous matrix making up the epiphyseal plate and loss of spongiotic and trabecular bone. These changes resulted in partial to complete closure of the epiphysis and were not reversible. Effects on incisors at ≥ 15 mg/kg were consistent with those observed in previous studies and consisted of loss/atrophy of odontoblasts and ameloblasts, with secondary degradation of dentin with scattered sequestra, formation of fluid-filled cysts in the dental pulp, hyperplasia of the periodontal ligament, and subacute inflammation. Follicular cysts were observed at 100 mg/kg/day and persisted at a low incidence at the end of the recovery phase. Pilomatricoma, a benign cutaneous neoplasm arising from the hair follicle, was observed at the recovery necropsy in 1 male and 1 female given 100 mg/kg/day. Pilomatricoma is an uncommon tumor in laboratory rats, and its occurrence in animals treated with vismodegib may have been related to the pharmacologically mediated effects on hair follicles, as evidenced by the observation of alopecia and follicular cysts at the same dose level. Taste buds were specifically evaluated in this study because of reports of dysgeusia in patients. A decrease in the number of taste buds was observed at ≥ 50 mg/kg/day at the end of dosing, with evidence of reversibility. A decrease in the number of corpora lutea at the terminal and recovery necropsies in females given 100 mg/kg/day was suggestive of an effect on ovarian activity. Decreases in percent motile sperm (not statistically significant) with no effects on sperm count or morphology were observed at the

			end of the dosing phase at 100 mg/kg/day and at the end of the recovery phase at ≥ 15 mg/kg/day. The differences in sperm motility were not associated with effects on sperm count or any histopathology findings.
05-1061 Non-GLP	Dog 2M/2F 7 days	0 150 400 1200 BID	Increases in serum cholesterol were noted in animals given ≥ 150 mg/kg/day. Minimal to mild prolongation of QTc at 1200 mg/kg/day. Mild degeneration/atrophy of the seminiferous tubules in one terminal male at 1200 mg/kg/day
05-1457 GLP	Dog 3M/3F 4 weeks + 4 weeks recovery 2M/2F	0 50 150 400 BID	Transient, moderate (counts <100,000/μL) to marked (counts <60,000/μL) decreases in platelet counts were observed in some dogs given 150 or 400 mg/kg/day. These values returned to predose levels prior to the end of treatment and were not associated with changes in coagulation parameters. Reversible increases in serum total cholesterol (up to approximately 3-fold) were observed in all vismodegib-treated groups throughout the dosing phase, and effects on both LDL and HDL cholesterol contributed to these differences. Histopathologic findings were limited to the testes and epididymides and were observed in the majority of vismodegib–treated males at all doses. Findings were characterized by the appearance of increased numbers of degenerating germ cells within the seminiferous tubules and were generally reflected in the epididymides by a relative paucity of spermatozoa and abnormal accumulation of cellular debris. At the end of the recovery phase, these changes were observed with lower incidence and severity, suggesting reversibility of these effects.
06-1003 GLP	Dog 3M/3F 13 weeks +13 weeks recovery 2M/2F	0 15 50 150 BID	Peracute multi-organ hemorrhage that was associated with a severe decrease in platelet count was observed in one high-dose (150 mg/kg/day) female. Decreases in platelet counts were also observed in several other high-dose animals at various intervals during the study but were reversible and were not associated with effects on coagulation parameters. Decreases in food consumption and decreases in body weight occurred at the 50 and 150 mg/kg/day dose levels in the initial part of the dosing phase and necessitated a 1-week dosing holiday beginning on Study Day 19. However, these effects were mitigated by offering canned food, and mean body weights in all groups were comparable by the end of the dosing phase. Test article–related, reversible clinical signs included areas of alopecia on the paws of all dogs given vismodegib (see correlating microscopic findings below) and alopecia on the muzzle (lips, periorbital) and/or dorsal area of 1 or more dogs in each of the vismodegib-treated groups. An increased incidence of discolored (black) liquid and/or mucoid feces was observed during the dosing phase in males and females given ≥50 mg/kg/day; however, this observation was not correlated with gross or microscopic pathology findings. Hematology findings were limited to transient, slight to moderate decreases in individual platelet values (counts <200,000/μL) at 150 mg/kg/day. With the exception of the high-dose group female that was euthanized on Day 15, platelet decreases resolved within 1 week of discontinuation of dosing. Alterations in the serum chemistry data observed in dogs given ≥15 mg/kg/day included the previously characterized, dose-dependent increases in LDL and HDL cholesterol that resulted in approximately 2- to 5-fold increases in total cholesterol. Increases in cholesterol values were observed at all intervals during the dosing phase; however, values decreased progressively during the recovery phase and were generally similar to or only slightly higher than those of control dogs at the end of the recovery phase. Vismodegib-related macroscopic findings were limited to alopecia on the paws, muzzle, or dorsal area. Alopecia was observed at all dose levels and was associated with microscopic correlates of focal hyperkeratosis and/or inflammation. Alopecia and the associated

			microscopic changes resolved in all animals by the end of the recovery period. Other test article–related microscopic changes in dogs surviving to terminal euthanasia were present in the kidney and adrenal glands but were of uncertain toxicological significance. In the kidneys, increased vacuolation of tubular epithelium was observed in females at all dose levels; this change persisted at the end of the recovery period. Decreased vacuolation of the adrenal cortex was observed in animals at all dose levels at the end of the dosing phase but demonstrated evidence of reversibility and was not correlated with any changes in clinical pathology parameters. In contrast to the findings observed at ≥50 mg/kg/day in relatively young animals in the 4-week dog toxicity study, no microscopic changes in the testes or epididymides or other effects on male reproductive parameters were observed in the sexually mature dogs in this study. No vismodegib-related effects on organ weights, electrocardiographic parameters, blood pressure measurements, respiratory parameters, body temperature, or ophthalmic parameters were observed.
07-1047 GLP	Dog 4M/4F 26 weeks + 13 weeks recovery 2M/2F	0 5 15 50 BID	Test article–related clinical signs observed in all vismodegib-treated groups included swollen or erythematous paws and alopecia. Sporadic incidences of fever, hypoactivity, dehydration, and body weight loss were observed in 1 animal given 15 mg/kg/day and 2 animals given 50 mg/kg/day. These effects were mitigated by offering additional canned food, by placing animals on dosing holidays, or by treatment with nonsteroidal anti-inflammatory agents or antibiotics. Swollen paws were observed as early as Study Week 10, but the severity and time-to-onset of this finding were not dose dependent. In some cases, swelling progressed to erythematous or broken skin on the paw pads and/or limited use of the affected legs. Alopecia was observed at high incidences in all vismodegib-treated groups and was most evident on the paws, muzzle, periorbital area, or hind legs. Clinical pathology findings associated with vismodegib administration included mildly to markedly increased total, HDL, and LDL-cholesterol at all dose levels. The increase in LDL-cholesterol was of higher magnitude than the relative increase in total or HDL-cholesterol. Minor test article–related effects included mildly lower albumin and minimally higher globulin resulting in a lower albumin-to-globulin ratio in males given 50 mg/kg/day. These clinical pathology findings were generally observed at all intervals during the dosing phase intervals and exhibited reversibility. Test article-related macroscopic findings included swollen paws and alopecia. These findings were observed at a high frequency in all vismodegib-treated groups at terminal necropsy but were generally reversible by the end of the recovery phase. Test article–related microscopic findings were limited to the skin/subcutis or paws and included follicular hyperkeratosis in the skin and paws and dermal inflammation in the paws. These changes were observed in all vismodegib-treated groups at the terminal necropsy and were partially reversed by the end of recovery phase. Increases in the mean absolute and relative adrenal weight at 50 mg/kg/day at the terminal necropsy were considered to be potentially secondary to stress. The adrenal weight change was not associated with microscopic findings and was not observed at the end of the recovery period. In contrast to the 4-week dog toxicity study, in which relatively young animals were used (approximately 6 to 7 months old at initiation of treatment), no test article-related microscopic effects on male reproductive organs were observed in the older (approximately 12 to 15 months old at initiation of treatment), sexually mature dogs used in this study. There were no effects on male reproductive assessments (sperm motility, count, and morphology) or female reproductive organs, and there were no vismodegib-related changes in ECG parameters, vital signs, blood pressure, or ophthalmic

			examinations in either sex.

Genotoxicity

Genotoxicity studies with vismodegib are summarised in the following table 6:

Table 6:

Type of test / study ID / GLP	**Test system**	**Concentrations / Concentration range / Metabolising system**	**Results Positive / negative / equivocal**
Gene mutations in bacteria 05-1451 /GLP	*Salmonella* strains TA98, TA100, TA1535, TA1537 and *E coli* WP2uvrA	10 – 5000 µg/plate +/- S9	Negative
Chromosomal abberations in mammalian cells 05-1452 / GLP	Primary human lymphocytes	without S9: 34.6-600 µg/ml with S9: 24.2-451 µg(ml	Negative
Chromosomal aberrations in vivo 05-1453 / GLP	Rat, micronuclei in bone marrow	500-2000 mg/kg PO	Negative

Carcinogenicity

Carcinogenicity studies have not been performed (see discussion on pre-clinical aspects).

A risk of tumorigenesis, based on the occurrence of pilomatricoma (a benign cutaneous neoplasm) in recovery group animals, was identified in the 26-week rat toxicity study and was considered to be potentially secondary to the effects of vismodegib on hair follicle morphogenesis. Pilomatricoma was observed in 1/9 male rats and 1/10 female rats in the highest dose group (100 mg/kg/day) at the end of the 13-week recovery period. Day 182 mean AUC_{0-24hr} exposures (239,000 ng•hr/mL for males and 251,000 ng•hr/mL for females) were comparable to the exposures typically observed in patients at steady state (approximately 225,000 ng•hr/mL based on a steady-state plasma concentration of 22.3 µM).

Reproduction Toxicity

No study on fertility or peri/postnatal development has been performed (see discussion on pre-clinical aspects). Reproductive assessments were integrated in repeat-dose GLP rat and dog toxicity studies and included organ weights and histopathologic evaluation of reproductive organs and detailed male reproductive (spermatogenesis) assessments.

Germ cell degeneration was observed in young male dogs given vismodegib for 4 weeks, but not in sexually mature males dosed for 13 weeks or 26 weeks. The effects of vismodegib on male and female reproductive parameters in the 26-week rat toxicity study included decreased sperm motility (with no effects on sperm count or associated testicular findings) and decreased number of corpora lutea.

An embryo-foetal development study was performed in rats to assess the teratogenic potential of vismodegib. In this study, rats were given vismodegib once daily by PO gavage on Gestation Days 6–17 (organogenesis period) at 10, 60, or 300 mg/kg/day. Maternal body weight gain was significantly reduced at 60 mg/kg/day (body weight 24% lower than control on Day 21) and 300 mg/kg/day (body weight 31% lower than control on Day 21), and maternal food consumption was significantly reduced at 300 mg/kg/day. No effect on maternal body weight gain or food consumption was observed at 10 mg/kg/day. Vismodegib was severely embryotoxic as evidenced by 100%

post-implantation loss at 60 or 300 mg/kg/day. Findings from foetuses of dams given the low dose of 10 mg/kg/day were consistent with the anticipated teratogenic properties of a Hh pathway antagonist. Morphologic examination of 70 foetuses from 5 pregnant dams given 10 mg/kg/day revealed 21 foetuses with malformations distributed among 4 litters. Malformations consisted primarily of absent and/or fused digits of the hind limb. In addition, major patterning defects were observed in one foetus that had an open perineum (gap between genital and presumed location of anus) and one foetus of a different litter that exhibited multiple craniofacial anomalies. The incidence of foetal retardations or variations (such as dilated renal pelvis or dilated ureter) and incompletely or unossified sternal elements, centra of cervical vertebrae, or proximal phalanges and claws was also increased at 10 mg/kg/day, indicative of foetotoxicity.

The maternal TK data are summarised in the following table.

Table 7

Dose (mg/kg/day)	Study Day	t_{max} (hr)	C_{max} (ng/mL)	AUC_{0-24} (ng • hr/mL)
10	1	3	6540	63600
10	10	1	7220	50500
60	1	7	17400	250000
60	10	7	50200	620000
300	1	7	36700	506000
300	10	1	75400	1030000

AUC_{0-24} = area under the plasma concentration–time curve from Time 0 to 24 hours post-dose;C_{max} = highest observed plasma concentration; t_{max} = time at which C_{max} occurred.

At 10 mg/kg/day, the systemic exposure was approximately 20% of that typically observed in patients at steady state.

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated have not been performed as vismodegib is only intended for adults.

Toxicokinetic data

Toxicokinetic data are summarised in the following table. See also section on Pharmacokinetics for time profiles.

Table 8

Study ID **Day of analysis**	**Daily Dose (mg/kg)**	**Animal total daily AUC_{0-24} (ng·h/ml)**	**Animal:Human Exposure Multiple**
05-1456 Rat 4 weeks Day 28	50 150 500	116000 197000 404000	0.52 0.88 1.80
06-1202 Rat 13 weeks Day 91	10 50 150 500	37600 167000 314000 295000	0.17 0.74 1.40 1.31

07-1224 Rat 26 weeks Day 182	15 50 100	77600 126000 245000	0.35 0.56 1.09
05-1457 Dog 4 weeks Day 28	50 150 400	503000 754000 749000	2.24 3.35 3.33
06-1003 Dog 13 weeks Day 90	15 50 150	344000 493000 488000	1.53 2.19 2.17
07-1047 Dog 26 weeks Day 183	5 15 50	151000 258000 447000	0.67 1.15 1.99

Human AUC = 225,000 ng • hr/mL based on a steady-state plasma concentration of 22.3 µM

Local Tolerance

No local tolerance studies were performed (see Discussion on Non-Clinical Aspects).

Other toxicity studies

An assessment of phototoxicity was conducted in Balb/c 3T3 fibroblasts as described by the Organisation for Economic Co-operation and Development 432 [10191] guidance document (Good Laboratory Practice Study 12-1121). When tested up to the highest achievable concentration of 17.1 mg/L, vismodegib demonstrated no cytotoxic effect (in the absence of ultraviolet radiation [UVR] exposure) or no phototoxic effect (with UVR exposure) in the assay by either the photo-irritancy factor or mean photo-effect criteria.

2.3.5. Ecotoxicity / environmental risk assessment

Table 9 Summary of main study results

Substance (INN / Invented Name): vismodegib / Erivedge			
CAS-number (if available): 879085-55-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 117	1.59	Not potential PBT
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	1.59	not B
	BCF		
Persistence	DT50 or ready biodegradability	See below OEC 308	P
Toxicity	NOEC or CMR	reprotoxic	T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default	0.75	µg/L	> 0.01 threshold
Other concerns (e.g. chemical class)			N
Phase II Physical-chemical properties and fate			

Study type	Test protocol	Results			Remarks
Adsorption-Desorption	OECD 106	$KOC_{, ads, all soils}$ = 2601 (2129 – 2941) l/kg $KOC_{, des, all soils}$ = 4098 (3057 – 5001) l/kg $KOC_{, ads, both sludges}$ = 692 (684 – 699) l/kg $KOC_{, des, both sludges}$ = 867 (839 – 895) l/kg $KOC_{, ads, all substrates}$ = 1837 (684 – 2941) l/kg $KOC_{, des, all substrates}$ = 2806 (839 – 5001) l/kg			
Ready Biodegradability Test	OECD 301	0 % BOD/ThOD, 28 d			Not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 3.3 d – 3.7d $DT_{50, sediment}$ > 1 year $DT_{50, whole system}$ > 1 year % shifting to sediment =75% - 85% (day 28)			very persistent
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Pseudokirchineriell subcapitata*	OECD 201	NOEC	69	µg/L	
Algae, Growth Inhibition Test/*Desmodesumus subspicatus*	OECD 201	NOEC	320	µg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	1.5	mg/L	
Fish, Early Life Stage Toxicity Test/*Danio rerio*	OECD 210	NOEC	1.6	mg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	1000	mg/L	
Phase IIb Studies					
Sediment dwelling organism / *Chironomus riparius*	OECD 218	NOEC	62.5	mg/kg	

2.3.6. Discussion on non-clinical aspects

In vitro studies show potent inhibition of hedgehog signalling. The activity at rat hedgehog appears to be somewhat lower than on human hedgehog (4 to 5-fold lower). There are no data on activity at dog hedgehog, but the number of expected toxicological findings in dog studies would suggest relevant pharmacological activity also in dogs. Most studies on anti-tumour activity have been performed with the murine *Ptch* $1^{+/-}$ medulloblastoma cell line, driven by mutational activation of the Hh-pathway. Anti-tumour activity has also been shown in xenograft models with human colon carcinoma cells and primary human adenocarcinoma cells. There are no studies with basal cell carcinoma, however this is not considered a deficiency, given the established role for hedgehog signalling in BCC. Pharmacodynamic / pharmacokinetic studies demonstrate the importance of continuous exposure to vismodegib for maintaining Hh inhibition and achieving optimal anti-tumour activity.

No pharmacodynamic drug interaction studies have been performed and as vismodegib is expected to be given to patients as monotherapy in advanced basal cell carcinoma, the lack of such studies is justified.

Although the exposure margin achieved in the dog studies was limited (about 4-fold), cardiovascular safety pharmacology studies do not suggest a concern for arrhythmic properties of vismodegib. The

non-clinical pharmacokinetics profile of vismodegib is sufficiently characterised. There are pronounced differences in pharmacokinetic behaviour between species. The terminal half-life in rats is about 1 hour, in dogs about 2 days and in humans about 11 days. This has implications on the interpretation of toxicity studies. While in both dogs and humans, daily or twice daily dosing will lead to accumulation, resulting in a flat steady state after a number of days; in rats the plasma exposure will be fluctuating and in all rat studies, the exposure will fall substantially before the first dose next day. As a result of this it is unlikely that continuous inhibition of hedgehog signalling was achieved in any of the rat studies. There may be adverse effects resulting from continuous pharmacological activity which will not be revealed in the rat studies.

Vismodegib exhibits high protein binding. There are some differences between rats, dogs and humans with respect to protein binding, but these are considered to be of minor importance when assessing exposure margins in the toxicity studies.

The metabolism appears to be very similar between humans, rats and dogs. In all three species, vismodegib represents >94% of drug-derived material in plasma.

No data have been generated on excretion of vismodegib in milk. However, given the very potent developmental toxicity of vismodegib, a strict contraindication against breast-feeding is warranted (see SmPC section 4.3).

Systemic exposures in the repeat-dose toxicity studies in rats and dogs did approximate clinical exposure but no substantial (> 5-fold) exposure multiples were achieved in the pivotal repeat-dose toxicity studies. However, it appears that the maximum tolerated dose was reached in both species, and in addition further increases in doses would not be likely to increase the exposure substantially, based on the data from the toxicokinetics studies. Thus, no formal deficiencies with the repeat-dose toxicity program have been identified.

In general, the tolerability of vismodegib in repeat-dose toxicity studies in rats and dogs was limited by nonspecific manifestations of toxicity including decreased body weight gain and food consumption. Additional findings at clinically relevant exposures included faecal changes; skeletal muscle twitching or tremors; alopecia; swelling, follicular hyperkeratosis, and inflammation in paw pads; and increased LDL and HDL cholesterol. Decreased haematocrit or platelet count were observed in some dogs at clinically relevant exposures; however, there was no evidence of a primary effect on bone marrow in affected animals.

Toxicity findings were in many cases clearly related to the pharmacological activity, such as findings on effects on growing teeth (incisors) and epiphyseal plate in rats, alopecia in rats and dogs and reduction of taste buds in rats. Similar effects have been observed or would be expected in humans.

There was no evidence of genotoxicity in *in vitro* assays (reverse bacterial mutagenesis [Ames] and human lymphocyte chromosome aberration assays) or in the *in vivo* rat bone marrow micronucleus assay.

As the proposed indication concerns patients which in most cases do not have a life-threatening disease, carcinogenicity studies are warranted (see section on Benefit-Risk). Pilomatricoma, a benign cutaneous tumour was observed in the chronic rat toxicity study. Pilomatricoma has not been reported in clinical trials with Erivedge, and the relevance of this finding to humans is therefore uncertain. In humans, pilomatricoma is a relatively common cutaneous neoplasm that occurs most frequently in children. The lesion is almost exclusively considered to be benign and is readily excisable. Because pilomatricoma is believed to originate with hair matrix cells, it is possible that the development of this neoplasm is related to pharmacologically mediated disruption of hair follicle morphogenesis (see Discussion on Clinical Safety and SmPC section 5.3).

Dedicated nonclinical trials to assess the potential of vismodegib 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 vismodegib. This concern is included in the SmPC. Germ cell degeneration and hypospermia were observed in the 4 week dog toxicity study but not in longer-duration studies with older dogs. Decreased number of corpora lutea in the ovary and decreased mean percent motile sperm in the 26 week rat toxicity study were not demonstrated to be reversible by the end of the 8 week recovery period. Longer duration nonclinical studies on male and female fertility will be submitted post approval (see RMP).

Severe embryotoxicity and malformations observed in teratogenicity studies were considered directly related to vismodegib treatment because of the minimal nature of the maternal effects. In an embryo-foetal development study in which pregnant rats were administered vismodegib daily during organogenesis, vismodegib crossed the placenta and was severely toxic to the conceptus. Malformations, including craniofacial anomalies, open perineum, and absent and/or fused digits, were observed in foetuses of dams at a dose which corresponded to 20 % of the typical steady-state exposure in patients, and a 100 % incidence of embryolethality was observed at higher doses. Based on the strong teratogenic potential, and the likely importance of hedgehog signalling also in later developmental stages, vismodegib is expected to exhibit pronounced foetal toxicity throughout the pregnancy and also to disturb postnatal development. Dedicated studies to assess the potential of vismodegib to affect post-natal development have not been performed. However, irreversible defects in growing teeth and premature closure of the femoral epiphyseal plate, observed in rat toxicity studies at clinically relevant exposures, represent risks to post-natal development. Erivedge should not be used in children and adolescents aged below 18 years. Adequate contraindications, warnings and information are provided in the SmPC (see sections 4.2, 4.3, 4.4 and 5.3).

Based on the intended route of administration (oral), and absence of relevant effects from toxicological studies no local tolerance studies were performed and this was considered acceptable. Vismodegib was not phototoxic.

Considering PECs based on the maximum daily dose and environmental-fate-relevant data as well as PNECs based on chronic ecotoxicological properties for Vismodegib, no indication for risk is apparent for the environmental compartments sewage treatment, surface waters, groundwater and sediment, hence no exposure levels of concern to the environment are to be expected. Moreover, while vismodegib is very persistent and toxic based on mammalian evidence, it is not bioaccumulative and therefore not a PBT substance.

2.3.7. Conclusion on the non-clinical aspects

Preclinical data demonstrate that vismodegib is highly teratogenic. This is translated into strict contraindications in the SmPC and the need for an Erivedge Pregnancy Prevention Programme.

Nonclinical carcinogenicity studies and studies on male and female fertility will be submitted post approval (see RMP).

2.4. Clinical aspects

2.4.1. Introduction

The clinical pharmacology of vismodegib was characterised in several Phase I, II and dedicated clinical pharmacology studies to assess single- and multiple- dose pharmacokinetics, absolute bioavailability,

mass balance, drug-drug interaction potential, food effect, QTc prolongation potential, dose schedule, and drug product bridging. These studies and assessments were conducted in patients with advanced solid tumours or advanced BCC and in healthy volunteers (female subjects of non-childbearing potential).

Clinical trials with vismodegib are listed in table 10. Study SHH4476g was the pivotal efficacy study. Efficacy and safety information from Study SHH3925g, safety data from randomized Phase II trials in other oncology indications (i.e., Studies SHH4489g in ovarian cancer and SHH4429g in colorectal cancer), and from the clinical pharmacology program, can be considered supportive.

The applicant received Scientific Advice on clinical aspects for treatment of BCC in patients with Gorlin syndrome from the CHMP on 16 December 2010. The Scientific Advice pertained to the methodological aspects, definition of the cohorts, dose selection, challenges related to the study design, proposed statistical analysis plan, proposed safety monitoring plan, endpoints, use of supportive assessments including quality of life.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

Table 10 - Tabular overview of clinical studies

Clinical Study	PK, PD objectives	Study type	Population	Dose
SHH4433g PK study	PK following a single dose	Single dose	Healthy women of non CBP	150mg single oral
SHH4683g Radiolabelled PK, mass balance				
Part A	Absolute bioavailability	Single dose IV/PO	Healthy women of non CBP	Single ^{14}C tracer IV admin 2 hr after a single 150mg PO dose
Part B	Characterise mass balance and metabolic profile	Single dose PO		150mg oral suspension dose labelled with ^{14}C tracer
Part C	Determine if IV PK parameters change with multiple dosing compared with single dose	Multi dose PO, single dose IV		150mg PO QDx7 days with single ^{14}C tracer IV 2hr after PO dose on day 7
Part D	Determine if PO PK parameters change with multiple dosing compared with single dose	Multi dose PO		150mg PO QD x 6 days with single ^{14}C tracer PO suspension on day 7
SHH4610g dose schedule	Effect of dosing schedule on vismodegib PK	2-period (loading and maintenance) randomised	Cancer patients	150 mg PO QD, TIW, QW
CTEP No 8395 food-effect study	Impact on food on vismodegib PK following single and multiple dosing	2-part single and multi-dose with or without food	Cancer patients	150 mg PO QD
SHHH4871g QTc study	Determine whether vismodegib causes QTc prolongation	Randomised double blind, (triple dummy) 3 arm parallel with placebo and positive controls	Healthy women of non CBP	Vismodegib 150 mg PO QD x 7 days Moxifloxacin 400 mg PO

Clinical Study	PK, PD objectives	Study type	Population	Dose
Single agent studies				
SHH3925g dose schedule	evaluate PK at 3 dose levels PD assessment of GLi1 expression Bridging Phase I, II formulations	Single and multi-dose	Advanced solid tumour patients	150, 270, 540 mg PO QD
SHH4381g	Assess plasma and CSF PK	Multi-dose	Paediatric medulloblastoma patient	50 mg PO QD
SHHH4476g	PK in advanced BCC	Multi-dose	BCC patients	150 mg PO QD
Combination therapy studies				
SHH4429g	Evaluate vismodegib PK and chemotherapy / bevacizumb PK when given in combination	Multi-dose,	Metastatic CRC first -line	150mg or placebo PO QD in combination with FOLFOX plus bevacizumab or FOLFIRI plus bevacizumab

The applicant claimed the approval for the following indication:

Erivedge is indicated for the treatment of adult patients with advanced basal cell carcinoma for whom surgery is inappropriate.

The final indication following CHMP review of this application is:

Erivedge is indicated for the treatment of adult patients with:

- symptomatic metastatic basal cell carcinoma
- locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy.

2.4.2. Pharmacokinetics

Total vismodegib in plasma was measured using a solid phase extraction liquid chromatography/ tandem mass spectrometry (LC-MS/MS) method. A method for measurement of unbound vismodegib was developed, using equilibrium dialysis followed by solid-phase extraction and LC-MS/MS.

Formulations

In phase I studies, a dry blend capsule (25 mg, 125 mg and 270 mg) was used. In addition to the capsule formulations, an *iv* solution (5 µg/ml) and an oral suspension (150 mg/30 ml) of vismodegib were prepared for use in the human ADME study.

Differences on bioavailability between the dry blend capsule and the wet granulation capsule were observed however this did not have an impact on the results from pivotal studies as the dry blend capsule was not used in the pivotal studies. The data may indicate that a difference in formulation can affect bioavailability, which needs to be taken into account if changes in the formulation of the product are proposed in the future. The manufacturing processes for the phase 2 pivotal study formulation versus the to-be-marketed formulation are identical in terms of granulation. In summary, sufficient evidence demonstrating that results obtained during development with different formulations employed are relevant to the product to be marketed was provided.

Absorption

Erivedge is a highly permeable compound with low aqueous solubility (BCS Class 2). It is only soluble at low pH, around 1. While in simulated gastric fluid, vismodegib is practically insoluble. The partition coefficient (log D) is 2.7. Absorption is saturable as evidenced by the lack of dose proportional increase in exposure after a single dose of 270 mg and 540 mg Erivedge. Under clinically relevant conditions (steady state), the PK of vismodegib is not affected by food.

After oral administration of a 150 mg capsule, a wide range of Tmax values was seen in different studies (1 hr to 7 days). Vismodegib plasma concentrations rose relatively fast, but the initial absorption phase was followed by a broad peak. According to a population pharmacokinetic analysis cancer patients had slower drug absorption than healthy volunteers, but with at most 5% impact on unbound vismodegib concentrations at steady-state.

The absolute oral bioavailability of vismodegib in fasting healthy volunteers was determined by administration of a single 14C tracer 10 µg intravenous (IV) dose administered 2 hr after a single oral unlabelled 150 mg dose administered as the proposed commercial formulation. Absolute bioavailability (%F) was calculated by dividing the dose-normalised mean AUC0-inf from unlabeled vismodegib administered orally by the mean dose-normalised AUC0-inf for 14C-vismodegib administered IV. The single dose mean (CV %) absolute bioavailability of vismodegib was 31.8 (14.5) %after a single 150 mg dose.

Data from food interaction studies

The effect of food on vismodegib bioavailability was evaluated in a study in patients with advanced malignancies, including a single-dose part (studying high-fat meal and low-fat meal compared to the fasting state) and a multiple-dose part (comparing fasting state to a “healthy breakfast”). Administration under fed conditions (high-fat meal) resulted in an 84 % increase in degree of absorption (AUC_{total}) compared to the fasting state in the single-dose part of the study, while a low-fat meal only resulted in a 3% increase in AUC_{total}. At steady-state, administration of a healthy breakfast resulted in an 18% increase in total AUC. Due to the sparse sampling and high variability, no statistical evaluation was performed on unbound concentrations, but data indicate a 37% increase in unbound steady-state concentrations.

Distribution

Vismodegib volume of distribution was determined by administration of an intravenous tracer ^{14}C-vismodegib dose of 10 µg 2 hr after administration of a single oral 150 mg dose and after 7 days of daily administration of 150 mg oral doses. The evaluation was part of the mass-balance study in healthy volunteers. Intravenous volume of distribution was, based on total concentration, determined to be 16.4 L after a single dose and 26.8 L at steady state. Thus, volume of distribution was about 60% greater at steady state than after a single dose, which may be explained by saturation of protein binding at the about 3- to 4-fold higher plasma concentrations at steady state.

The *in vitro* blood-plasma ratio for vismodegib ranged between 0.61 and 0.82 in human blood at vismodegib concentrations of 1 – 100 µM.

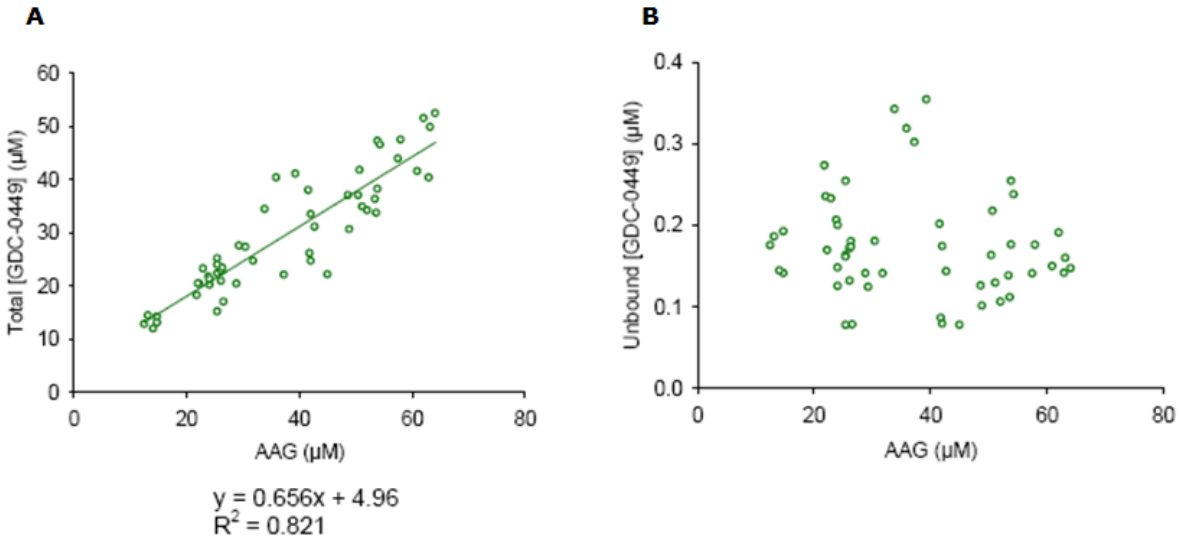
In pooled plasma, the *in vitro* binding of vismodegib to human plasma proteins was high (97%) and was independent of vismodegib concentration between 1 and 100 µM. However, in blank plasma spiked with AAG or human serum albumin (HSA) within their physiological concentration ranges, binding to AAG was saturable over the vismodegib concentration range tested (5-120 µM). Vismodegib plasma concentrations at steady state (150 mg daily) are in the range of 20-30 µM. Thus, saturation of AAG

binding *in vitro* was seen within the clinically and physiologically relevant concentration range for vismodegib and AAG, respectively.

In clinical study samples, fraction unbound (fu) was considerably lower (<1%) than the fu determined *in vitro*. Thus, the *in vitro* experiments seem to have underestimated *in vivo* protein binding.

Plasma data across clinical studies demonstrated a strong correlation between vismodegib total concentrations and AAG plasma levels, while there was no significant correlation between unbound vismodegib plasma concentration and AAG, exemplified below by data from study SHH4610. In individual patients, the total plasma concentration of vismodegib varied with AAG concentration over time. Moreover, the clinical study data show an increase in fu with increased plasma concentrations of vismodegib. Together, these data indicate that one mechanism behind the observed non-linearity in total concentration of vismodegib is saturable binding to AAG.

Figure 1. Relationship between total vismodegib (A) and unbound vismodegib (B), respectively, and AAG concentration (150 mg vismodegib once daily) in study SHH4610g



Elimination

After oral administration, vismodegib is slowly eliminated, by a combination of metabolism and biliary excretion of parent drug. The $t_{1/2}$ was around 12 days after a single dose, while based on the population pharmacokinetic analysis, effective $t_{1/2}$ was about 4 days at steady state. Following a single 150 mg oral dose in the mass-balance study, the majority of drug-related material was recovered in the faeces (82% of the administered dose). In the early faecal samples (0-72 hr) vismodegib was the predominating compound, accounting for 22% of the dose, which may to some extent be due to unabsorbed drug. In later faecal samples (72-312 hr), which may to greater extent mirror the relative importance of metabolism and biliary excretion of parent, metabolite M3 accounted for 12%, M1 for 1%, M13 for 3%, M18 for 2% and vismodegib for 9% of the dose. Thus, metabolism may be more important than biliary excretion. However, altogether only 52% of the recovered dose could be quantified as vismodegib and metabolites in faeces. Detectable levels of other identified metabolites were observed in urine and faeces, but these could not be quantified.

Urinary excretion of vismodegib and metabolites accounted for about 4.4% of a single oral dose. If the absolute bioavailability of 32% approximates the fraction absorbed (which is unclear), urinary excretion may be estimated to account for at most about 14% of the elimination of *absorbed* drug. Thus, urinary excretion appears to be a minor elimination pathway for vismodegib.

In a human mass-balance study, vismodegib was predominant in plasma, corresponding to > 98% of the total circulating radioactivity at 4, 24, 168, and 312 hours. Only trace levels of M3, M4 and M5 were detected in plasma. Radioactivity was largely recovered in feces, where M3 was the most abundant metabolite (15%).

Metabolic pathways of vismodegib in humans include oxidation (M1, M3 and M14), glucuronidation (M4 and M5), and pyridine ring cleavage (M13 and M18). The major oxidative metabolite recovered in faeces (M3) is produced by CYP2C9 and, to a lesser extent, by CYP3A4/5, while another oxidative metabolite (M1) is formed primarily by recombinant CYP3A4/5, but multiple isoforms are capable of forming both metabolites.

In vitro data indicate that vismodegib is a substrate for the efflux transporter Pgp and possibly for BCRP. These transporters may be of importance for the elimination of vismodegib.

Dose proportionality and time dependencies

Vismodegib displays non-linear pharmacokinetics in total as well as unbound concentrations, with less than dose-proportional increases in exposure. The Applicant suggests that this is due to two different mechanisms, saturable binding to AAG and solubility-limited absorption.

Over studies with once daily administration, steady state was reached within 7-21 days and accumulation was around 3- to 4-fold for total concentrations and 7- to 11-fold for unbound concentrations.

In a dose-finding study in patients, study SHH 3925g, vismodegib pharmacokinetics after single-dose and once daily multiple-dose administration of Erivedge 150 mg, 270 mg or 540 mg capsules was evaluated. After a single dose, mean total and unbound C_{max} increased with dose escalation from 150 mg to 270 mg. However, at 540 mg, the mean total and unbound plasma C_{max} values were similar to those observed at 270 mg and steady state levels of total and unbound vismodegib, respectively, were the same across all dosing cohorts, i.e. there was no further increase in vismodegib exposure at doses higher than 150 mg. For total concentrations, the plateau can partly be explained by the saturable protein binding. However, saturable protein binding should not affect unbound concentrations, as unbound concentrations are not dependent on fraction unbound (fu), but on fraction absorbed and intrinsic clearance (CLu). The data from study SHH3925 therefore supports the assumption that there is also another non-linear mechanism, possibly solubility-limited absorption.

In study SHH4610 different doses were achieved by prolonging the dose interval for the 150 mg dose, instead of administering higher doses per occasion. Therefore, concentration dependency in vismodegib pharmacokinetics could be evaluated without the confounding factor of a different bioavailability (F) due to solubility-limited absorption (dose dependency). The trend for total concentrations was the same, i.e. with less-than dose proportional increases in dose, although a plateau was not reached. Total concentrations were highly correlated with AAG levels and fu increased with increasing vismodegib concentrations, confirming that the non-linearity in total concentrations is to some extent determined by saturable protein binding. However, also in this study, a non-linearity in unbound concentrations was seen. At a 7-fold decrease in dose, from once daily to once weekly administration, the unbound AUC only decreased 3.5-fold, while trough levels decreased dose-proportionally.

The peak-trough fluctuation at steady state was about 1.6-fold and 1.2-fold for unbound and total concentrations, respectively, i.e. the plasma-concentration time curve is relatively flat.

Population pharmacokinetic analysis

Combined data from clinical studies were used to quantitatively describe the pharmacokinetics of vismodegib and evaluate the effects of relevant covariates that might affect vismodegib exposure in a population pharmacokinetic analysis. Both total and unbound vismodegib were analysed simultaneously where available. Because of the strong impact of alpha-1-acid glycoprotein (AAG) on vismodegib pharmacokinetics and the fluctuation of AAG levels in cancer patients, individual AAG concentration from corresponding time points was included in the analysis.

Moderate inter-subject variability was estimated for vismodegib disposition parameters in the population pharmacokinetic analysis (approximately 50% for $CL_{unbound}$ and Vc, 20% for KD_{AAG}). Intra-subject variability estimates were 27% and 42% for total and unbound plasma vismodegib, respectively. No difference in the degree of PK variability between cancer patients and healthy subjects was identified.

Pharmacokinetics in target population

In the population pharmacokinetic analysis, the typical patient was 60 years old patient with a body weight of 75 kg and AAG of 30 µM. Modelling and simulations suggested that time to steady-state is approximately 7 days in the typical population with continuous daily dosing of 150-mg vismodegib.

AAG concentration was the most important factor influencing steady-state plasma concentrations of vismodegib. Variability of total vismodegib concentration at steady-state was predominantly explained by the range of AAG concentration, with extreme AAG concentrations corresponding to 47–101% variation of total vismodegib concentrations. While AAG was also the most influential factor for the steady-state concentration of unbound vismodegib, extreme AAG values corresponded to only ± 21% variation of unbound vismodegib concentrations.

Cancer patients showed slower drug absorption (lower first-order absorption rate constant [ka]) than did healthy volunteers, but with no significant impact on vismodegib exposure at steady-state.

Estimated duration of pregnancy prevention

As there is no pharmacokinetic data beyond 56 days after vismodegib treatment discontinuation, the Applicant used a modelling approach to estimate the recommended duration of pregnancy prevention in female patients, and female sexual partners of male patients after the last dose of vismodegib. As a safe threshold vismodegib plasma level, 1/10 of the estimated NOEL in the rat embryo foetal development study was used (which gives 0.0037 µM for total concentration). The simulation was made for a typical patient and adding a ±50% variability. For a female partner to a male patient the plasma exposure was estimated by calculating a daily dose assuming similar vismodegib levels in semen as in plasma, exposure to 6 ml semen daily and 100% bioavailability from the vagina. Based on these simulations, the time to reach plasma levels below 0.0037 µM was estimated to be 7 months post-treatment in females treated with vismodegib and 2 months post-treatment in female partners to males treated with vismodegib. Limited data obtained thereafter indicated that vismodegib levels in semen are less than 10% of those in plasma, adding a 10-fold safety factor to the estimation for female partners to male patients. Because of a case report of suspected prolonged vismodegib exposure beyond 7 months post-treatment, the Applicant performed new pharmacokinetic simulations, using the population pharmacokinetic model. A total of 4000 patients were simulated, and a not negligible fraction of vismodegib-treated patients may still have levels above 0.0037 µM at 7 months after treatment discontinuation.

Special populations

An updated population pharmacokinetic analysis indicated that vismodegib CLu/F was dependent on age but not on weight or gender. The effect of age on CLu/F was modest, <20%, and is not likely to be clinically relevant.

Data were insufficient to evaluate effect of race. Paediatric pharmacokinetic data are at present only available from a single patient and are not further discussed here, as there is currently no relevant indication for vismodegib in children.

Pharmacokinetic interaction studies

A clinical DDI study was conducted to evaluate the effect of vismodegib on the cytochrome P2C8 (CYP2C8) substrate, rosiglitazone.

Table 11 Non-Specific Microsomal Binding for Vismodegib

Vismodegib Concentration	Microsomal Protein Concentration		
	0.03 mg/mL	0.2 mg/mL	0.6 mg/mL
	fu_{mic} ± SD	fu_{mic} ± SD	fu_{mic} ± SD
1 µM	0.914 ± 0.040	0.705 ± 0.051	0.535 ± 0.003
10 µM	0.915 ± 0.031	0.714 ± 0.050	0.479 ± 0.016
100 µM	0.857 ± 0.033	0.442 ± 0.043	0.527 ± 0.042

fu_{mic} = fraction unbound in microsomes.

Pharmacokinetics using human biomaterials

The potential for vismodegib to inhibit P450 was investigated in human liver microsomes using selective probe substrates in two studies (Table 12).

Table 12: **IC_{50} values of P450 inhibition by vismodegib in human liver microsomes**

P450 Isoforms	IC_{50} (Probe Substrate) (Study 05-1528)	IC_{50} (Probe Substrate) (Study 08-1984)
1A2	36.5 µM (phenacetin)	> 50 µM (phenacetin)
2B6	ND	26 µM (bupropion)
2C8	24.0 µM (paclitaxel)	7.2 µM (paclitaxel)
2C9	29.3 µM (warfarin)	5.3 µM (diclofenac)
2C19	26.7 µM (mephenytoin)	NC (mephenytoin)
2D6	42.9 µM (dextromethorphan)	27 µM (bufuralol)
3A4/5	> 50.0 µM (testosterone)	> 50 µM (testosterone)
3A4/5	> 50.0 µM (midazolam)	> 50 µM (midazolam)

IC_{50} = 50% inhibitory concentration; NC = not calculable; ND = not determined.
Note: Data suggest IC50 is between 16 and 50 µM.

The P450 inhibition constant (Ki) and the mode of inhibition were assessed for P450 isoforms 2C8, 2C9, and 2C19 (Table 13). Vismodegib does not appear to be a potent time-dependent inhibitor of P450 3A4/5.

Table 13: Vismodegib P450 Inhibition Constants (Ki) for 2C8, 2C9, and 2C19 in Human Liver Microsomes (Study 08-1983)

P450 Isoforms	Ki (Probe Sustrate)	Likely mode of inhibition
2C8	6.0 ± 0.2 µM (paclitaxel)	Non-competitive
2C9	5.4 ± 0.4 µM (diclofenac)	Competitive
2C19	24 ± 1 µM (mephenytoin)	Competitive

Vismodegib inhibited CYP2C8 and 2C9 *in vitro* at Ki levels lower than $50*C_{max,unbound}$, indicating that an *in vivo* interaction may be possible. However, the *in vivo* study with the CYP2C8 substrate rosiglitazone showed no relevant effect on rosiglitazone pharmacokinetics. Therefore, there should be no risk for clinically relevant effects on CYP2C8 or CYP2C9 substrates. The *in vitro* data suggest that vismodegib is not a relevant *in vivo* inhibitor of CYP1A2, CYP2B6, CYP2C19 or CYP2D6, as Ki or IC50 for these enzymes was higher than $50*C_{max,unbound}$. There was an *in vitro* signal of mechanism-based CYP3A4 inhibition but it is considered too weak to be clinically relevant.

In vitro studies investigating P450 induction potential are presented in table 14.

Table 14: Induction potential of vismodegib

Type of study	**Concentration ranging (µM)**	**IC_{50} (µM)**	**Results**	**GLP** aspects
Cryopreserved hepatocytes from 3 human donors (ref: 08-1985)	0.1 to 100 µM Incubation for 48 hours Omeprazole, phenobarbital, and rifampicin = positive controls for P450s 1A2, 2B6, and 3A4/5 induction	-	- P450s 1A2, 2B6, and 3A4/5 enzyme activities did not increase in cells exposed to up to 10 µM	No
PXR competitive binding TR-FRET assay (ref: 09-0054)	The TR-FRET ratios were plotted vs. log GDC-0449 concentration (concentration range 7.0×10-6 to 100 µM) and then analyzed using IDBS XLfit® 4.2.	83.3	- Vismodegib does not appear to be a potent binder of PXR	-

Based upon hepatocyte induction studies, vismodegib does not appear to be a potent P450 inducer. In addition, it does not appear to be a potent binder of pregnane X receptor (PXR). However, at concentrations superior to 10µM, a decrease of enzymatic activity was observed, without cellular toxicity. No studies were performed to investigate the interaction potential related to UGTs.

A study on P-glycoprotein transport and inhibition and 2 studies on BCRP transport and inhibition are submitted (described in tables 15 and 16)

Table 15: P-glycoprotein transport and inhibition of vismodegib

Type of study	**Concentration ranging (µM)**	**Results**	**GLP** aspects
MDR1-MDCK cell system cyclosporin A = a known P-glycoprotein inhibitor (ref: 08-1880)	15 µM	- Vismodegib appears to be a P-glycoprotein substrate but not an inhibitor in an *in vitro* system	No

Table 16: BCRP transport and inhibition of vismodegib

Type of study	Concentration ranging (µM)	IC_{50} (µM)	Results	GLP aspects
Caco-2 and CPT-B1 (BCRP knockdown cell line) cell monolayer systems (ref: 09-0806)	15 µM	-	- Vismodegib reduced the efflux ratio of E3S from 15.7 to 0.71 in CPT-P1 cell monolayers. - Vismodegib can be classified as having inhibition potential on E3S efflux transport activity, possibly mediated by BCRP	No
The inhibition of prazosin (a BCRP substrate) transport in MDCKII-BCRP cell monolayers (ref: 09-2611)	0.3, 1, 3, 10, 30 µM. On the bi-directional permeability ^{3}H-prazosin	2.4	- The efflux ratio of prazosin was reduced from 8.5 to approximately 1.6 in the presence of vismodegib with an IC_{50} estimate of 2.4 µM. - Vismodegib does not appear likely to be a clinically relevant inhibitor of BCRP.	No

Vismodegib appears to be a P-glycoprotein substrate, but not an inhibitor in MDR1-MDCK cells. Vismodegib does not appear to be a breast cancer resistance protein (BCRP) substrate. In MDCKII-BCRP cells, vismodegib inhibited the efflux ratio of prazosin efflux with an IC_{50} of 2.4 µM.

In vitro studies have been conducted in both recombinant UGT's and human liver microsomes investigating the inhibition potential of vismodegib on UGT's 1A1, 1A4, 1A6, 1A9, 2B7, and 2B15 to cover the primary UGTs involved in the glucuronidation of drugs and also those UGTs responsible for morphine (2B7) and paracetamol (1A1, 1A6, 1A9, 2B15) glucuronidation.

Table 17 IC_{50} Concentrations for Recombinant UGT and Human Liver Microsomes

	Recombinant UGT	Human Liver Microsomes
UGT	IC_{50} (µM) ± SD	IC_{50} (µM) ± SD
1A1	> 100	> 100
1A4	> 100	> 100
1A6	91.5 ± 0.909	> 100
1A9	36.6 ± 6.26	46.3 ± 18.1
2B7	80.8 ± 5.75	> 100
2B15	87.9 ± 7.37	> 100

IC_{50} = half maximal inhibitory concentration; UGT = UDP-glucuronosyltransferase.

2.4.3. Pharmacodynamics

Mechanism of action

Pharmacodynamic down-modulation in the hedgehog pathway shown by a decrease in *GLI1* expression by more than a factor of two, as compared with pre-treatment biopsy-sample analysis, in 10 of 13 patients has been reported (Von Hoff *et al.,* 2009).

Primary and Secondary pharmacology

The potential for vismodegib to prolong the QTc interval was assessed in two clinical studies, SHH3925g (Phase I study in cancer patients) and SHH4871g (dedicated QTc study in healthy volunteers) discussed in Clinical Safety section.

2.4.4. Discussion on clinical pharmacology

Vismodegib pharmacokinetics is characterised by high-affinity binding to alfa-1-acid glycoprotein (AAG), slow elimination via hepatic mechanisms, a very long half-life (about 11-12 days after a single dose) and non-linearity, with less than dose proportional increases in total as well as unbound concentrations. The non-linearity in total concentrations is explained by saturable protein binding, while the mechanisms behind the non-linearity in unbound concentrations can largely be explained by solubility-limited absorption. There appear to be two different non-linear mechanisms in vismodegib pharmacokinetics, saturable protein binding (affecting total concentrations) and solubility-limited absorption (affecting also unbound concentrations). There are also some indications of time-dependent pharmacokinetics as absolute bioavailability appeared to decrease at multiple dosing.

Altogether, the pharmacokinetic data indicate that total concentration is not a good marker for unbound concentration. Although at higher doses (270 mg, 540 mg) in study SHH3925 total and unbound concentrations appeared to be parallel (possibly due to solubility-limited absorption), this was not the case in study SHH4610, and may not be the case in situations where elimination (CLu) is affected, such as at organ impairment or an interaction. However, the concentration-effect relationships for efficacy and safety were primarily determined using total concentrations of vismodegib, which proved to be of limited value due to non-linear and AAG-dependent pharmacokinetics. Further PK/PD analysis, indicated that unbound concentration is more suitable than total concentration for detecting potential exposure-response relationships, which was also supported by basic pharmacokinetic theory.

Erivedge is suggested to be a highly permeable compound with low aqueous solubility (BCS Class 2), but high permeability cannot be definitely concluded. The single dose mean (CV %) absolute bioavailability of Erivedge is 31.8 (14.5) %. After multiple doses absolute bioavailability appears to decrease to around 7%. Absorption is saturable as evidenced by the lack of dose proportional increase in exposure after a single dose of 270 mg and 540 mg Erivedge.
The effect of a high-fat meal on unbound concentration is unknown, but might be larger compared to the observed effect on total concentrations. However, the healthy breakfast administered in the multiple-dose part of the study is probably more representative of the real-life situation. Under these clinically relevant conditions (steady state), the PK of vismodegib is not affected by food. Therefore, Erivedge may be taken without regard to meals.

Due to the pH-dependent solubility, an interaction study with a proton pump inhibitor is planned. Until data are available the SmPC contains a relevant interaction warning that medicinal products that alter the pH of the upper gastrointestinal (GI) tract (e.g., proton pump inhibitors, H_2-receptor antagonists, and antacids) may alter the solubility of vismodegib and reduce its bioavailability.

Due the current uncertainties regarding the disposition of vismodegib, the incompletely evaluated elimination and interaction potential is included as missing information in the RMP.

The elimination of vismodegib appears to be primarily via hepatic routes. A combined renal/hepatic impairment study is included in the RMP. As a difference in elimination capacity (intrinsic CL) at organ impairment might not be seen in total concentrations but only in unbound concentrations due to the saturable protein binding of vismodegib free concentrations will be determined. Awaiting the study results, a warning of caution has been introduced in the SmPC for moderate to severe hepatic impairment, as vismodegib is primarily eliminated via hepatic routes. Based on the low urinary excretion of vismodegib, mild-moderate renal impairment would not be expected to lead to clinically relevant increases in unbound concentrations of vismodegib. However, severe renal impairment might affect also metabolism and transport, and a warning of caution at severe renal impairment has been implemented in the SmPC.

In vitro studies indicate that vismodegib is a substrate of the efflux transporter P-glycoprotein (P-gp) and the drug metabolising enzymes CYP2C9 and CYP3A4, but involvement of these enzymes transporters has not yet been confirmed *in vivo*. When vismodegib is co-administered with medicinal products that inhibit P-gp (e.g. clarithromycin, erythromycin, azithromycin, verapamil, cyclosporin), CYP2C9 (amiodarone, fluconazole or miconazole), or CYP3A4 (boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, or voriconazole), systemic exposure of vismodegib and incidence of adverse events of vismodegib may be increased. When vismodegib is administered with CYP inducers (rifampicin, carbamazepine, phenytoin, St. John´s wort), exposure to vismodegib may be decreased. Relevant warnings and contraindications are also reflected in the SmPC. Studies with a CYP2C9 and a CYP3A4/Pgp inhibitor, are included in the RMP. If the results of these studies do not support involvement of those enzymes/transporters, additional data might be needed to elucidate the elimination mechanisms for vismodegib.
In vitro studies to investigate whether vismodegib is substrate to or inhibitor of additional transport proteins will be performed and are included in the RMP.

Determining the effect of vismodegib on oral contraceptives is important due to the teratogenic potential of vismodegib. An interaction study with an oral contraceptive has been submitted, demonstrating no effect on ethinyl estradiol and norethindrone upon 7 days pre-treatment with vismodegib. However, as the vismodegib treatment period might have been too short to obtain an induction effect, data on whether vismodegib may give rise to reduced plasma levels of hormonal contraceptives are not reassuring. Hormonal contraceptive methods that may be sensitive to induction can therefore presently not be recommended as highly effective. Two contraceptive methods are recommended in the SmPC, one highly effective method of contraception, and one barrier method.

An interaction study with rosiglitazone confirmed that clinically relevant effects of vismodegib on concomitant substrates of CYP2C8 or 2C9 are unlikely. However, data are not sufficient to exclude a risk for time-dependent inhibition of CYP3A4. Therefore, further *in vitro* data or a study with midazolam is included in the RMP. As vismodegib is likely to be a BCRP inhibitor, a study with a BCRP substrate is recommended.

A case report of suspected prolonged vismodegib exposure beyond 7 months post-treatment triggered the need for additional PK simulations, using the population pharmacokinetic model and thereby taking into account the distribution of co-variates for vismodegib PK in the population (as opposed to the previous simulation for a typical, “average” patient). 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. To avoid potential foetal exposure during pregnancy, male patients must always use a condom (with spermicide, if available), even after a vasectomy, when having sex with a female partner while taking Erivedge and for 2 months after the final dose. Patients should not donate blood while taking Erivedge and for 24 months after the final dose. Male patients should not donate semen while taking Erivedge and for 2 months after the final dose. In order to assist health care providers and patients to avoid embryonic and foetal exposure to Erivedge the Marketing Authorisation Holder will provide educational materials (Erivedge Pregnancy Prevention Programme) to reinforce the potential risks associated with the use of Erivedge (see RMP).

No data have been generated on excretion in milk, and given the very potent developmental toxicity of vismodegib, breast-feeding is contraindicated for women treated with Erivedge.

2.4.5. Conclusions on clinical pharmacology

As discussed above, uncertainties in the pharmacology of vismodegib is addressed by strict recommendations in the SmPC until further data requested to the Applicant will be available.

Due to the risk of embryo-foetal death or severe birth defects caused by vismodegib, women of child bearing potential (WCBP) treated with it must be able to comply with the Erivedge Pregnancy Prevention Programme using effective contraceptive measures; these consist of two methods of recommended contraception including one highly effective method and a barrier method during Erivedge therapy and for 24 months after the final dose. WCBP, whose periods are irregular or stopped, must follow all the advice on effective contraception. Erivedge is contraindicated in WCBP who do not comply. As vismodegib is contained in semen, to avoid potential foetal exposure during pregnancy, a male patient must use the recommended contraception during treatment and for 2 months after his final dose (see SmPC sections 4.3, 4.4 and 4.6).

The CHMP considered RMP measures necessary to address issues related to pharmacology (see RMP).

2.5. Clinical efficacy

The application is based on data from the pivotal study SHH4476g, supportive efficacy and safety information from study SHH3925g, supportive safety data from randomized Phase II trials in other oncology indications (studies SHH4489g in ovarian cancer and SHH4429g in colorectal cancer), and from the clinical pharmacology program.[11,12]

Table 18 Primary Studies in Support of Efficacy of Vismodegib in Patients with Advanced BCC

Study, FPI–LPI, Data Cutoff Date	Title	No. of Patients	Dose Regimen	Primary Endpoints
SHH3925g 23 January 2007 through 3 November 2009; CSR data cutoff date was 12 November 2010	An Open-Label, Phase I Study of Systemic Hedgehog Pathway Antagonist, GDC-0449, in Patients with Locally Advanced or Metastatic Solid Tumors That are Refractory to Standard Therapy or for Whom No Standard Therapy Exists	68 (33 aBCC)	150, 270, or 540 mg daily by mouth	Safety, pharmacokinetics, and determination of the MTD [b]
SHH4476g 10 February 2009 through 26 February 2010; CSR data cutoff date was 26 November 2010	A Pivotal Phase II, Multicenter, Single-Arm, Two-Cohort Trial Evaluating the Efficacy and Safety of GDC-0449 in Patients with Advanced Basal Cell Carcinoma	104 (33 mBCC, 71 laBCC)	150 mg daily by mouth	ORR per IRF assessment [a]

aBCC = advanced basal cell carcinoma; CSR=Clinical Study Report; FPI = first patient in; IRF =independent review facility; laBCC = locally advanced basal cell carcinoma; LPI = last patient in; mBCC = metastatic basal cell carcinoma; MTD = maximum tolerated dose; ORR = objective response rate; SF-36 = Short Form 36 (Health Survey).

[a] Secondary endpoints included ORR per investigator assessment, duration of response and progression-free survival per IRF and investigator assessment, overall survival, histopathological response, and SF-36 patient-reported outcomes.

[b] Tumor response per investigator assessment was a secondary endpoint.

2.5.1. Dose response study

The starting dose of 150 mg/day (92.5 mg/m2/day) of vismodegib for the Phase I trial SHH3925g in cancer patients was determined based on animal toxicity studies. This was estimated as corresponding to a 32-fold safety margin over the STD10 in rats (500 mg/kg/day or 3000 mg/m2/day), as well as a 32-fold safety margin over the HNSTD in dogs (150 mg/kg/day or 3000 mg/m2/day). In the Phase I dose-escalation study, vismodegib was administered daily at a 150-, 270-, or 540-mg dose level. Because no dose-limiting toxicities or other significant toxicities were observed at the 150-mg/day Phase I starting dose, administration of a lower dose was not expected to provide any additional benefit to patients, and doses lower than 150 mg were therefore not evaluated in Phase I.

Following a single dose of 270 or 540 mg vismodegib with a 7-day observation period, vismodegib plasma exposure was greater than that observed following the 150-mg dose. However, upon continued daily dosing in the same patients, steady-state plasma concentrations of vismodegib were equivalent for the three dose levels. No additional dose escalations were conducted because of the lack of an increase in steady-state concentrations with dose and the absence of dose-limiting toxicities at the 270- or 540-mg dose levels. No association between increased response rates and daily dose level was observed in this study, an observation consistent with the finding of similar steady-state plasma concentrations across dose levels. The recommended Phase II dose was 150 mg/day.

In the Phase II study SHH4476g, no relationship was observed between tumour response (complete response, partial response, stable disease, or progressive disease) and steady-state total plasma concentration of vismodegib (see Clinical efficacy section).

In addition, no obvious relationship was observed between weight loss, alopecia, dysgeusia, fatigue, or muscle spasms and total (studies SHH3925g and SHH4476g combined) or unbound (SHH3925g only) vismodegib plasma concentration.

2.5.2. Main study

Study SHH4476g

This was a multicentre, Single-Arm, Two-Cohort Trial Evaluating the Efficacy and Safety of Vismodegib in Patients with Advanced Basal Cell Carcinoma.

Methods

Study Participants

Main Inclusion Criteria

- Men and women aged ≥ 18 years;
- Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2;
- For patients with locally advanced BCC, at least one histologically confirmed lesion ≥ 10 mm in the longest diameter that was considered to be inoperable or had a medical contraindication to surgery, in the opinion of a Mohs dermatologic surgeon, head and neck surgeon, or plastic surgeon; Patients with clinical Gorlin's syndrome were not excluded.
- For patients with metastatic BCC, histologic confirmation of metastasis (e.g., lung, liver, lymph nodes, or bone), with metastatic disease that was RECIST measurable using CT or MRI
- Adequate hematopoietic capacity ; Adequate hepatic function;

- Agreement to use two acceptable methods of contraception for women of childbearing potential / men with female partners of childbearing potential during the study and for 12 months / 3 months after discontinuation of vismodegib
- Agreement not to donate blood or blood products during the study and for at least 12 months after discontinuation of vismodegib; for male patients, agreement not to donate sperm during the study and for at least 3 months after discontinuation of vismodegib

Main Exclusion Criteria

- Prior treatment with vismodegib or other antagonists of the Hh pathway.
- Pregnancy or lactation.
- Life expectancy of < 12 weeks.
- Patients with superficial multifocal BCC considered unresectable due to breadth of involvement.
- Concurrent non–protocol-specified anti-tumour therapy (e.g., chemotherapy, other targeted therapy, topical therapy such as 5-fluorouracil or imiquimod, radiation therapy, or photodynamic therapy).
- History of other malignancies within 3 years of Day 1, except for tumours with a negligible risk for metastasis or death, such as adequately treated squamous-cell carcinoma of the skin, ductal carcinoma in situ of the breast, or carcinoma in situ of the cervix.
- Uncontrolled medical illnesses such as infection requiring treatment with intravenous antibiotics.
- History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding which gave reasonable suspicion of a disease or condition that contraindicated use of an investigational drug that could have affected interpretation of the results of the study or rendered the patient at high risk from treatment complications.

Treatments

Patients received 150 mg of vismodegib daily by mouth, beginning on Day 1, and continuously until unequivocal disease progression, intolerable toxicity attributable to vismodegib or withdrawal from the study. No dose modification or reductions in study drug were allowed *per protocol*. Treatment with vismodegib may have been interrupted for up to 4 weeks for evaluation of an intolerable toxicity finding or up to 8 weeks for a planned surgical procedure. In addition, treatment with vismodegib may have been interrupted for up to 4 weeks if a patient became temporarily unable to swallow capsules.

Objectives

The primary objective was to estimate the clinical benefit of vismodegib given as therapy for patients with locally advanced or metastatic BCC, as measured by objective response rate (ORR).

Secondary objectives included estimation of the duration of objective response, progression-free survival (PFS), and overall survival (OS), assessment of the safety, tolerability of vismodegib in this patient population, PK of vismodegib in this population (at participating sites only), assessment of patient-reported outcomes, assessment of the histopathologic effect of vismodegib in tumour biopsies obtained at baseline and following vismodegib treatment in patients with locally advanced BCC, evaluation of the status of the Hh signalling pathway using quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) in archival tissue.

Exploratory objectives included the evaluation of the effect of vismodegib treatment on the Hh signalling pathway using qRT-PCR and/or other approaches in tissue obtained at baseline and following vismodegib treatment in patients with locally advanced BCC, evaluation of the relationship between the effects of vismodegib treatment on the Hh signalling pathway and efficacy in patients with locally advanced BCC.

Outcomes/endpoints

Primary endpoint was ORR as assessed by independent review facility (IRF).

Secondary endpoints were: Duration of response, PFS assessed by IRF and by investigator.

Additional secondary endpoints were included: Patient-reported outcomes, effect of vismodegib in tumour biopsies, status of the Hh signalling pathway using quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) in archival tissue.

During treatment, tumour assessments were conducted every 8 weeks and at study completion or early termination visit as appropriate. Patients assessed as having an objective response (defined as a complete or partial response, RECIST1) underwent confirmatory tumour assessments ≥ 4 weeks after the initial documentation of the objective response.

Progressive disease was defined according to RECIST or new ulceration of target lesion without evidence of healing for at least 2 weeks per IRF. Per investigator assessed non-target lesion progression was also defining PD.

Sample size

The sample size was chosen to 100 patients, as with respect to efficacy, this study had approximately 80% probability of rejecting the null hypothesis (see Statistical methods) given a true ORR of 37% in the metastatic BCC cohort (with 20 treated patients) and 34% in the locally advanced BCC cohort (with 80 treated patients).

Randomisation

Patients were not randomized in this study.

Blinding (masking)

Not applicable.

Statistical methods

The magnitude of ORR (determined as a function of a radiographic IRF, photographic IRF, and pathological IRF) was formally tested in two parallel analyses using one-sided exact binomial tests in the metastatic and locally advanced BCC cohorts.

The following hypothesis was tested at the one-sided $\alpha = 0.025$ level in the metastatic BCC cohort:

$H_0: ORR \leq 0.10$ versus $H_a: ORR > 0.10$

Similarly, the following hypothesis was tested at the one-sided $\alpha = 0.025$ level in the locally advanced BCC cohort:

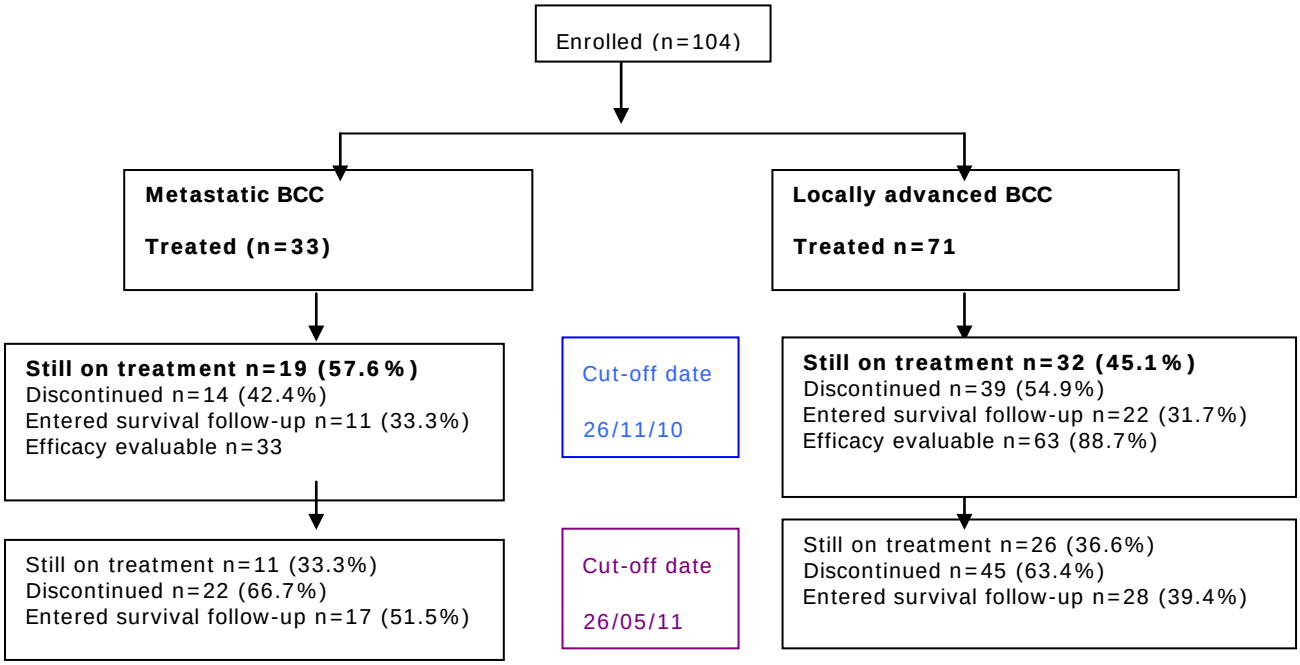
$H_0: ORR \leq 0.20$ versus $H_a: ORR > 0.20$

Efficacy analyses were performed on the efficacy-evaluable patient population. Analyses of primary and key secondary efficacy parameters were repeated for all enrolled patients by IRF and by investigator. Data are also presented for the tissue-confirmed population that consisted of all treated patients for whom either a baseline biopsy or archival tissue showed evidence of BCC. The primary analysis population for efficacy consisted of all treated patients for whom the independent pathologist's interpretation of archival tissue or baseline biopsies was consistent with BCC (the efficacy-evaluable population). In locally advanced BCC cases when there was a conflicting interpretation of archival tissue versus a baseline biopsy by the independent pathologist, the baseline biopsy was used to determine inclusion in the efficacy analyses.

Patients without interpretable baseline or archival tissue, as determined by the independent pathologist, or by pathology report from the study site documenting a pathologist's determination of BCC, were excluded from the efficacy analyses. Patients who have received at least one dose and who discontinued for any reason prior to undergoing one post-baseline response evaluation were considered non-responders in the primary analysis and disease progression was be censored at the date of baseline tumour assessment +1 day. Duration of objective response and PFS were censored at the last tumour assessment date for patients without disease progression who had not died within 30 days of last exposure to study treatment.

Results

Participant flow



Patient Disposition (All Treated Patients) -updated as of 28 November 2011

Status	Metastatic BCC (n = 33)	Locally Advanced BCC (n = 71)	All Patients (n = 104)
Patients still on treatment	7 (21.2%)	*22 (31.0%)*	29 (27.9%)
Discontinued treatment			
Total	26 (78.8%)	49 (69.0%)	75 (72.1%)
Adverse event	4 (12.1%)	14 (19.7%)	18 (17.3%)
Death	1 (3.0%)	2 (2.8%)	3 (2.9%)
Lost to follow-up	1 (3.0%)	2 (2.8%)	3 (2.9%)
Physician decision to discontinue treatment	2 (6.1%)	2 (2.8%)	4 (3.8%)
Patient decision to discontinue treatment	4 (12.1%)	20 (28.2%)	24 (23.1%)
Disease progression	14 (42.4%)	*8 (11.3%)*	22 (21.2%)
Other	0	1 (1.4%)	1 (1.0%)

Recruitment

A total of 104 patients were enrolled at 31 study sites in the United States (72), England (2), France (7), Germany (14), Belgium (7), and Australia (2).

The study was activated on 10 February 2009 (first patient in) and enrolment was completed on 26 February 2010 (last patient in). The study Period was from 10 February 2009 to 26 November 2010, data cut off; with follow-up updates and data cut off on 26 May 2011, report date 2 November 2011.

Conduct of the study

As of the database cut-off date (November 2010), protocol had been amended twice.

Baseline data

Demographic and Baseline characteristics for the efficacy-evaluable patients are given in the following tables 19 and 20.

Table 19 Demographic characteristics, efficacy evaluable

	Metastatic BCC (n = 33)	Locally Advanced BCC (n = 63)	All Patients (n = 96)
Age (yr)			
N	33	63	96
Mean (SD)	61.6 (11.4)	61.4 (16.9)	61.5 (15.2)
Median	62.0	62.0	62.0
Range	38–92	21–101	21–101
Age group (yr)			
N	33	63	96
18-40	1 (3.0%)	7 (11.1%)	8 (8.3%)
41-64	18 (54.5%)	26 (41.3%)	44 (45.8%)
≥ 65	14 (42.4%)	30 (47.6%)	44 (45.8%)
Sex			
N	33	63	96
Male	24 (72.7%)	35 (55.6%)	59 (61.5%)
Female	9 (27.3%)	28 (44.4%)	37 (38.5%)
Ethnicity			
N	33	63	96
Hispanic or Latino	0	1 (1.6%)	1 (1.0%)
Not Hispanic or Latino	33 (100.0%)	61 (96.8%)	94 (97.9%)
Not available	0	1 (1.6%)	1 (1.0%)
Race			
N	33	63	96
White	33 (100.0%)	63 (100.0%)	96 (100.0%)
Weight (kg)			
N	33	62	95
Mean (SD)	76.50 (15.30)	86.13 (21.49)	82.78 (20.02)
Median	74.80	82.20	79.50
Range	54.2–122.0	52.0–170.0	52.0–170.0

Table 20, Baseline disease characteristics, efficacy evaluable

	Metastatic BCC (n = 33)	Locally Advanced BCC (n = 63)	All Patients (n = 96)
	ECOG performance status		
n	33	63	96
0	13 (39.4%)	48 (76.2%)	61 (63.5%)
1	19 (57.6%)	13 (20.6%)	32 (33.3%)
2	1 (3.0%)	2 (3.2%)	3 (3.1%)
	Number of target lesions		
	33	63	96
1	9 (27.3%)	40 (63.5%)	49 (51.0%)
2	4 (12.1%)	12 (19.0%)	16 (16.7%)
3	9 (27.3%)	6 (9.5%)	15 (15.6%)
>3	11 (33.3%)	5 (7.9%)	16 (16.7%)

BCC = basal cell carcinoma; ECOG = Eastern Cooperative Oncology Group.

For patients with locally advanced BCC, the most frequent sites of target lesions were the scalp (18), forehead (15), and “other” sites (19). Sites on the face, including those on the nose (9), ear (8), and cheek (8), were also frequent sites of target lesions. Altogether 22 patients with a medical history of Gorlin syndrome or suspected Gorlin syndrome were enrolled in Study SHH4476g.

Baseline Disease Characteristics and Prior Therapies: Efficacy-Evaluable Population

Characteristic	Metastatic BCC (n = 33)	Locally Advanced BCC (n = 63)
Time from initial diagnosis of any BCC until study treatment (mo)		
Mean (SD)	98.6 (108.4)	196.0 (151.7)
Median (range)	66.1 (1–522)	169.4 (1–512)
Locally advanced BCC considered:		
Inoperable		24 (38.1%)
Medical contraindication [a]		39 (61.9%)
Recurrent disease		16 (25.4%)
Significant morbidity or deformity		32 (50.8%)
Locally advanced BCC: patient received prior radiotherapy?		
Yes		13 (20.6%)
No		50 (79.4%)
Radiotherapy was inappropriate		15 (23.8%)
Radiotherapy was contraindicated		35 (55.6%)
Any prior treatment	32 (97.0%)	59 (93.7%)
Prior surgery	32 (97.0%)	56 (88.9%)
Prior radiotherapy	19 (57.6%)	17 (27.0%)
Prior systemic therapy [b]	10 (30.3%)	7 (11.1%)

BCC = basal cell carcinoma.

[a] More than one medical contraindication could have been chosen.

[b] Included systemic and/or topical therapies.

Source: Tables 10.1/10, 10.1/12, and 10.1/14.

Numbers analysed

Table 21

Region and Analysis Population	Metastatic BCC (n=33)	Locally Advanced BCC (n=71)	All Patients (n=104)
Total			
Enrolled	33 (100.0%)	71 (100.0%)	104 (100.0%)
Treated	33 (100.0%)	71 (100.0%)	104 (100.0%)
Efficacy-evaluable	33 (100.0%)	63 (88.7%)	96 (92.3%)

The efficacy-evaluable population consisted of 96 patients (all enrolled 33 patients with mBCC and 63 patients with laBCC). In 8 pts with laBCC, the pathologic diagnosis was not confirmed histologically based on biological biopsy, these were excluded from efficacy-evaluable population.

Outcomes and estimation

Table 22: Primary endpoint: IRF-determined ORR (efficacy-evaluable patients)

	Metastatic BCC (n = 33)	Locally Advanced BCC (n = 63)	All Patients (n = 96)
Patients with objective response	10 (30.3%)	27 (42.9%)	37 (38.5%)
Complete response	0	13	13
Partial response	10	14	24
Stable disease	21	24	45
Progressive disease	1	8	9
Missing (no post-baseline tumour assessment)	1	4	5
95% CI for objective response [a]	(15.6%, 48.2%)	(30.5%, 56.0%)	(28.8%, 48.9%)
p-value for objective response [b]	0.0011	< 0.0001	—

[a] The 95% CI for response rate was computed using Blyth–Still–Casella method. Complete response as best objective response required a CR confirmed by a CR, otherwise the best objective response was a partial response.
[b] The p-value was derived from an exact binomial test of objective response ≤ 10% in the metastatic BCC cohort and ≤ 20% in the locally advanced BCC cohort.

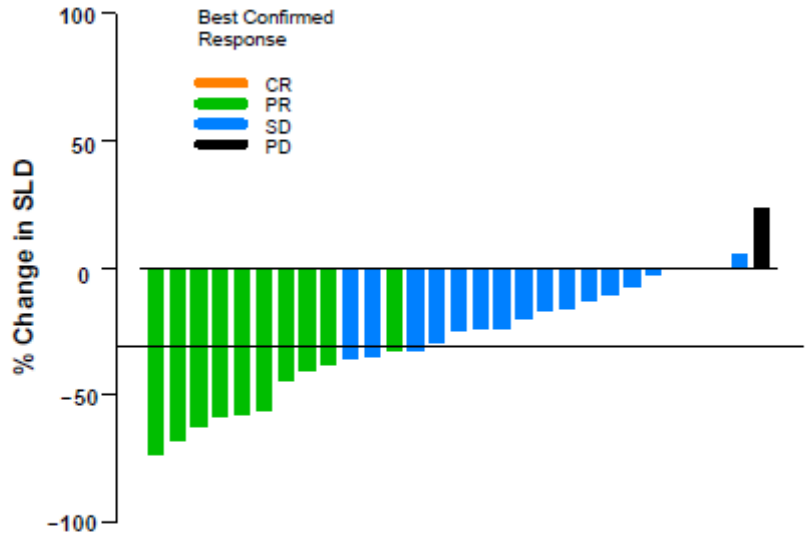
Table 23: Secondary endpoint: investigator-determined ORR (efficacy-evaluable patients)

	Metastatic BCC (n = 33)	Locally Advanced BCC (n = 63)	All Patients (n = 96)
Patients with objective response	15 (45.5%)[1] 16 (48.5%)[2]	38 (60.3%)	53 (55.2%)[1] 54 (56.3%)[2]
Complete response	0	20	20
Partial response	15[1] 16[2]	18	33[1] 34[2]
Stable disease	15[1] 14[2]	15	30[1] 29[2]
Progressive disease	2	6	8
Unable to evaluate	0	1	1
Missing	1	3	4
No post-baseline tumour assessment	1	2	3
No baseline tumour assessment	0	1	1
95% CI for objective response [a]	(28.1%, 62.2%)[1] (30.8%, 66.2%)[2]	(47.2%, 71.7%)	(44.7%, 65.4%)[1] (45.7%, 66.4%)[2]

[1]Cut-off date 26/11/10
[2]Cut-off date 26/05/11
Same figures for both cut-off dates
Note: CR as best objective response required a CR confirmed by a CR, otherwise the best objective response was a partial response.
[a] The 95% CI for response rate was computed using Blyth–Still–Casella method.

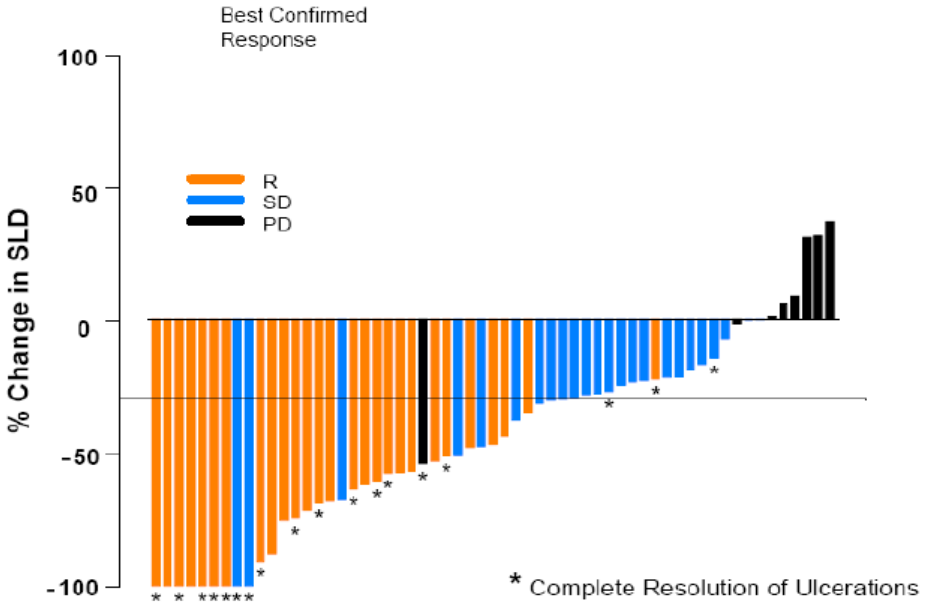
Figure 7

Maximum Percent Tumor Shrinkage in SLD from Baseline by IRF Assessment: Metastatic BCC Cohort



BCC=basal cell carcinoma; CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease; SLD=sum of the longest dimension (of target lesion[s]).
Note: Of the 33 patients in the metastatic BCC cohort, 3 patients had a best percent change in SLD of 0; these represent the gap in the figure. Three patients did not have measurements, and 1 patient was "UE" (unable to evaluate) for assessment of best confirmed response; these 4 patients were excluded from the analysis.
Source: Figure 10.2/5.

Maximum Percent Tumor Shrinkage in SLD from Baseline by IRF Assessment: Locally Advanced BCC Cohort



BCC=basal cell carcinoma; IRF=independent review facility; PD=progressive disease; R=response; SD=stable disease; SLD=sum of the longest dimension (of target lesion[s]).
Note: Four patients did not have lesion measurements and were not included in the plot.

Table 24: Secondary endpoints: duration of objective response; duration of PFS; duration of OS (efficacy-evaluable patients)

	Metastatic BCC (n = 33)	Locally Advanced BCC (n = 63)
Duration of objective response by IRF assessment		
Number of progressive events/deaths (number censored)	3 (7)[1]	13 (14)[1]
Median (mo) (95% CI)	7.6 (5.62, NE)[1]	7.6 (5.65, 9.66)[1]
Duration of objective response by investigator assessment		
Number of progressive events/deaths (number censored)	6 (9)[1]	11 (27)[1]
	7 (9)[2]	12 (26)[2]
Median (mo) (95% CI)	12.9 (5.55, 12.91[1])	7.6 (7.43, NE[1])
	12.9 (5.55, NE)[2]	NE (7.62, NE)[2]
Progression-free survival by IRF assessment		
Number of progressive events/deaths (number censored)	15 (18)[1]	33 (30)[1]
Median (mo) (95% CI)	9.5 (7.36, NE)[1]	9.5 (7.39, 11.93)[1]
Progression-free survival, by investigator assessment		
Number of progressive events/deaths (number censored)	17 (16)[1]	26 (37)[1]
	19 (14)[2]	27 (36)[2]
Median (mo) (95% CI)	9.2 (7.39, NE)[1]	11.3 (9.46, 16.82)[1]
	9.3 (7.39, 16.59)[2]	12.9 (10.22, NE)[2]
Overall survival		
Number of deaths (number censored)	7 (26)[1]	6 (57)[1]
	10 (23)[2]	8 (55)[2]
Median (mo) (95% CI)	NE (13.86, NE)[1]	NE (17.61, NE)[1]
	NE (18.10, NE)[2]	NE (NE, NE)[2]

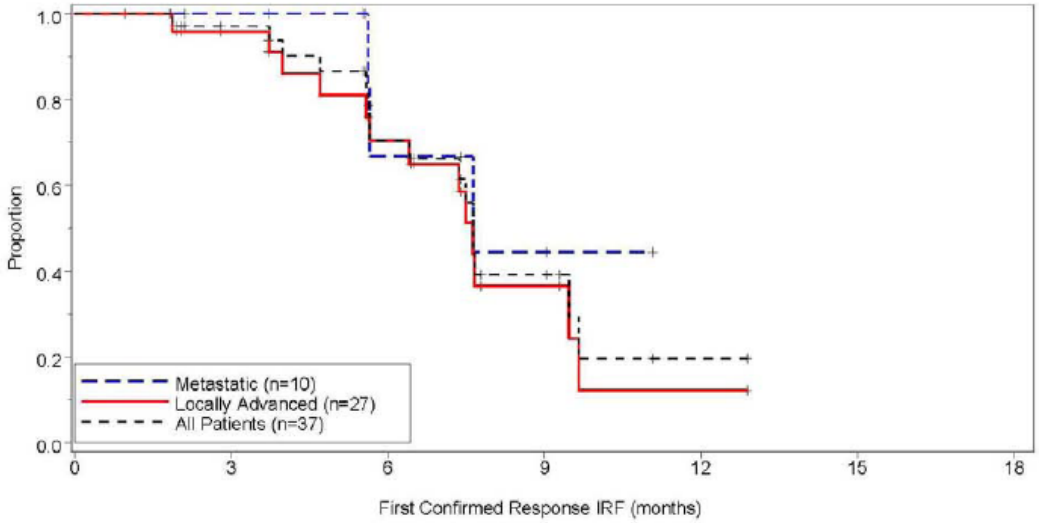
[1]Cut-off date 26/11/10
[2]Cut-off date 26/05/11

NE = not estimable.

Figures below show the Kaplan–Meier curves for duration of objective response and PFS as assessed by the IRF (Efficacy-Evaluable Patients).

The OS data are still immature and the median OS was not reached for either cohort.

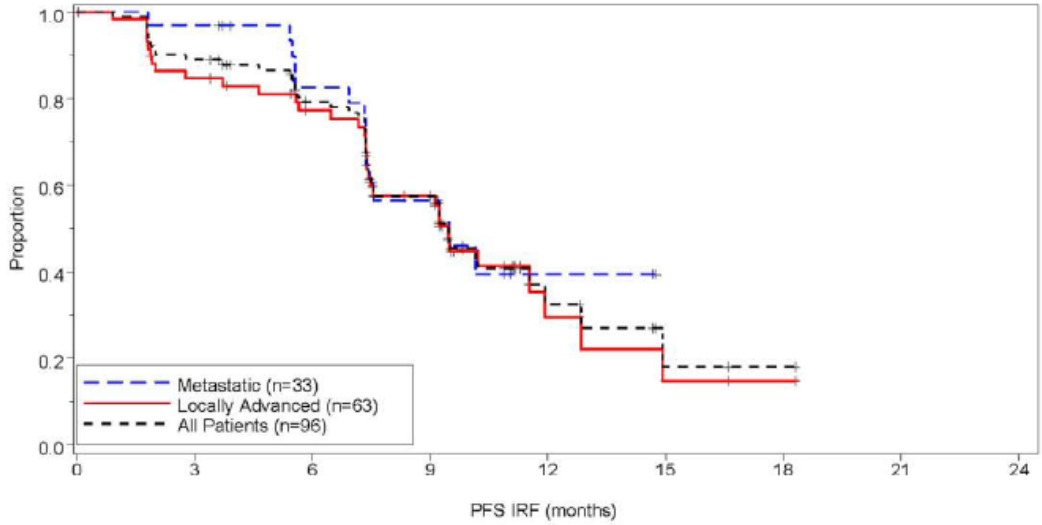
Figure 2: Duration of Objective Response



Number at Risk:							
Metastatic	10	9	4	2	0	0	0
Locally Advanced	27	20	13	4	1	0	0
All Patients	37	29	17	6	1	0	0

Cut-off date 26/11/10

Figure 3: Progression-Free Survival



Number at Risk:									
Metastatic	33	31	23	13	2	0	0	0	0
Locally Advanced	63	49	40	26	5	2	1	0	0
All Patients	96	80	63	39	7	2	1	0	0

Cut-off date 26/11/10

Other secondary endpoints: histopathologic response (efficacy-evaluable patients)

Table 25 Clinical response

	Metastatic BCC (N=33)	Locally Advanced BCC (N=63)
Clinical Response	NA	27 (42.9)
Presence of residual BCC in Post-Baseline Biopsy*		
Yes**	NA	8 (12.7)
No***	NA	19 (30.2)
At (or before date of best confirmed response)	NA	13 (20.6)
After date of best confirmed response	NA	6 (9.5)
SD	NA	24 (38.1)
PD	NA	8 (12.7)
Missing	NA	4 (6.3)

*Patients with more than one post−baseline biopsy were included only once. In case a patient had different post−baseline biopsy results, the biopsy without residual BCC was used.
**Included biopsy results of 'unable to evaluate' and 'not applicable'.
***As assessed by independent pathology review. Patients with more than one biopsy absent of BCC (taken at different dates) were included only once: the biopsy with a date at or before date of best confirmed response was used.
Cut-off date 26/11/10

Ancillary analyses

Table 26: *Subgroup Analyses:* Efficacy-Evaluable Patients

		Responders				
Baseline Characteristic	n	Metastatic BCC (n = 33)	n	Locally Advanced BCC (n = 63)	n	All Patients (n = 96)
All patients	33	15 (45.5%)	63	38 (60.3%)	96	53 (55.2%)
Metastatic BCC cohort	33	15 (45.5%)	0	(0.0%)	0	(0.0%)
Locally advanced BCC cohort	0	(0.0%)	63	38 (60.3%)	0	(0.0%)
ECOG performance status						
0	13	6 (46.2%)	48	30 (62.5%)	61	36 (59.0%)
1 or 2	20	9 (45%)	15	8 (53.3%)	35	17 (48.6%)
1	19	9 (47.4%)	13	8 (61.5%)	32	17 (53.1%)
2	1	(0.0%)	2	(0.0%)	3	(0.0%)
Age (yr)						
< 65	19	10 (52.6%)	33	24 (72.7%)	52	34 (65.4%)
≥ 65	14	5 (35.7%)	30	14 (46.7%)	44	19 (43.2%)
Region						
Europe, Australia	7	3 (42.9%)	21	15 (71.4%)	28	18 (64.3%)
United States	26	12 (46.2%)	42	23 (54.8%)	68	35 (51.5%)
Sex						
Female	9	5 (55.6%)	28	19 (67.9%)	37	24 (64.9%)
Male	24	10 (41.7%)	35	19 (54.3%)	59	29 (49.2%)
Race						
White	33	15 (45.5%)	63	38 (60.3%)	96	53 (55.2%)
Ethnicity						
Hispanic or Latino	0	(0.0%)	1	1 (100.0%)	1	1 (100.0%)
Not Hispanic or Latino	33	15 (45.5%)	61	37 (60.7%)	94	52 (55.3%)

Table 26: *Subgroup Analyses:* Efficacy-Evaluable Patients

		Responders				
Baseline Characteristic	n	Metastatic BCC (n = 33)	n	Locally Advanced BCC (n = 63)	n	All Patients (n = 96)
Not available	0	(0.0%)	1	(0.0%)	1	(0.0%)
Number of target lesions at baseline						
1	9	1 (11.1%)	40	24 (60.0%)	49	25 (51.0%)
2	4	1 (25.0%)	12	6 (50.0%)	16	7 (43.8%)
3	9	5 (55.6%)	6	5 (83.3%)	15	10 (66.7%)
> 3	11	8 (72.7%)	5	3 (60.0%)	16	11 (68.8%)

BCC = basal cell carcinoma; ECOG = Eastern Cooperative Oncology Group.
Cut-off date 26/11/10

In patients with Gorlin's syndrome an exploratory analysis was performed based on data cutoff date 28/11/2011, ORR was 14/21 by IRF and 17/21 by investigator assessment. Median duration of response was 21.4 months by IRF assessment and not estimable by investigator assessment.

Table 27: Histopathology Effect in Tissue Biopsy (Target Lesions Only): Efficacy-Evaluable patients

	Locally Advanced BCC (n = 63)
Baseline biopsy available	59 (93.7)
Pathology confirmed BCC in baseline biopsy	58 (92.1)
Post-baseline biopsy available [a]	51 (81.0)
Post-baseline biopsy assessed by independent pathologist	51 (81.0)
Absence of residual BCC [b]	34 (54.0)
Prior to Week 24	6 (9.5)
At Week 24 [c]	27 (42.9)
After Week 24	1 (1.6)
Post-baseline biopsy not available	7 (11.1)

BCC = basal cell carcinoma.

Note: Post-baseline biopsies were taken from target lesions only.

[a] Patients with more than one post-baseline biopsy were included only once.

[b] As assessed by independent pathology review. For patients with a biopsy of a target lesion(s) obtained at more than one timepoint, those with at least one timepoint showing absence of residual BCC were included; if more than one sample at a given timepoint was free of residual BCC, the earliest timepoint was used. For patients with more than one target lesion, biopsies from all target lesions had to be free of residual BCC.

[c] At Week 24 = 24 × 7 days from first drug intake ± 7 days time window (prior to Week 24 and after Week 24 defined accordingly).

Cut-off date 26/11/10

Biomarkers

The analyses of ORR by *GLI1* and *PTCH2* expression in Archival Tumor Tissue in efficacy-evaluable patients are summarized below.

Table 28 ORR by *GLI1* and *PTCH2* Expression: Efficacy-Evaluable Patients

	IRF Assessments				Investigator Assessments			
	Metastatic BCC		Locally Advanced BCC		Metastatic BCC		Locally Advanced BCC	
Tissue Marker	n	ORR	n	ORR	n	ORR	n	ORR
All patients	33	10 (30.3%)	63	27 (42.9%)	33	15 (45.5%)	63	38 (60.3%)
Patients included in subgroup analysis qRT-PCR *GLI1* relative expression	22		53		22		53	
≤ 33rd percentile	5	3 (60.0%)	19	9 (47.4%)	5	3 (60.0%)	19	13 (68.4%)
33rd–67th percentile	11	2 (18.2%)	14	7 (50.0%)	11	4 (36.4%)	14	10 (71.4%)
> 67th percentile	6	1 (16.7%)	20	7 (35.0%)	6	4 (66.7%)	20	12 (60.0%)
qRT-PCR *PTCH2* relative expression								
≤ 33rd percentile	10	4 (40.0%)	16	8 (50.0%)	10	7 (70.0%)	16	10 (62.5%)
33rd–67th percentile	5	0 (0.0%)	19	8 (42.1%)	5	1 (20.0%)	19	12 (63.2%)
> 67th percentile	7	2 (28.6%)	18	7 (38.9%)	7	3 (42.9%)	18	13 (72.2%)

BCC = basal cell carcinoma; GLI1 =glioma-associated oncogene homolog 1; ORR = objective response rate; PTCH = Patched; qRT-PCR = quantitative reverse-transcriptase polymerase chain reaction.
Cut-off date 26/11/10

Over-expression of *GLI1* and *PTCH2* in archival tissue was observed relative to normal skin, but there was no apparent relation between expression level and tumour response. All patients evaluable for biomarkers had over-expression of *GLI* and *PTCH2*.

Summary of main study

The following table summarise the efficacy results from the main studies supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 29: Summary of Efficacy for trial SHH4476g

Title: SHH4476g: A Pivotal Phase II, Multicenter, Single-arm, Two-cohort trial evaluating the efficacy and safety of GDC-0449 in Patients with Advanced Basal Cell Carcinoma.			
Study identifier	Report number: CSR SHH4476g Eudract number: 2008-004945-27		
Design	Pivotal Phase II, single-arm, two-cohort, multicenter clinical trial evaluating the efficacy and safety of 150 mg daily of vismodegib in patients with advanced BCC		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		at least 9 months after first treatment of the last enrolled patient. Median of 9.84 months on study treatment not applicable 6 months follow-up data. Median of 12.93 months on study treatment
Hypothesis	Superiority (versus a fixed value chosen by the applicant)		
Treatment group	Advanced BCC (2 cohorts)		104 patients treated (33 mBCC & 71 laBCC) with 150 mg of vismodegib daily by mouth, beginning on Day 1, and continuously until disease progression, intolerable toxicity, most probably attributable to vismodegib, or withdrawal from the study
Endpoints and definitions	Primary endpoint	IRF-determined ORR (objective response rate)	Objective response was defined as a Complete Response or Partial Response determined on two consecutive assessments ≥ 4 weeks apart (Best Confirmed Response). - mBCC cohort: tumour response assessed by the IRF according to RECIST. - laBCC cohort: a composite endpoint (including tumour dimensions, ulceration and RECIST) was created and determined as a function of a radiographic IRF, photographic IRF, and pathology IRF.
	Secondary endpoints	<label>	- investigator-determined ORR - duration of objective response (IRF & investigator), - PFS (IRF & investigator), - OS, - Change from Day 1 in patient-reported outcome (SF-36), - Absence of residual BCC in patients with locally advanced BCC.
Database lock	26 November 2010 Addendum provided: 26 May 2011		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Safety analyses: all-treated patient population Efficacy analyses: efficacy evaluable population (i.e. all treated patients for whom the independent pathologist's interpretation of archival tissue or baseline biopsies was consistent with BCC) Assessments at baseline, then every 8 weeks and at the study completion or early termination visit, as appropriate (taking into account the primary endpoint: unscheduled tumour assessment possible at a monthly visit)		
Descriptive statistics and estimate	Treatment group	mBCC cohort	laBCC cohort

variability	Number of subject	33 efficacy evaluable	63 efficacy evaluable
	IRF-determined ORR	10	27
	(95% CI)	(15.6%, 48.2%)	(30.5%, 56.0%)
	duration of objective response (IRF) median (mo)	7.6	7.6
	(95% CI)	(5.62, NE)	(5.65, 9.66)
	PFS (IRF) median (mo)	9.5	9.5
	(95% CI)	(7.36, NE)	(7.39, 11.93)
	OS median (mo)	NE	NE
	(95% CI)	(13.86, NE)	(17.61, NE)
Effect estimate per comparison	Primary endpoint	Comparison groups	mBCC cohort / Response rates of > 10%
		difference	10 (30.3%) significantly higher than the minimal clinical benefit of 10%
		(95% CI)	(15.6%, 48.2%)
		P-value	0.0011 (one-sided exact binomial test)
	Primary endpoint	Comparison groups	laBCC cohort / Response rates of > 20%
		difference	27 (42.9%) significantly higher than the minimal clinical benefit of 20%
		(95% CI)	(30.5%, 56.0%)
		P-value	< 0.0001 (one-sided exact binomial test)
Notes			

Table 30: Summary of Efficacy, November 2010 cut-off, Primary Analysis

	Metastatic BCC (n = 33)	Locally Advanced BCC (n = 63)
Primary endpoint		
Objective response rate by IRF assessment (%)	10 (30.3%)	**27 (42.9%)**
(95% CI)	(15.6%, 48.2%)	(30.5%, 56.0%)
Complete response	0	**13**
Partial response	10	14
Secondary endpoints		
Objective response rate, by investigator assessment (%)	15 (45.5%)	**38 (60.3%)**
(95% CI)	(28.1%, 62.2%)	(47.2%, 71.7%)
Complete response	0	**20**
Partial response	15	18
Duration of objective response by IRF assessment		
Number of progressive events/deaths (number censored)	**3 (7)**	**13 (14)**
Median (mo) (95% CI)	7.6 (5.62, NE)	7.6 (5.65, 9.66)
Duration of objective response by investigator assessment		
Number of progressive events/deaths (number censored)	**6 (9)**	**11 (27)**
Median (mo) (95% CI)	12.9 (5.55, 12.91)	7.6 (7.43, NE)
Progression-free survival by IRF assessment		
Number of progressive events/deaths (number censored)	15 (18)	33 (30)
Median (mo) (95% CI)	9.5 (7.36, NE)	9.5 (7.39, 11.93)
Progression-free survival, by investigator assessment		
Number of progressive events/deaths (number censored)	17 (16)	26 (37)
Median (mo) (95% CI)	9.2 (7.39, NE)	11.3 (9.46, 16.82)
Overall survival		
Number of deaths (number censored)	7 (26)	6 (57)
Median (mo) (95% CI)	NE (13.86, NE)	NE (17.61, NE)

BCC = basal cell carcinoma; CI = confidence interval; IRF = independent review facility; NE = not estimable.

Updated Efficacy Data as of 28 November 2011

Table 31: Summary of IRF and Investigator Assessed Efficacy Results at the 28 November 2011 Data Cut off Dates (Efficacy-Evaluable Patients)

	IRF 28 November 2011 Data Cut			Investigator 28 November 2011 Data Cut		
	Metastatic BCC (n = 33)	Locally Advanced BCC (n = 63)	Total (n = 96)	Metastatic BCC (n = 33)	Locally Advanced BCC (n = 63)	Total (n = 96)
Patients with objective response	11 (33.3%)	30 (47.6%)	41 (42.7%)	16 (48.5%)	38 (60.3%)	54 (56.3%)
(95% CI)	(19.2%, 51.8%)	(35.5%, 60.6%)	(32.9%, 53.2%)	(30.8%, 66.2%)	(47.2%, 71.7%)	(45.7%, 66.4%)
Complete response	0	**14**	14	0	20	20
Partial response	11	**16**	27	16	18	34
Stable disease	20	22	42	14	15	29
Progressive disease	1	8	9	2	6	8
Median duration of response, months (95% CI)	(n = 11) 7.6 (5.5, 9.4)	(n = 30) **9.5** (7.4, 21.4)	(n = 41) 7.7 (7.4, 9.7)	(n = 16) 14.7 (5.6, NE)	(n = 38) NE (9.0, NE)	(n = 54) **16.1** (9.5, NE)
Median PFS, months (95% CI)	9.5 (7.4, 11.1)	9.5 (7.4, 14.8)	9.5 (7.5, 11.5)	9.3 (7.4, 16.6)	12.9 (10.2, NE)	12.8 (9.5, 18.0)
Median OS, months (95% CI)				24.1 (14.3, NE)	NE (NE, NE)	NE (NE, NE)
1-year survival rate, % (95% CI)				78.0% (63.6, 92.4)	93.1% (86.6, 99.6)	NA

BCC = basal cell carcinoma; CI = confidence interval, NA = not available; NE = not estimable; OS = overall survival; PFS = progression-free survival. The 95% CI for response rate was computed using the Blyth–Still–Casella method.

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Independent review of Clinical Benefit

The Applicant has undertaken an Independent review of Clinical Benefit in patients with laBCC. This review was done by three experts in dermato-oncology independently classifying baseline severity and clinical benefit followed by a consensus review.

Baseline severity was graded from 1 to 5, where 5 was defined as “disfigurement without possibility for reconstruction or prosthetics” (see table 31) and clinical benefit from 1 to 5, where 5 was defined as “significant clinical benefit”.

Table 32: Disease Severity at Baseline—Severity Index

Severity Index	Score	Cosmetic Outcome	Functional Outcome
Very Severe	5	Disfigurement without possibility for reconstruction or prosthetics	Significant impairment
Moderately Severe	4	Disfigurement with need for reconstruction or prosthetics	Some impairment
Severe	3	Some disfigurement without need for reconstruction	Mild impairment
Moderate	2	Notable Scarring without disfigurement	None
Mild	1	Limited to No Scarring	None

Table 33: Baseline Disease Severity versus Clinical Benefit: Consensus Review Assessment of Efficacy—Evaluable Patients with Locally Advanced BCC.

Baseline Severity score	Clinical benefit score				
	1	**2**	**3**	**4**	**5**
1	0	0	0	2	8
2	0	1	0	0	1
3	0	0	0	0	4
4	0	0	0	1	7
5	7	3	2	4	21

"Significant clinical benefit" was thus overall reported in 41/63 (65%) of patients and among patients with baseline severity of 5 in 21 patients (57%).

Analysis performed across trials (pooled analyses and meta-analysis)

No studies submitted.

Clinical studies in special populations

No studies submitted.

Supportive study

See dose-response study.

2.5.3. Discussion on clinical efficacy

Locally advanced BCC not amenable to alternative therapies is rare and metastatic BCC is an extremely rare condition. Obviously, a long-term placebo-controlled trial without cross-over would have provided the ideal data set for a benefit (and risk) assessment in patients with metastatic BCC. Also in the locally advanced setting such a study would be informative, not only about the benefit of therapy in terms of tumour response and duration of response, it would also make possible an assessment of benefit in terms of time to progression and delay in progression until disfiguring lesions. However, the

difficulties to perform comparative trials in this very limited population are acknowledged and the proposed clinical trial design appears justified. Despite the non-randomised design of the pivotal trial, the antitumor activity in terms of tumour shrinkage (ORR) observed in the pivotal trial can reasonably be attributed to vismodegib in view of the natural history of the disease, without the need for a parallel control. In case of locally advanced disease and symptomatic metastatic diseases, tumour shrinkage as measured by objective partial or complete response is considered to be of clinical relevance. Historical comparisons cannot be reliable to interpret survival data. Thus, the chosen endpoint appears justified.

In the November 2011 analysis for locally advanced disease the ORR by IRF was 30/63 (48%) and the median duration of response of about 9.5 months. A review of the photo documentation was undertaken by three experienced oncology-dermatologists independently grading severity of lesions at baseline and grading outcome in terms of clinical benefit, followed by consensus assessment. The results are considered credible and the "significant clinical benefit" rate in patents with the highest severity score at baseline was reported as 21/37 (57%).
The ORR (IRF) was 11/33 and median duration about 8 months, investigator 16/33 and 15 months, respectively.

The majority of responses were reported at the first scheduled visit, i.e. after 8 weeks. Median time to maximum tumour shrinkage was about 7 months.

Altogether, patient benefit as measured by durable tumour responses and "significant clinical benefit" has been documented in at least 50% of patients with locally advanced BCC enrolled.

Additional expert consultation

Following the CHMP request, a Scientific Advisory Group meeting was convened on 9 January 2013 to provide advice on the following issues on efficacy and optimal treatment duration:

1. Evidence of efficacy of vismodegib in the proposed indication treatment of locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy. The following issues were discussed;

    - A post hoc analysis of patient benefit was undertaken independently by three experts followed by a consensus statement. This review was done with the aim to complement conventional tumour response data. The SAG was asked if these "patient benefit data" can be considered credible.

      SAG answer: Based on the good concordance between investigators and the independent experts, the review is considered reproducible and therefore credible. However, the adjudication of presence or absence of clinical benefit is a subjective judgement that was not assessed using a validated scale. Thus, although this clinical expert judgement is likely to be related to favourable cosmetic and possibly functional outcomes, the precise quantitative interpretation of clinical benefit in terms of e.g., symptom improvement, health-related quality of life, is unknown.

    - The SAG was asked if -in combination with tumour response and duration of response data-, the available data are altogether considered to be quantitatively and qualitatively sufficient to estimate patient benefit.

      SAG answer: For locally advanced disease, the observation of major responses including a high number of complete responses in exposed areas of the skin, the long response duration, the frequent healing of ulceration and the investigators' and clinical experts' assessment of clinical benefit allow concluding that treatment with vismodegib is associated with a clinically relevant benefit. For metastatic disease, however, the clinical relevance of the antitumour activity associated with vismodegib is questionable although not necessarily absent. This is due to the

relatively low response rate, the absence of complete responses, the unlikely clinical relevance of an effect on asymptomatic lesions, and the varying cosmetic importance of tumour shrinkage depending on the site of the lesion. Due to the relatively low response rate, it is also not possible to assume that the observed activity could result in a clinically relevant benefit in terms of progression-free survival or overall survival. In addition, the effects observed for locally advanced disease cannot be easily extrapolated to the metastatic setting as the biology of the two conditions is likely to be different. Thus, the potential clinical importance of the observed activity in the metastatic setting warrants further characterisation before reliable conclusions can be drawn.

2. metBCC is an extremely rare condition and attempts from the Applicant to provide historical data enabling an assessment of putative survival benefit is judged to be non-informative. The SAG was asked if in the absence of a randomized control and informative historical data, an estimation of patient benefit can be based solely on ORR and duration of response.

   SAG answer: Although this is in principle not excluded, there is a need to establish the clinical relevance of the effect observed in terms of response rate and duration of response. See answer to previous question.

3. It is suggested that treatment should continue until stable response, followed by a treatment-free interval until progression with the aim to improve tolerability without loss in efficacy. This recommendation is not based on the design of the study, only on rapid reversibility of adverse reactions when treatment was withdrawn and apparent slow development of resistance. The SAG-O was asked if it is supportive of this recommendation.

   SAG answer: Individual decisions about continuing treatment, based on perceived benefits and tolerability as well as other considerations, are common in clinical practice. However, it is currently difficult to recommend a different approach from the one used in the pivotal study due to the lack of data about other approaches.

   Although the proposed approach has some merit in terms of avoiding unnecessary toxicity when maximal benefit appears to have been reached, one cannot exclude that this might lead to loss of efficacy or even acquiring of resistance. The optimal treatment duration aiming to further improve the benefit-risk is currently uncertain. It is recommended to further assess the proposed intermittent schedule in a prospective clinical trial. In addition, the value of dose escalation for patients not responding and in the absence of unacceptable toxicity should be explored.

Additional efficacy data needed in the context of a conditional MA

Conditional approval is warranted with reference to the need to provide further efficacy data in patients with metastatic BCC (see Benefit-Risk Balance, Uncertainty in the knowledge about the beneficial effects).

2.5.4. Conclusions on the clinical efficacy

In locally advanced BCC, patient benefit has been established. Given the difficulties to evaluate efficacy in mBCC, established benefit can be considered in those metastatic patients who are symptomatic.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- Additional efficacy data on metastatic BCC from final analysis from study MO25616

2.6. Clinical safety

Patient exposure

The assessment of safety is mainly based on data from the pivotal study SHH4476g. Supportive safety information is presented from the exploratory study SHH3925g, supportive safety data from randomized Phase II trials in other oncology indications (i.e., Studies SHH4489g in ovarian cancer and SHH4429g in colorectal cancer), and from a comprehensive clinical pharmacology program.

Table 34: Patient exposure 1 April 2011

Study	Diagnose	Phase	Treatment	Dose	Number of patients	Median duration of treatment (months)
SHH4476g (pivotal)	BCC Locally advanced/ Metastatic	II	Singlearm	150 mg	104 Locally advanced (n=71) Metastatic (n=33)	9.84 (0.7-18.7)
SHH3925	Solid tumours (BCC)	I	Single arm dose escalation	150, 270, 540 mg	68 (33 bcc)	2.4 (0.2-27) Bcc 10.7 (1.2-27) Nonbcc?
SHH4610	Solid tumours	Ib	Dose scheduling	150 mg QD,TIW,QW	63 (1 bcc)	1.7 (0.03-1.8)
SHH4437g	BCC	Open-label extension	Singlearm	150, 300mg QD	13 (from SHH3925g n=12, SHH4610 n=1)	?
SHH4489g	Ovarian cancer (in remission)	II	Vismodegib/Placebo	150mgQD/placebo	104 (52/52)	5.5 (1-16) vismodigib
SHH4429g	Metastatic colorectal carcinoma (first-line)	II	Vismodegib/Placebo in combination with FOLFOX7bevacizumab or FOLFIRI/bevazicumab	150mg QD/placebo	199 (98/101)	6.0 (0.23-25.23) vismodigib 7.51 (0.20-23.66) placebo
SHH4871g	Healthy women (QT)	Ib	Vismodigib Moxifloxacin	150 mg (400 mg Moxifloxacin)	61 (21 vismodigib)	8 days
SHH4683	Healthy women	Ib	PK/Mass balance	150 mg	24	Single dose
SHH4433g	PK	I	Vismodegib	150mg	3	Single dose
SHH4811g	BCC (Ia or met)	Expanded access	Vismodegib	150mg	38	

In the pivotal study 104 patients were treated. The pooled safety population consist of a total of 138 advanced BCC patients from study SHH4476g (n = 104, 75.4%), SHH3925g (n = 33), and SHH4610g (n = 1; 0.7%).

The median duration of treatment was almost 10 months in the pivotal study.

Information was provided in the first update and 72 patients in the pooled safety population was treated >12 months and 49 patients were treated >18 months.

As of the last update per 28 May 2012, 56 (54%) and 37 (36%) of the population in the pivotal study have been treated $\geq$12 and $\geq$18 months respectively. The median duration of treatment is almost 13 months (12.93 months in the total population, 13.27 in the metastatic group and 12.68 in the locally advanced group.)

Adverse events

All patients in the pivotal study population experienced at least one AE, the majority 57.7 % were of grade 1-2. The most common treatment-emergent adverse events were muscle spasms (68.3%), alopecia (63.5%), dysgeusia (51.0%), weight decreased (46.2%), fatigue (35.6%), and nausea (28.8%).

The events clearly related to vismodegib seem to be rather late in appearance with muscle spasms with a median first appearance around day 200 and alopecia around day 100. Other common events are diarrhoea and constipation in around 20% of the patients. The majority of the events, 57%, are of grade 1-2. The most common events of grade > 3 were weight loss in 7.2%, fatigue in 5.8% and muscle spasms in 3.6% of the patients. Grade 3-5 events were reported somewhat more often in the locally advanced group (46.5% vs. 33.3%), this could be attributed to longer duration of treatment.

Although no explicit information regarding the clinical appearance of muscle spasms has been provided, there seems to be a reversibility and most patients seem to endure the muscle spasms as only few quit explicitly due to this adverse event, however in a not negligible number of patients muscle spasms are contributing in some way to study termination.

Twelve cases of squamous epithelial carcinoma of the skin were reported in the pivotal study. Although the intended population is at increased risk for this malignancy the lack of control group makes it hard to evaluate the potential impact of treatment. In total there were 28 cases detected reported on days 96-614, however the majority of events were detected around day 200-300. No cases of squamous epithelial carcinomas are detected in other patients than the BCC population. These patients have risk factors for CuSCC, hence a connection is even more difficult to establish.

In the pivotal study, as well in the other studies, a few additional other cancers are reported; in the pivotal study one case each of oesophageal carcinoma and sarcoma and in the pooled safety population two adenocarcinoma pancreas. There is no obvious pattern with regards to timing or type of malignancies, although the significance of these findings is not yet established.

As the safety population is small the relevance of less common events is hard to establish. One relatively common event was eye disorders reported in 17% in the pivotal study. Events such as keratitis, keratopathy, ulcerative keratopathy, conjunctivitis were reported and although these are different events, eye disorders could be of concern. However, as a comparison the only eye disorder event reported in the colorectal study was increased lacrimation (see discussion), therefore these events are not considered to be translated into ADRs for the moment.

Other events that could be of concern are osteonecrosis and fractures, Hedgehog pathway inhibitors has in pre-clinical studies shown impairment on bone and teeth development. Apart from the apparent risk in case of off label use in children, this could be of concern also in adults as bone is constantly remodelling. Data provided are inconclusive both with regards to preclinical and clinical data, although findings are not clearly indicative of an effect, it cannot be completely ruled out (see discussion).

Arthralgias (15%) and other musculoskeletal events and muscle related events like muscle pain events were commonly reported. As with muscle spasms no clear mechanism of action is described.

In total four thromboembolic events were reported, also syncope/presyncope, hypotension and cardiac events are reported in a few patients.

One study suggests importance of Hh signalling in maintenance of cardiac musculature, furthermore Hh signalling is believed to have a role in maintaining the stemcell niche in the subventricular zone and hippocampus. The clinical implications especially with regards to long-term treatment are not known.

Table 35: Adverse events in the pivotal study SHH4476g (extract)

MedDRA Organ class	BCC locally advanced or metastatic N=104 number (%)	Most common events or events of interest
Blood and lymphatic system disorders	5 (4.8%)	Anemia 5 (4.8%)
Cardiac disorders	8 (7.7%)	AMI 2 (1.9%) Cardiac failure 2 (1.9%) Tachycardia 2 (1.9%)
Eye disorders	18 (17.3%)	Konjunctivitis 3 (2.9%), Visual acuity decreased 3 (2.9%), Keratitis, Keratopathy, Ulcerative keratitis 3 (2.9%), Lacrimation increased 2 (1.9%)
Gastrointestinal disorders	71(68.3%)	Nausea 30 (28.8%) Diarrhoea 23 (22.1%) Constipation 17 (16.3%) Small intestinal obstruction 1 (1%) Tongue spasm 1 (1.0%)
General disorders and administration site conditions	54 (51.9%)	Fatigue 37 (35.6%) Asthenia 9 (8.7%)
Hepatobiliary disorders	1 (1%)	Cholestasis 1 (1%)
Infections and infestations	53 (51%)	Nasopharyngitis 10 (9.6%) Upper respiratory tract infection 7 (6.7%) Pneumonia 4 (3.8%)
Investigations	51 (49%)	Weight decreased 48 (46.2%)
Metabolism and nutrition disorders	30 (28.8%)	Decreased appetite 24 (23.1%)
Musculoskeletal and connective tissue disorders	79 (76%)	Muscle spasm 71 (68.3%) Athralgia 16 (15.4%) Fractures 6 (5.8%) Pain in jaw 2 (1.9%) Osteonecrosis 1 (1.0%)
Neoplasms benign, malignant and unspecified	19 (18.3%)	Squamous cell carcinoma 12 (11.5%) Basosquamous carcinoma 1 (0.7%) Squamous cell carcinoma of the skin 1 (0.7%) Metastatic squamous cell carcinoma 1 (0.7%) Malignant melanoma 1(0.7%) Metastatic malignant melanoma 1 (0.7%) Oesophageal carcinoma 1 (0.7%) Sarcoma 1 (0.7%)
Nervous system diorders	83 (79.8%)	Dysgeusia 53 (51%) Ageusia 12 (11.5%) Hypogeusia 11 (10.6%) Peripheral neuropathy 4(3.8%) Balance disorder 2 (1.9%) Presyncope 1(1%) Syncope 1(1%)
Skin and subcutaneous tissue disorders	80 (76.9%)	Alopecia 66 (63.5%) Actinic keratosis 4 (3.8%) Decubitus ulcer 2(1.9%)
Vascular disorders	15 (14.4%)	Hypotension 3 (2.9%) Deep vein thrombosis 2(1.9%) Hypertension 2 (1.9%) Orthostatic hypotension 1 (1.0%)

Table 36: Incidence of grade ≥3 AEs occurring in more than 2 patients in the pooled safety population.

MedDRA Preferred Term	Highest NCI CTCAE Grade	
	All Grades (n = 138)	Grade ≥ 3
Any NCI CTCAE	138 (100.0%)	61 (44.2%)
Weight decreased	62 (44.9%)	10 (7.2%)
Fatigue	55 (39.9%)	8 (5.8%)
Muscle spasms	99 (71.7%)	5 (3.6%)
Hyponatremia	5 (3.6%)	4 (2.9%)
Death [a]	3 (2.2%)	3 (2.2%)
Pneumonia	6 (4.3%)	3 (2.2%)
Decreased appetite	35 (25.4%)	3 (2.2%)
Dyspnea	12 (8.7%)	3 (2.2%)
Cardiac failure	2 (1.4%)	2 (1.4%)
Keratitis	2 (1.4%)	2 (1.4%)
Gastrointestinal hemorrhage	2 (1.4%)	2 (1.4%)
Pain	12 (8.7%)	2 (1.4%)
Asthenia	11 (8.0%)	2 (1.4%)
Urinary tract infection	7 (5.1%)	2 (1.4%)
Cellulitis	5 (3.6%)	2 (1.4%)
Dehydration	6 (4.3%)	2 (1.4%)
Squamous cell carcinoma	12 (8.7%)	2 (1.4%)
Adenocarcinoma pancreas	2 (1.4%)	2 (1.4%)
Presyncope	2 (1.4%)	2 (1.4%)
Deep vein thrombosis	2 (1.4%)	2 (1.4%)

Notes: Multiple occurrences of a specific adverse event for a patient were counted once at the highest NCI CTCAE grade.

Events occurring after 12 and 18 months of treatment

In the pooled safety population, adverse events occurring ≥ 12 months after treatment initiation with vismodegib were consistent with the overall safety profile of vismodegib, with common adverse events being muscle spasms (36.1%), diarrhoea (25.0%), weight decreased (23.6%), nausea (18.1%), fatigue and constipation (each 13.9%), alopecia (12.5%), and decreased appetite (11.1%)

Adverse events occurring ≥ 18 months after treatment initiation with vismodegib were also consistent with the overall safety profile of vismodegib, with the most common adverse events being muscle spasms (24.5%), diarrhoea (18.4%), weight decreased (12.2%), nausea (8.2%), fatigue (14.3%), constipation (10.2%), and alopecia (10.2%)

The majority of events both after 12 and 18 months were of grade 1-2.

Table 37: Treatment-Emergent Adverse Events of Any Grade Occurring in ≥ 10% of All Treated Patients in Study SHH4476g: All Treated Patients

MedDRA Preferred Term	Metastatic BCC (n=33)	Locally Advanced BCC (n=71)	All Patients (n=104)
Any adverse events	33 (100.0%)	71 (100.0%)	104 (100.0%)
Muscle spasms	22 (66.7%)	52 (73.2%)	74 (71.2%)
Alopecia	21 (63.6%)	47 (66.2%)	68 (65.4%)
Dysgeusia	23 (69.7%)	34 (47.9%)	57 (54.8%)
Weight decreased	15 (45.5%)	38 (53.5%)	53 (51.0%)
Fatigue	14 (42.4%)	30 (42.3%)	44 (42.3%)
Nausea	11 (33.3%)	23 (32.4%)	34 (32.7%)
Decreased appetite	11 (33.3%)	17 (23.9%)	28 (26.9%)
Diarrhea	9 (27.3%)	19 (26.8%)	27 (26.9%)
Constipation	7 (21.2%)	13 (18.3%)	20 (19.2%)
Cough	9 (27.3%)	11 (15.5%)	20 (19.2%)
Vomiting	7 (21.2%)	11 (15.5%)	18 (17.3%)
Arthralgia	4 (12.1%)	13 (18.3%)	17 (16.3%)
Headache	4 (12.1%)	11 (15.5%)	15 (14.4%)
Nasopharyngitis	3 (9.1%)	10 (14.1%)	13 (12.5%)
Squamous cell carcinoma	3 (9.1%)	9 (12.7%)	12 (11.5%)
Ageusia	2 (6.1%)	10 (14.1%)	12 (11.5%)
Hypogeusia	3 (9.1%)	8 (11.3%)	11 (10.6%)

Table 38: Grade 3-5 Treatment-Emergent Adverse Events of Any Grade Occurring in 2 or More Patients Overall in Study SHH4476g: All Treated Patients

MedDRA Preferred Term	Metastatic BCC (n=33)	Locally Advanced BCC (n=71)	All Patients (n=104)
Any Grade 3–5 adverse events	14 (42.4%)	40 (56.3%)	54 (51.9%)
Weight decreased	1 (3.0%)	6 (8.5%)	7 (6.7%)
Muscle spasms	0	6 (8.5%)	6 (5.8%)
Fatigue	2 (6.1%)	3 (4.2%)	5 (4.8%)
Pneumonia	1 (3.0%)	3 (4.2%)	4 (3.8%)
Syncope	2 (6.1%)	2 (2.8%)	4 (3.8%)
Diarrhea	1 (3.0%)	2 (2.8%)	3 (2.9%)
Asthenia	1 (3.0%)	2 (2.8%)	3 (2.9%)
Death	1 (3.0%)	2 (2.8%)	3 (2.9%)
Decreased appetite	1 (3.0%)	2 (2.8%)	3 (2.9%)
Cellulitis	2 (6.1%)	1 (1.4%)	3 (2.9%)
Squamous cell carcinoma	1 (3.0%)	2 (2.8%)	3 (2.9%)
Gastrointestinal hemorrhage	0	2 (2.8%)	2 (1.9%)
Pain	1 (3.0%)	1 (1.4%)	2 (1.9%)
Dyspnea	2 (6.1%)	0	2 (1.9%)
Deep vein thrombosis	1 (3.0%)	1 (1.4%)	2 (1.9%)
Cardiac failure	0	2 (2.8%)	2 (1.9%)
Fall	0	2 (2.8%)	2 (1.9%)
Hip fracture	1 (3.0%)	1 (1.4%)	2 (1.9%)
Amenorrhea	0	2 (2.8%)	2 (1.9%)

Safety data from supportive studies.

In the study SHH4489g (ovarian cancer) 98.1% of patients in the vismodegib group and 86.5% of the patients in the placebo group experienced an AE, in the study SHH4429g (metastatic colorectal cancer) the numbers were 99 and 100% respectively.

Table 39:

MedDRA Preferred Term	Placebo: Ovarian (n = 52)	Vismodegib Ovarian (n = 52)	Placebo Colorectal (n=98)	Vismodegib Colorectal (n=98)	Vismodegib: aBCC (n = 104)
Adverse event of any NCI CTCAE grade	45 (86.5%)	51 (98.1%)	97(99%)	(100%)	104 (100.0%)
Muscle spasms	1.9%	67.3%	2%	16.3%	68.3%
Alopecia	7.7%	53.8%	18.4%	19.4%	63.5%
Dysgeusia	17.3%	67.3%	9.2%	41.8%	51.0%
Fatigue	**28.8%**	**26.9%**	72.4%	68.4%	35.6%
Weight decreased	1.9%	11.5%	36.7%	45.9%	46.2%
Nausea	17.3%	32.7%	62.2%	62.2%	28.8%
Cardiac disorders	0	3.8%	0	0	7.7%
Eye disorders	1.9%	5.8%	15.3%	16.3%	17.3%
Neoplasms	0	1.9%	0	0	18.3%
Osteonecrosis	0	0	0	0	1%
Pain in jaw	1.9%	0	0	0	1.9%
Presyncope/Syncope	0	1,9%	3.1%	6.1%	2%
Deep vein thrombosis/ Pulmonary embolism	0	3.8%	12.2%	15.3%	3.8%

In the safety update (data cut off date, 28 Nov 2011; pooled safety population), further information was added from the expanded access study **SHH4811g** and 150 patients from the global safety study **MO25616**.

Table 40:

	Pooled Safety Population [a] (n = 138)	Study SHH4811g (n = 97)	Study MO25616 (n=150)
Adverse events	138 (100.0%)	90 (92.8%)	143 (95.3%)
Serious adverse events	43 (31.2%)	12 (12.4%)	22 (14.7%)
Grade ≥ 3 adverse events	71 (51.4%)	21 (21.6%)	56 (37.3%)
Grade 5 adverse events	8 (5.8%)	0	6 (4.0%)
Adverse events leading to discontinuation of study drug	22 (15.9%)	4 (4.1%)	18 (12.0%)
All deaths	25 (18.1%)	1 (1.0%)	8 (5.3%)

Serious adverse event / deaths / other significant events

In the pivotal study as of data cut off date, 26 November 2010, serious adverse events occurred in 26 patients overall (25%), of these seven (21.2%) in the metastatic population and 19 (26.8%) in the locally advanced population.

The most common SAEs in the pivotal study were infections 4.8%, neoplasms 4.8%, vascular disorders 4.8%, cardiac disorders 3.8% and nervous system disorders 3.8%.

Table 41:

MedDRA	Bcc pivotal study SHH4476g N=104	Bcc pivotal study SHH4476g metastatic n=33	Bcc pivotal study SHH4476g Locally advanced n=71	Bcc pooled safety population N=138
Any SAE	26(25.0%)	7 (21.2%)	19 (26.8%)	36 (26.1%)
Death [a]	3 (2.9%)	1 (3.0%)	2 (2.8%)	3 (2.2%)
Pneumonia	2 (1.9%)	0	2 (2.8%)	3 (2.2%)
Cardiac failure	2 (1.9%)	0	2 (2.8%)	2 (1.4%)
Gastrointestinal hemorrhage	1 (1.0%)	0	1 (1.4%)	2 (1.4%)
Pulmonary embolism	2 (1.9%)	0	2 (2.8%)	2 (1.4%)
Deep vein thrombosis	2 (1.9%)	1 (3.0%)	1 (1.4%)	2 (1.4%)
Hemorrhage	1 (1.0%)	0	1 (1.4%)	2 (1.4%)

In the **pivotal study** also other cardiac serious adverse events like acute myocardial infarction, angina pectoris, myocardial infarction, restrictive cardiomyopathy and vascular/ neurologic events such as hypotension, orthostatic hypotension, syncope and hypovolemic shock occurred in singular cases. In total six tumours were reported in four patients (malignant melanoma, metastatic malignant melanoma, squamous cell carcinoma, metastatic squamous cell carcinoma, esophageal carcinoma and sarcoma).

Deaths

Seven metastatic BCC patients and nine locally advanced patients had died as of the primary cutoff date, in metastatic patients' progressive disease was the most frequent cause of death (n = 5). In the locally advanced cohort four died from adverse events and one patient because of progressive disease within 30 days of treatment. The corresponding Grade 5 serious adverse events were hypovolemic shock, acute myocardial infarction, meningeal disorder and "death of unknown cause". Four patients died >30 days post-treatment. Two were deaths of unknown cause and one ischaemic stroke, one patient died from disease progression.

At the last update, cut-off date 29 May 2012, there were in total 27 deaths reported, 15 in the metastatic population and 12 in the locally advanced group. In total 6 deaths were reported on or within 30 days of treatment and 21 were reported in follow up. The majority of events were progressive disease (11 in the metastatic group and 4 in the locally advanced group). Seven of the deaths were due to adverse events (one in the metastatic group and six in the locally advanced group.

Laboratory findings

A number of anaemias were reported as AEs. In preclinical data decreased platelets were observed.

An increase in cholesterol was seen in both rats and dogs. In total cholesterol was recorded in 42 patients and hypercholesterolemia was found in 3.

Hyponatraemia seems to be the most common laboratory abnormality grade 1 and was reported in about 30 % of the patients and grade $\geq$ 3 (Na 120-130mmol/l) in about 5% of the patients.

There is an increase in hepatic parameters in about 20% of the patients; however no patient met the criteria for Hy's law.

The major finding in vital signs is weight loss, with a median decrease of 5.7 kg.

The QT study in 61 women did not show any meaningful change in QTc compared to baseline. The dosing was discussed and deemed sufficient. There were no preclinical signals with regards to QT.

The QT study in 61 women dosed with 150 mg vismodegib once daily for seven days did not show any meaningful change in QTc compared to baseline. The dosing was discussed and deemed sufficient. There were no preclinical signals with regards to QT.

Safety in special populations

Age

In the pooled safety population the majority of patients were <65 years old.

AEs with a more >10% difference between age groups (pooled safety population).

Table 42:

	Vismodegib (n = 138)	
MedDRA Preferred Term	< 65 yrs (n = 84)	≥ 65 yrs (n = 54)
Muscle spasms	64 (76.2%)	35 (64.8%)
Alopecia	63 (75.0%)	25 (46.3%)
Diarrhea	28 (33.3%)	12 (22.2%)
Appetite decreased	18 (21.4%)	17 (31.5%)
Cough	20 (23.8%)	6 (11.1%)
Musculoskeletal chest pain	9 (10.7%)	0
Squamous cell carcinoma	4 (4.8%)	8 (14.8%)

The most common events had a higher incidence in younger patients (<65 years old), but the grade ≥3 events were more common in the older age group. More squamous epithelial carcinoma, cough and cardiac events are reported in the older age group. This could in part be related to age. Overall no major differences were seen.

Sex

About one third of the patients were female.

More nausea and vomiting is reported in the female population, in general regarding chemotherapies women have a higher degree of nausea and vomiting. Furthermore more pain in extremities is seen in the female group. More female patients experienced grade ≥3 adverse events. No major clinically relevant differences were shown.

Renal and hepatic impairment

Not studied, data from a study in renal and hepatic impairment will be available in March 2015 (see conditions).

Children

Not studied. Children are not affected by BCC if they do not have Gorlin syndrome.

There are limited data on bone and teeth formation of uncertain significance from a paediatric study (PBTC-025) on medulloblastoma.

Immunological events

This part was not specifically analysed by the applicant. However, especially in study SHH4489g some AEs as rash and pruritus were reported.

Safety related to drug-drug interactions and other interactions

There are currently no relevant *in vivo* interaction data for vismodegib, but only *in vitro* data and the metabolism of vismodegib has not been fully elucidated. A reduced concentration of contraceptive hormones of 10-20% cannot be excluded. With regards to teratogenicity this is of concern.

Discontinuation due to adverse events

Table 43: Reasons for discontinuations pivotal study all patients

Disposition	Metastatic BCC (n=33)	Locally Advanced BCC (n=71)	All Patients (n=104)
Patients still on treatment	19 (57.6%)	32 (45.1%)	51 (49.0%)
Discontinued treatment			
Total	14 (42.4%)	39 (54.9%)	53 (51.0%)
Adverse event	1 (3.0%)	11 (15.5%)	12 (11.5%)
Death	1 (3.0%)	2 (2.8%)	3 (2.9%)
Lost to follow-up	2 (6.1%)	1 (1.4%)	3 (2.9%)
Physician's decision to discontinue treatment	2 (6.1%)	1 (1.4%)	3 (2.9%)
Patient's decision to discontinue treatment	2 (6.1%)	18 (25.4%)	20 (19.2%)
Disease progression	6 (18.2%)	5 (7.0%)	11 (10.6%)
Other	(0.0%)	1 (1.4%)	1 (1.0%)

Muscle spasms accounted for discontinuation in 2 patients. All other events were singular. However there are about 20% of the patients leaving study due to "own decision". A total of 30 patients in Study SHH4476g discontinued treatment because of "patient decision" or "physician decision." In these cases site interviews were conducted to determine the underlying reasons for discontinuations. Based on the interviews, the most common reasons for treatment discontinuation were described as "prolonged AEs are intolerable" (36.7%), "other" (26.7%), and "logistic challenges with travel and treatment" (20.0%).

Adverse Drug Reactions.

Table 44: Listing of ADRs

MedDRA SOC	Very Common (%)	Common (%)
Metabolism and nutrition disorders	Decreased appetite (29%)	Dehydration (5.1%)
Nervous system disorder	Dysgeusia (57.2%) Ageusia (10.9%)	Hypogeusia (8.7%)
Gastrointestinal disorders	Nausea (34.8%) Diarrhoea (32.6%) Constipation (23.2%) Vomiting (15.9%)	Dyspepsia (9.4%) Upper abdominal pain (5.8%) Abdominal pain (5.8%)
Skin and subcutaneous tissue disorders	Alopecia (65.2%) Pruritus (10.1%)	Rash (9.4%) Madarosis (4.3%) Abnormal hair growth (4.3%)
Musculoskeletal and connective tissue disorders	Muscle spasms (74.6%)	Arthralgia (16.7%) Pain in extremity (10.1%) Back pain (10.1%) Musculoskeletal chest pain (8.0%) Myalgia (5.8%) Flank pain (3.6%) Musculoskeletal pain (3.6%)
Reproductive system and breast disorders	Amenorrhea* (30%)	
General disorders and administration site conditions	Weight decreased (48.6%) Fatigue (44.9%)	Pain (9.4%) Asthenia 12 (8.7%)

All reporting is based on ADRs of all grades using National Cancer Institute - Common Terminology Criteria for Adverse Events v3.0 except where noted.

*Of the 138 patients with advanced BCC, 10 were women of child bearing potential. Amongst these women, amenorrhea was observed in 3 patients (30 %).

MedDRA = Medical Dictionary for Regulatory Activities.

Additional information

A case report was received informing of a female patient of non-child-bearing potential, enrolled on an investigator-sponsored study who experienced persistent alopecia. Upon analysis, blood concentration of vismodegib at 11 months post-treatment was 2.5 µM. A second sample from the same patient at 14 months post-treatment showed no quantifiable vismodegib levels (see Clinical Pharmacology). Based on the analysis of the second sample, it was considered that results from the first sample was unlikely to have occurred 11 months post-treatment discontinuation. No postmarketing data were submitted.

2.6.1. Discussion on clinical safety

As vismodegib is a first in class compound, no background data can be drawn from class effects. The safety data base is limited with regards to numbers treated in the sought indication, the pivotal study is a single arm study that included 104 patients and further 34 further patients with advanced BCC are included in the pooled safety population.

Information regarding 150 patients from the global safety study MO25616 and about 97 patients from expanded access study SHH4811 is provided. Both grade 1-2 and grade 3-4 events as well as SAEs are reported in a markedly lower frequency compared to the pivotal study. This could have different explanations one of which is shorter duration of therapy. The safety information that could be obtained

from other oncologic studies is of limited importance mainly because of the much shorter duration of the treatment (5 vs. 10 months), but also with regards to clearly different populations.

The dose intensity was high, over 95% in the pivotal study, and only about 11% discontinued treatment due to adverse events indicating that the regimen is tolerable. However adverse events were a contributing factor also in cases reported as patient´s decision.

In humans a defect in Hedgehog signalling can give rise to severe foetal malformations such as failure of forebrain development, microcencephaly, cyclopia or absent nose. The teratogenicity is of great concern although the women in the intended population are mainly of non-reproductive potential. As vismodegib is found in semen, warnings on pregnancy prevention concern also female partners of men treated with vismodegib. The indication sought may also include patients with locally advanced tumours that can be inoperable due to location, but small and not life threatening per se. It is expected that the majority of patients will have a locally advanced disease and not metastatic disease. As a consequence, a contraindication in pregnancy and a pregnancy prevention plan are included (see also Clinical Pharmacology).

The most common adverse events in the pivotal study were muscle spasms 68.3%, alopecia 63.5%, dysguesia 51.0%, weight decreased 46.2%, fatigue 35.6% and nausea 35.6%. Also similar events as ageusia (11.5%), hypogeusia (10.6%) and asthenia 8.7% were common. The vast majority of these events were of grade 1-2. Weight decrease in 7.2% of the patients was the most common grade 3 event. Other common events were constipation, diarrhoea and decreased appetite, reported in about 20% each and arthralgia reported in 15% in the pivotal study. Further muscular events like muscle pain, myalgia, back pain and similar were reported in 3-6% of patients each. Preclinical data has also shown impaired fertility. In the safety population about 30% premenopausal women became amennorhoic.

Neoplasms were reported in 19 patients (18.3%) in the pivotal study, the absolute majority were squamous epithelial carcinomas of the skin. Compared to the 3-year risk of developing a SCC after a BCC of about 6% at 3 years or lower [13] the numbers detected in the studies was higher, furthermore there are preclinical findings with regards to pilomatricomas in rats that could be related to effect on hair follicles but this is not fully elucidated. Squamous epithelial carcinomas are when detected early amenable to surgical excision. Recommendations are included in the SmPC to alert the treating physician to this event.

Both in the pivotal study and in other studies malignancies have been reported such as pancreatic carcinoma, esophageal carcinoma, sarcoma and adenocarcinoma of the lung. Second primary malignancies are added as a potential risk in the RMP and will be followed in the safety study MO25616.

Eye disorders were reported in 17.3% in the pivotal study. Many different events were reported both symptomatic like “eye irritation”, “eye pain” and “eye swelling” and diagnoses like keratitis, keratopathy and ulcerative keratitis. Hedgehog signalling has been proposed to be involved in corneal epithelial cell proliferation. Keratitis is addressed as a potential risk in the RMP and will be adjudicated by the data safety monitoring board in the safety study MO25616.

With regards to preclinical data on bone and teeth development, rare events of “pain in jaw” 1.9%, osteonecrosis (1.9%) and fractures were observed. There were clear data on impaired bone development in the postnatal period in animals and as bone is constantly remodelling this could tentatively also have impact in adult bone tissue. Fractures are addressed as potential risk in the RMP, including additional pharmacovigilance activities (see Pharmacovigilance). There are data on bone and teeth of uncertain significance from a paediatric study (PBTC-025) on medulloblastoma. Exposure to vismodegib in the post-natal period in children may have effects on dentition, but any effect on teeth

may not be apparent until eruption of the adult teeth. Information regarding preclinical findings is added in the SmPC.

In total four thromboembolic events were reported, also syncope/presyncope and cardiac events are reported in a few patients, these events are discussed in the context of hedgehog signalling. As an example Hedgehog signalling has been implicated to have a complex role in ischaemic tissue repair for example in myocardial ischaemia. Venous thromboembolic events are included as potential risks in the RMP (see Pharmacovigilance).

There did not seem to be any clinically relevant differences with regards to sex or age >/< 65 years. Other ethnic populations apart from white and special populations with hepatic or renal impairment were not studied. Data on cancer patients with hepatic or renal impairment will be available post-authorisation (see Pharmacovigilance).

With regards to laboratory abnormalities, the most common event was hyponatremia reported in about 30% of the patients, and of grade ≥3 (<130-120 mmol /l) in about 5% of the patients. In about 20% of the patients there was an increase in transaminases, this was mostly grade 1-2, the issue is addressed in the RMP. The adverse events associated with vismodegib treatment have been adequately reflected in the SmPC.

Additional expert consultations

The following questions related to safety were posed to the SAG-Oncology meeting of 9 January 2013.

Vismodigib targets fundamental mechanisms related to stem cell proliferation, largely of unknown importance in adults. To this should be added a very small safety database, especially with respect to number of patients treated long-term.

- The SAG-O was asked if the available safety data are considered sufficient to support licensure

SAG-O Answer: The available data are considered sufficient for assessing the overall toxicity profile and the benefit-risk balance. Overall, in view of the established clinical benefit in locally advanced disease, the toxicity profile is considered acceptable.

- The SAG-O was asked if it would be acceptable to achieve further safety data post marketing in the context of a post-approval safety study.

Additional post marketing toxicity data, including longer term data are necessary due to the new mechanism of action, the limited safety database, the observed toxicity and risks. The post-approval safety study should include careful assessment of the risk of developing second malignancies based on a sufficiently long follow-up. In addition, relatively infrequent symptoms for other anticancer therapies, such as muscle spasm and keratitis, necessitate comprehensive clinical and biological characterization. Also, the possible interference with stem cell function and regeneration of damaged tissues requires thorough evaluation, including long-term follow-up. Lastly, it is recommended to assess if an intermittent schedule could be associated with a more favourable toxicity profile, including long-term toxicity.

Additional safety data needed in the context of a conditional MA

The applicant should provide a safety update of the pooled safety population, a final report from SHH4476g (pivotal study) and an interim analysis of a global safety MO25616 of 500 patients with a final report after projected enrolment of 800 patients. The initial primary objective is to assess the safety of vismodegib (GDC-0449) in patients with locally advanced or metastatic BCC. Cases of

squamous cell carcinoma, death, fracture and keratitis will be monitored and patients with amenorrhea will be evaluated.

Conclusions on the clinical safety

The available data are considered sufficient for assessing the overall toxicity profile and the benefit-risk balance. Overall, in view of the established clinical benefit in locally advanced disease, the toxicity profile is considered acceptable.
To increase the safety data base the global safety study MO25616 is planned to include more than 1000 patients over 3.5 years with a projected analysis of 500 patients treated > 12 months by 2014.

The common side effects like muscle spasms, alopecia, taste disorders and weight decreased seem to be manageable/ tolerable in the proposed dosing.

With regards to more uncommon side effects, including neoplasms (particularly squamous epithelial carcinoma of the skin), eye disorders, syncope, thromboembolic events and cardiac events will be further followed in the RMP as potential risks and in the safety study MO25616.

Hedgehog signalling is of known importance in embryonal development. Severe teratogenicity is well established in preclinical models, in humans a defect in Hedgehog signalling can give rise to severe foetal malformations such as failure of forebrain development, microcencephaly and cyclopia. This important identified risk requires additional pharmacovigilance activities and risk minimisation activities (see Pharmacovigilance).

The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA:

Further data on long-term safety:

- The applicant should provide a safety update of the pooled safety population, a final SHH4476g (pivotal study) and an interims analysis of study MO25616 of 500 patients with a potential one year follow up by June 2014.

Further data on safety:

- Final analysis of MO25616.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

Table 45 Summary of the Risk Management Plan

Safety Concern	Pharmacovigilance Activities (Routine and Additional Pharmacovigilance)	Risk Minimisation Activities (Routine and Additional)
Important Identified Risks		
Teratogenicity	Routine pharmacovigilance: • Examination of demographic data in PSURs by country • Cumulative and periodic review in all PSURs Additional pharmacovigilance activities: • Monitoring of implementation of Erivedge Pregnancy Prevention Programme on a country-specific basis in accordance with the local legal framework. • Expedited reporting of all pregnancies as a serious event • Global centralised data collection (safety database) and reporting of pregnancies by Pregnancy report forms in Physician education brochures • Follow-up of all pregnancies until outcome and until final diagnosis for cases of congenital malformation	SmPC Sections 4.3, Contraindications; 4.4, Special warnings and precautions for use; 4.6, Fertility, pregnancy and lactation; and 5.3, Preclinical safety data. Pregnancy Prevention Programme • Educational brochure for physicians • Educational brochure for patients • Patient reminder card • Healthcare provider reminder card • Contraceptive measures • Recommended regular pregnancy testing for women of child-bearing potential • Procedures will be applied to all Roche-sponsored studies and all compassionate use programmes.
Muscle spasms	Routine Pharmacovigilance: • Reporting of cases of muscle spasms • Examination of demographic data in PSURs by country • Cumulative and periodic review in all PSURs	SmPC Sections 4.8, Undesirable effects;
Important Potential Risks		
Post-natal developmental defects	Routine Pharmacovigilance: • Reporting of all cases of post-natal developmental defects • Examination of demographic data in PSURs by country • Cumulative and periodic review in all PSURs Additional pharmacovigilance activities None	SmPC Sections 4.2, Posology and 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.
Impairment of fertility	Routine Pharmacovigilance: • Reporting of cases of impairment of fertility • Examination of demographic data in PSURs by country	SmPC Section 4.4, Special warnings and precautions for Use; Section 4.6, Fertility, pregnancy, and

Safety Concern	Pharmacovigilance Activities (Routine and Additional Pharmacovigilance)	Risk Minimisation Activities (Routine and Additional)
	• Cumulative and periodic review in all PSURs Additional pharmacovigilance activities • Monitoring and follow-up of amenorrhea cases reported from clinical trials and in spontaneous safety reports, which will be adjudicated by an independent internal expert group. • Clinical investigations within MO25616, when possible, for evaluation of patients with irregular menses or amenorrhea including abdominal ultrasound and serum hormone evaluation • Nonclinical fertility studies are planned to further characterise this risk • Reporting of all events of amenorrhoea in the RegiSONIC study	lactation, Section 5.3, Preclinical safety data Package Leaflet The package leaflet provides information to the user that is consistent with the SmPC.
Second primary malignancies	Routine Pharmacovigilance • Reporting of cases of second primary malignancy • Examination of demographic data in PSURs by country • Cumulative and periodic review in all PSURs Additional Pharmacovigilance • Nonclinical carcinogenicity studies are planned to further characterise this risk. • Adjudication of second primary malignancies reported in MO25616 by an expert group for independent opinion • Reporting from the RegiSONIC study of second primary malignancies that have been identified by the investigator as serious adverse events.	SmPC and Package Leaflet: 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.
Squamous cell carcinoma	Routine Pharmacovigilance • Reporting of cases of squamous cell carcinoma • Examination of demographic data in PSURs by country • Cumulative and periodic review in all PSURs Additional Pharmacovigilance • Nonclinical carcinogenicity studies are planned to further characterise this risk	SmPC and Package Leaflet: 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.

Safety Concern	Pharmacovigilance Activities (Routine and Additional Pharmacovigilance)	Risk Minimisation Activities (Routine and Additional)
	• Adjudication of cases by an independent internal group • Adjudication of events of squamous cell carcinoma reported in MO25616 by an expert group for independent opinion • Reporting from the RegiSONIC study of squamous cell carcinomas that have been identified by the investigator as serious adverse events.	
Death NOS/Sudden death/Cardiac death	Routine Pharmacovigilance • Reporting of cases of sudden cardiac death • Examination of demographic data in PSURs by country • Cumulative and periodic review in all PSURs Additional Pharmacovigilance • Adjudication of cases by an independent internal group • Adjudication of events of death NOS/sudden death/cardiac death in MO25616 to an expert group for independent opinion • Reporting of events of death NOS/sudden death/cardiac death as serious adverse events in the RegiSONIC study.	SmPC and Package Leaflet: 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.
Off-label use in paediatric medulloblastoma	Routine pharmacovigilance: • Reporting of all adverse events associated with off-label use in paediatric medulloblastoma • Examination of demographic data in PSURs by country • Cumulative and periodic review in all PSURs	SmPC Section 4.2, Posology and method of administration, Section 4.3, Special populations, Section 4.4 Special warnings and precautions for Use; Section 4.6, Fertility, pregnancy, and lactation, Section 5.3, Preclinical safety data Package Leaflet Section 2 Children and adolescents
Off-label use in BCC appropriate for treatment with surgery or radiotherapy	Routine pharmacovigilance: • Reporting of all adverse events associated with off-label use in BCC appropriate for treatment with surgery or radiotherapy • Examination of demographic data in PSURs by country • Cumulative and periodic review in all PSURs	SmPC Section 4.2, Posology and method of administration, Section 4.4, Special warnings and precautions for Use; Section 5.3, Preclinical safety data Package Leaflet Section 1 What is Erivedge
Off-label use in other	Routine pharmacovigilance:	SmPC

Safety Concern	Pharmacovigilance Activities (Routine and Additional Pharmacovigilance)	Risk Minimisation Activities (Routine and Additional)
cancers	• Reporting of all adverse events associated with off-label use in cancers other than BCC. • Examination of demographic data in PSURs by country • Cumulative and periodic review in all PSURs <u>Additional pharmacovigilance activities</u> None	Section 4.2, Posology and method of administration, Section 4.4, Special warnings and precautions for Use; Section 5.3, Preclinical safety data <u>Package Leaflet</u> Section 1 What is Erivedge and what is it used for
Keratitis / ulcerative keratitis	<u>Routine pharmacovigilance:</u> • Reporting of cases of keratitis • Examination of demographic data in PSURs by country • Cumulative and periodic review in all PSURs <u>Additional pharmacovigilance activities:</u> • Adjudication of events reported in MO25616 by an expert group for independent opinion • Reporting of events of keratitis/ulcerative keratitis that qualify as serious adverse events in the RegiSONIC study.	<u>SmPC and Package Leaflet:</u> 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.
Fracture	<u>Routine pharmacovigilance:</u> • Reporting of cases of fracture • Examination of demographic data in PSURs by country • Cumulative and periodic review in all PSURs <u>Additional pharmacovigilance activities:</u> • Adjudication of events reported in MO25616 to an expert group for independent opinion • Reporting of events of fracture that qualify as serious adverse events in the RegiSONIC study.	<u>SmPC and Package Leaflet:</u> 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.
Venous thromboembolic events	<u>Routine pharmacovigilance:</u> • Reporting of cases of VTEs • Examination of demographic data in PSURs by country • Cumulative and periodic review in all PSURs	<u>SmPC and Package Leaflet:</u> These documents highlight the risks associated with the use of Erivedge. Erivedge labeling documents will be updated with information specific to

Safety Concern	Pharmacovigilance Activities (Routine and Additional Pharmacovigilance)	Risk Minimisation Activities (Routine and Additional)
	Additional pharmacovigilance activities: • Reporting of all venous thromboembolic events (specifically DVT and PE) in the RegiSONIC study	this risk as appropriate on the basis of data obtained from pharmacovigilance activities.
Syncope	Routine Pharmacovigilance: • Reporting of all cases of syncope • Examination of demographic data in PSURs by country • Cumulative and periodic review in all PSURs Additional pharmacovigilance activities • Reporting of events of syncope that qualify as serious adverse events in the RegiSONIC study.	SmPC and Package Leaflet: 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.
Hyponatremia	Routine Pharmacovigilance: • Reporting of all cases of hyponatremia • Examination of demographic data in PSURs by country • Cumulative and periodic review in all PSURs Additional pharmacovigilance • Monitoring of laboratory result changes, including hyponatremia, in Study MO25616.	SmPC and Package Leaflet: SmPC Section 4.8, Undesirable effects (not an identified ADR)
Missing information		
Use in hepatic impairment	Routine pharmacovigilance • Analysis and reporting of adverse events in patients with hepatic impairment in. • Examination of demographic data in PSURs by country • Cumulative and periodic review in all PSURs Additional pharmacovigilance Additional studies • Study GP27839, an ongoing Roche-sponsored Phase Ib open-label pharmacokinetics and safety study of vismodegib in patients with advanced solid malignancies, including hepatocellular carcinoma, with varying degrees of renal or hepatic function.	SmPC Sections 4.2, Posology and method of administration; and 5.2, Pharmacokinetic properties.
Use in renal impairment	Routine pharmacovigilance • Analysis and reporting of adverse events in patients with renal impairment.	SmPC Sections 4.2, Posology and method of administration; and 5.2, Pharmacokinetic properties.

Safety Concern	Pharmacovigilance Activities (Routine and Additional Pharmacovigilance)	Risk Minimisation Activities (Routine and Additional)
	• Examination of demographic data in PSURs by country • Cumulative and periodic review in all PSURs Additional pharmacovigilance • Study GP27839, an ongoing Roche-sponsored Phase Ib open-label pharmacokinetics and safety study of vismodegib in patients with advanced solid malignancies, including hepatocellular carcinoma, with varying degrees of renal or hepatic function.	Additional studies GP27839 is a Roche-sponsored Phase Ib study of vismodegib in patients with varying degrees of renal or hepatic function.
Interaction with other medications	Routine pharmacovigilance • Specific analysis of any identified interactions in PSURs. • Cumulative and periodic review in all PSURs • Examination of demographic data in PSURs by country Additional pharmacovigilance: • Despite the low potential for DDI, Roche will conduct an in vivo study, GP28465, studying the effect of a proton pump inhibitor, a CYP3A4/P-gp inhibitor, and an inhibitor of CYP2C9, on the PK of vismodegib. • A second drug-drug interaction study is being planned to investigate the effect of vismodegib on the exposure of oral contraceptives	SmPC Section 4.3, Contraindications, Section 4.4, Special warnings and precautions for use, and Section 4.5, Interaction with other medicinal products and other forms of interaction. Package Leaflet Section 2 Other medicines and Erivedge
Long-term use of vismodegib in patients with advanced BCC (locally advanced and metastatic BCC)	Routine pharmacovigilance • Specific analysis in PSURs of adverse events that occur in patients who have long-term (over one year) usage of vismodegib. • Examination of demographic data (age and gender) in PSURs by country. Additional pharmacovigilance • Final analysis of Study SHH4476g at study closure, corresponding to 30 months of additional follow-up beyond primary analysis. • Interim analysis of MO25616 after 500 patients (including patients with mBCC) have had the potential to be treated for 1 year	SmPC Sections 4.2, Posology and method of administration

Safety Concern	Pharmacovigilance Activities (Routine and Additional Pharmacovigilance)	Risk Minimisation Activities (Routine and Additional)
	on vismodegib. • MO25616 CSR will include: o -Resolution of adverse events after treatment discontinuation o -PK obtained in patients with persistent adverse event	
Vismodegib exposure after discontinuation of treatment	Additional pharmacovigilance: • PK cohort in MO25616.	SmPC and Package Leaflet: 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.

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities (table 45) in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Table 46: Additional pharmacovigilance activities (summarized here, please refer to details as described in detail Table 44):

Description	Due date
In vivo drug interactions with:	In vivo study GP28465 Feb 2015
- CYP2C9 inhibitor and based on the obtained results discuss a) the exposure in CYP2C9 PMs, and b) whether any specific treatment recommendations are needed for CYP2C9 inhibitors - a potent CYP3A4 and Pgp inhibitor and based on the *in vivo* inhibition studies (CYP2C9 and 3A4) to discuss how much of the elimination that has been characterised and whether additional studies are needed. - DDI with drugs increasing gastric pH. (Evaluations should be based on unbound concentrations.)	
In vitro evaluation whether vismodegib is a substrate for or an inhibitor of the hepatic transporters OATP1B1 and OATP1B3	June 2014
Interaction study (planning is ongoing) with an oral contraceptive having duration of the vismodegib treatment of at least 21 days.	12/2018
Impairment of fertility: Preclinical study The potential effect of vismodegib on fertility and other reproductive parameters (including hormone measurements in females) will be evaluated following chronic administration to male and female rats. Study expected to begin in 2013	Final study report: 10/2015
Impairment of fertility: Amenorrhoea	

Description	Due date
Amenorrhoea in clinical trials • Monitoring and follow-up of amenorrhea cases reported from clinical trials Specific information on hormonal tests with regards to amenorrhoea • Clinical investigations when possible within MO25616 for evaluation of patients with irregular menses or amenorrhea including abdominal ultrasound and serum hormone evaluation. Serum hormone evaluation should include ▪ follicle-stimulating hormone (FSH) ▪ luteinizing hormone (LH), ▪ estradiol (E2), ▪ thyroid stimulating hormone (TSH).	MO25616: Interim: 06/14 CSR in 2015 RegiSONIC study report Dec 2020
Nonclinical carcinogenicity study The carcinogenic potential of vismodegib will be evaluated in a 26-week carcinogenicity bioassay in the rasH2 transgenic mouse model and a 2-year carcinogenicity bioassay in Sprague Dawley rats	Study Reports: Oct 2017
PK substudy (within the safety study) to further evaluate the time for washout of vismodegib after treatment discontinuation	MO25616- CSR in 2015
Adverse events	MO25616: Interim: 06/14 CSR in 2015 RegiSONIC study report Dec 2020
Second primary malignancies: Reporting events of second primary cancer Specifically for squamous cell carcinoma: Reporting events of squamous cell carcinoma	
Sudden cardiac death : Reporting of all events of death/sudden death/cardiac death as serious adverse events.	
Syncope : Reporting of events of syncope	
Hyponatraemia: Monitoring of laboratory result changes	
Fractures : Reporting of events of fracture that qualify as serious adverse events.	
Keratitis / ulcerative keratitis : Reporting of events of keratitis/ulcerative keratitis that qualify as serious adverse events	
Venous thromboembolic events : Reporting of all serious adverse events related to venous thromboembolic events (specifically DVT and PE)	
Evaluation of the pharmacokinetics of vismodegib in patients with hepatic and renal impairment - study GP 27839 GP27839 is an ongoing Roche-sponsored Phase Ib open-label pharmacokinetics and safety study of vismodegib in patients with advanced solid malignancies, including hepatocellular carcinoma, with varying degrees of renal or hepatic function. The study is expected to enroll 30 patients in five cohorts, organised by their renal and hepatic function. The evaluation should be based on unbound concentrations.	March 2015

Risk minimisation

The MAH shall distribute a Direct Healthcare Professional Communication letter at launch of the product, which should contain the following:

- A core text as agreed by the CHMP
- National specific requirements as agreed with the National Competent Authority regarding:
    - Distribution of the product
    - Measures to ensure that all appropriate actions have been performed prior to Erivedge being prescribed and dispensed

The MAH shall continuously ensure that all physicians who are expected to prescribe Erivedge are provided with the following:

Product information
Healthcare professional educational material
Healthcare professional reminder card
Patient educational material
Patient reminder card

The healthcare professional educational material for Erivedge should contain the following key elements:

- Brief background on Erivedge, its licensed indication and posology
- A requirement to inform patients of the teratogenic risks associated with Erivedge and the need to avoid foetal exposure
- Description of the pregnancy prevention programme and categorisation of patients based on sex and childbearing potential
- Information on the recommended forms of contraception both for women and men
- Obligations of the health care professional in relation to the prescribing of Erivedge
    - The need to provide comprehensive advice and counselling to patients
    - To ensure that patients are capable of complying with the requirements for the safe use of Erivedge
    - The need to provide patients with the patient educational material and patient reminder cards
- Safety advice for women of childbearing potential
    - The need for adequate contraceptive measures (even if the woman has amenorrhoea) during treatment and for 24 months after Erivedge treatment
    - Pregnancy test within 7 days prior to treatment initiation, and monthly medically supervised pregnancy tests during treatment
    - The need to stop Erivedge immediately upon suspicion of pregnancy
    - The need for the patient to report a suspected pregnancy immediately to the treating healthcare professional
- Safety advice for men
    - The need to use condoms if his sexual partner is pregnant or a women of childbearing potential (even if the man has had a vasectomy) during treatment and for 2 months after Erivedge treatment
    - The need for the patient to report immediately to the treating healthcare professional if his partner becomes pregnant whilst he is taking Erivedge or shortly after he has stopped taking Erivedge

    - Not to donate semen
- Requirements in the event of pregnancy
    - Instructions to stop Erivedge upon suspicion of pregnancy
    - The need to refer the patient to a physician specialised or experienced in dealing with teratology and its diagnosis for evaluation and advice
    - Local contact details for reporting of any suspected pregnancy
    - Pregnancy reporting form
- Inform patients that they should not donate blood during treatment with Erivedge and for 24 months after their final dose
- Check list for healthcare professional ensuring that patients receive the appropriate counselling
- The need to ensure all patients complete and sign the Erivedge Verification of Counselling Form which is to be present in the healthcare professional educational material
- Adverse event reporting forms
- Information on the HCP Erivedge web portal and the need to complete patient information using it

The patient educational material for Erivedge should contain the following key elements:

- Information for patients on the teratogenic risks associated with Erivedge and the need to avoid foetal exposure
- Description of the patient reminder card
- The need for adequate contraception and definition of adequate contraception
- National or other applicable specific arrangements for a prescription for Erivedge to be dispensed
- Not to give Erivedge to any other person
- Information on the disposal of unwanted medication
- The need to keep Erivedge capsules out of sight and reach of children
- That the patient should not donate blood during treatment and for 24 months after Erivedge treatment
- That the patient should not breastfeed during treatment and for 24 months after Erivedge treatment
- That the patient should tell the healthcare professional about any adverse event
- Information for women of childbearing potential
    - Description of the pregnancy prevention programme
    - The need for adequate contraceptive measures during treatment and for 24 months after Erivedge treatment
    - Pregnancy test within 7 days prior to treatment initiation, and monthly medically supervised pregnancy tests during treatment
    - The need to stop Erivedge immediately upon suspicion of pregnancy
    - The need for the patient to report a suspected pregnancy immediately to the treating healthcare professional
- Information for men
    - The need to use condoms (even if the man has had a vasectomy) if his sexual partner is pregnant or a women of childbearing potential during treatment and for 2 months after Erivedge treatment

    - That if his partner becomes pregnant he should inform the treating healthcare professional immediately
    - Not to donate semen

The healthcare professional's reminder card should contain the following key elements

- Information for women of childbearing potential
    - The need for monthly pregnancy tests even if the patient has amenorrhoea
    - The need for adequate contraceptive measures during treatment and for 24 months after Erivedge treatment
    - Not to breastfeed during treatment and for 24 months after Erivedge treatment
- Information for men
    - The need to use condoms when having sex with a female partner during treatment and for 2 months after Erivedge treatment
    - Not to donate semen
- The need to tell patients to report immediately to the treating healthcare professional if pregnancy is suspected in a female patient, or in a female partner of a male patient
    - The healthcare professional should assess the pregnancy status, counsel the patient on teratogenicity risk and refer to an appropriate physician specialised or experienced in dealing with teratology and its diagnosis for evaluation and advice
    - The healthcare professional should report confirmed pregnancies to the MAH
- Remind patients to return unused capsules to the pharmacist or doctor
- Remind patients not to donate blood during treatment and for 24 months after the final dose

The patient reminder card should contain the following key elements:

- Information for patients of the teratogenic risks associated with Erivedge and the need to avoid foetal exposure
- Not to donate blood during treatment and for 24 months after Erivedge treatment
- Information for women of childbearing potential
    - The need for monthly pregnancy tests
    - The need for adequate contraceptive measures
    - The need to contact the healthcare professional immediately if a pregnancy is suspected during treatment or in the 24 months following treatment
- Information for men
    - The need to use condoms when having sex with a female partner
    - Not to donate semen
    - The need to contact the healthcare professional if the female partner suspects that she is pregnant while the patient is treated with Erivedge or in the 2 months following treatment
- To return unused capsules as per local requirements
- Emergency contact phone numbers

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Most BCC lesions are small and are treated using various surgical methods, photodynamic therapy, and approved topical treatments. Cure rates are generally high irrespective of modality if properly applied. However, a very small proportion of BCC may progress to an advanced stage that is no longer amenable to available treatments. In these cases progressive disease results in morbidity from local tissue invasion and destruction particularly on the face, head and neck. These lesions include both locally advanced BCC, that is either inoperable or in patients who have medical contraindications to surgery and for whom radiotherapy was unsuccessful or contraindicated, or very rarely, metastatic BCC. Vismodegib is a small molecule inhibitor of the Hh signalling pathway, which is an important signalling pathway in BCC.

The pivotal efficacy data presented are based on a single-arm trial in which ORR by IRF in locally advanced BCC patients was 30/63 (48%) with 14 (22%) complete responses, and median duration of response was 9.5 months. For locally advanced disease, the observation of major responses including a high number of complete responses in exposed areas of the skin, the long response duration, the frequent healing of ulceration and the investigators' and clinical experts' assessment of clinical benefit allow concluding that treatment with vismodegib is associated with a clinically relevant benefit.

For metastatic disease, the ORR by IRF was 11/33 (33%) with no complete responses, and median duration of response of 7.6 months. In case of symptomatic disease, similarly to locally advanced disease, it is possible to conclude that treatment with vismodegib will be associated with a clinically relevant benefit. However, the efficacy data in this group were limited (see Uncertainty in the knowledge about the beneficial effects).

An assessment was undertaken independently by three dermato-oncologists followed by consensus assessment, provided credible qualitative information in support of conventional tumour response data. The overall "significant clinical benefit" response rate was 65% and in patients with worst baseline severity 21/37 (57%).

Uncertainty in the knowledge about the beneficial effects.

For metastatic disease, the demonstration of efficacy is based on a very small subgroup of 33 patients. Although it is acknowledged that this is a very small proportion of BCC, additional data are needed to confirm the benefit for symptomatic metastatic patients. In view of the observed benefits, the high unmet need in the target indication that includes patients with a severely mutilating disease, it is acceptable for such data to be submitted post-approval (see Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation).

Risks

Unfavourable effects

The most common adverse events associated with vismodegib are muscle spasms, alopecia, taste disorders and weight loss. Muscle spasms and taste disorders were reported in almost 70% of the patients, alopecia in 60 % and weight loss in 45%, these events are clearly defined also with regards to preclinical findings. were tolerable and only very few patients stop treatment due to side effects. Other common side effects were fatigue/asthenia in about 40% of the patients, gastrointestinal events such as nausea, decreased appetite, diarrhoea, and constipation and musculoskeletal events such as arthralgia and muscle pain in about 20-30% of the patients. The most common grade $\geq$3 events were weight decrease, fatigue, muscle spasms and hyponatremia occurring in 7, 6, 3 and 4% of the patients based on most recent safety update, respectively. The most common SAEs in the pivotal study were neoplasms, vascular disorders, infections, cardiac disorders and nervous system disorders all reported in less than 5%. More uncommon events were relatedness cannot be ruled out will be followed as potential risks in the RMP and more data provided in the safety study MO 25616.

An established serious unfavourable effect is teratogenicity. Hedgehog signalling is of known importance in embryonal development. Preclinical data has shown malformations and foetal death. Although there is no human exposure of vismodegib in pregnancy, defective hedgehog signalling in human has shown severe embryo- and foetotoxicity with mid line defects, cyclopia, ancephali and death. There are also preclinical findings on impairment of fertility which could be irreversible. Impairment of fertility is addressed in the RMP. Contraindication in pregnancy, warnings and recommendations on contraception for both male and female patients are included in the SmPC and a pregnancy prevention program is to be implemented.

Uncertainty in the knowledge about the unfavourable effects

As the proposed indication concerns patients which in most cases do not have a life-threatening disease, carcinogenicity studies are warranted. Squamous epithelial skin cancers and other second malignancies will also be further followed. In view of the observed benefits, the high unmet need in the target indication that includes patients with a severely mutilating disease, it is acceptable for such data to be submitted post-approval (see RMP).

The safety data in BCC patients are limited. The pivotal single-arm study included 104 patients; furthermore 34 patients from phase 1 studies are added in the pooled safety data base. Given the small number studied, the knowledge in particular with regards to less common events is limited. Missing information identified include use in hepatic impairment, use in renal impairment, interaction with other medications, and long-term use of vismodegib in patients with advanced BCC (locally advanced and metastatic BCC). However, in view of the observed benefits, the high unmet need in the target indication that includes patients with a severely mutilating disease, it is acceptable for such data to be submitted post-approval (see Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation).

Benefit-risk balance

Importance of favourable and unfavourable effects

Moderate to high anti-tumour activity in terms of ORR and durable responses in the locally advanced as well as in the metastatic setting have been proven. In locally advanced disease and symptomatic metastatic disease, this activity is considered to be of clinical relevance.

The most common side effects as muscle spasms, taste disorders and weight loss are considered to be manageable. Contraindication and warnings against pregnancy are included in the SmPC and a pregnancy prevention program is agreed.

Benefit-risk balance

Overall, in patients with locally advanced or symptomatic metastatic BCC, clinical benefit is considered established. The toxicity is considered manageable and adequate pharmacovigilance activities and risk minimisation measures have been described.

The benefit/risk of vismodegib in the treatment of adult patients with symptomatic metastatic basal cell carcinoma, or locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy is considered favourable.

Discussion on the benefit-risk balance

The clinical benefit of vismodegib is demonstrated in locally advanced basal cell carcinoma and in symptomatic metastatic BCC patients with manageable toxicity. In view of the unmet medical need and recognised difficulties to perform comparative trials in this population it is considered important that the product is available. However, with respect to the limited efficacy and safety data, further clinical studies are warranted to provide comprehensive data on the benefit-risk balance.

The applicant will provide a safety update of the pooled safety population, the final updated analysis of the pivotal study SHH4476g, an interim analysis of study MO25616 of 500 patients in June 2014 with a potential one year follow up and a final report from the study in June 2015.

Study MO25616 is planned to enrol a total of more than 800 patients over 3.5 years, projected as 630 patients in EU, it is estimated that 70 metastatic patients will be included. The primary objective is to assess the safety of vismodegib in patients with locally advanced or metastatic BCC. Secondary objectives will be overall response in those patients with measurable disease as permitted by local regulatory requirement and other efficacy parameters such as time to response, duration of response, progression-free survival and overall survival and QoL.

The CHMP considered that Erivedge falls under the scope of Article 2(1) of Commission Regulation (EC) No 507/2006:

- Medicinal products which aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases

and is thus eligible for a Conditional Marketing Authorisation.

Furthermore, all the requirements listed in Article 4(1) of the Commission Regulation (EC) No. 507/2006 apply to vismodegib on the basis of the following reasons:

a) The risk-benefit balance of the product is positive.

See Discussion on benefit-risk balance.

b) It is likely that the applicant will be able to provide comprehensive clinical data:

The applicant will provide further comprehensive clinical data to confirm efficacy and safety of vismodegib in the proposed indications from the update of the pivotal clinical trial and interim and final reports from trial MO25616. The study is currently ongoing. Thus, it is likely that the applicant will be able to provide comprehensive clinical data.

c) Fulfilment of unmet medical need in the proposed indications:

Currently there are no approved treatment options for the patients that fit the proposed indication. The target population of advanced basal cell carcinoma concerns patients no longer amenable to available treatments. In these cases progressive disease results in morbidity from local tissue invasion and destruction particularly on the face, head and neck. These lesions include both locally advanced BCCs, that are either inoperable or in patients who have medical contraindications to surgery and for whom radiotherapy was unsuccessful or contraindicated, or symptomatic metastatic BCC.

d) The benefits to patients of the immediate availability outweigh the risks inherent in the fact that additional data are still required:

In view of the favourable benefit-risk profile and the unmet medical need (see above), the immediate availability of vismodegib outweighs the risk inherent in the fact that additional data are still required. The applicant was consulted and agreed with the proposal of the CHMP recommending the granting of a conditional MA.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers majority decision that the risk-benefit balance of Erivedge in the treatment of adult patients with:

- Symptomatic metastatic basal cell carcinoma
- Locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy

is favourable and therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreeed subsequent updates of the RMP.

An updated RMP shall be submitted in June 2013.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

The MAH shall distribute a Direct Healthcare Professional Communication letter at launch of the product, which should contain the following:

- A core text as agreed by the CHMP
- National specific requirements as agreed with the National Competent Authority regarding:
    - Distribution of the product
    - Measures to ensure that all appropriate actions have been performed prior to Erivedge being prescribed and dispensed

The MAH shall continuously ensure that all physicians who are expected to prescribe Erivedge are provided with the following:

Product information
Healthcare professional educational material
Healthcare professional reminder card
Patient educational material
Patient reminder card

The healthcare professional educational material for Erivedge should contain the following key elements:

- Brief background on Erivedge, its licensed indication and posology
- A requirement to inform patients of the teratogenic risks associated with Erivedge and the need to avoid foetal exposure
- Description of the pregnancy prevention programme and categorisation of patients based on sex and childbearing potential
- Information on the recommended forms of contraception both for women and men
- Obligations of the health care professional in relation to the prescribing of Erivedge
    - The need to provide comprehensive advice and counselling to patients
    - To ensure that patients are capable of complying with the requirements for the safe use of Erivedge
    - The need to provide patients with the patient educational material and patient reminder cards
- Safety advice for women of childbearing potential

    - The need for adequate contraceptive measures (even if the woman has amenorrhoea) during treatment and for 24 months after Erivedge treatment
    - Pregnancy test within 7 days prior to treatment initiation, and monthly medically supervised pregnancy tests during treatment
    - The need to stop Erivedge immediately upon suspicion of pregnancy
    - The need for the patient to report a suspected pregnancy immediately to the treating healthcare professional
- Safety advice for men
    - The need to use condoms if his sexual partner is pregnant or a women of childbearing potential (even if the man has had a vasectomy) during treatment and for 2 months after Erivedge treatment
    - The need for the patient to report immediately to the treating healthcare professional if his partner becomes pregnant whilst he is taking Erivedge or shortly after he has stopped taking Erivedge
    - Not to donate semen
- Requirements in the event of pregnancy
    - Instructions to stop Erivedge upon suspicion of pregnancy
    - The need to refer the patient to a physician specialised or experienced in dealing with teratology and its diagnosis for evaluation and advice
    - Local contact details for reporting of any suspected pregnancy
    - Pregnancy reporting form
- Inform patients that they should not donate blood during treatment with Erivedge and for 24 months after their final dose
- Check list for healthcare professional ensuring that patients receive the appropriate counselling
- The need to ensure all patients complete and sign the Erivedge Verification of Counselling Form which is to be present in the healthcare professional educational material
- Adverse event reporting forms
- Information on the HCP Erivedge web portal and the need to complete patient information using it

The patient educational material for Erivedge should contain the following key elements:

- Information for patients on the teratogenic risks associated with Erivedge and the need to avoid foetal exposure
- Description of the patient reminder card
- The need for adequate contraception and definition of adequate contraception
- National or other applicable specific arrangements for a prescription for Erivedge to be dispensed
- Not to give Erivedge to any other person
- Information on the disposal of unwanted medication

- The need to keep Erivedge capsules out of sight and reach of children
- That the patient should not donate blood during treatment and for 24 months after the final dose
- That the patient should not breastfeed during treatment and for 24 months after the final dose
- That the patient should tell the healthcare professional about any adverse event
- Information for women of childbearing potential
    - Description of the pregnancy prevention programme
    - The need for adequate contraceptive measures during treatment and for 24 months after Erivedge treatment
    - Pregnancy test within 7 days prior to treatment initiation, and monthly medically supervised pregnancy tests during treatment
    - The need to stop Erivedge immediately upon suspicion of pregnancy
    - The need for the patient to report a suspected pregnancy immediately to the treating healthcare professional
- Information for men
    - The need to use condoms (even if the man has had a vasectomy) if his sexual partner is pregnant or a women of childbearing potential during treatment and for 2 months after Erivedge treatment
    - That if his partner becomes pregnant he should inform the treating healthcare professional immediately
    - Not to donate semen

The healthcare professional's reminder card should contain the following key elements

- Information for women of childbearing potential
    - The need for monthly pregnancy tests even if the patient has amenorrhoea
    - The need for adequate contraceptive measures during treatment and for 24 months after Erivedge treatment
    - Not to breastfeed during treatment and for 24 months after Erivedge treatment
- Information for men
    - The need to use condoms when having sex with a female partner during treatment and for 2 months after Erivedge treatment
    - Not to donate semen
- The need to tell patients to report immediately to the treating healthcare professional if pregnancy is suspected in a female patient, or in a female partner of a male patient.
    - The healthcare professional should assess the pregnancy status, counsel the patient on teratogenicity risk and refer to an appropriate physician specialised or experienced in dealing with teratology and its diagnosis for evaluation and advice
    - The healthcare professional should report confirmed pregnancies to the MAH
- To return unused capsules as per local requirements
- Remind patients not to donate blood during treatment and for 24 months after the final dose

The patient reminder card should contain the following key elements:

- Information for patients of the teratogenic risks associated with Erivedge and the need to avoid foetal exposure
- Not to donate blood during treatment and for 24 months after Erivedge treatment
- Information for women of childbearing potential
    - The need for monthly pregnancy tests
    - The need for adequate contraceptive measures
    - The need to contact the healthcare professional immediately if a pregnancy is suspected during treatment or in the 24 months following treatment
- Information for men
    - The need to use condoms when having sex with a female partner
    - Not to donate semen
    - The need to contact the healthcare professional if the female partner suspects that she is pregnant while the patient is treated with Erivedge or in the 2 months following treatment
- To return unused capsules to the pharmacist or doctor
- Emergency contact phone numbers

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
The applicant should provide a safety update of the pooled safety population, a final SHH4476g (pivotal study) and an interims analysis of study MO25616 of 500 patients with a potential one year follow up.	June 2014
The applicant should provide further data on safety and data on efficacy in patients with symptomatic metastatic BCC from the final analysis of MO25616.	June 2015

Divergent position to the majority recommendation is appended to this report.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that vismodegib is qualified as a new active substance.

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