25 June 2015
EMA/472165/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Odomzo

International non-proprietary name: sonidegib

Procedure No. EMEA/H/C/002839/0000

Note

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

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List of abbreviations

AE	adverse event
AUC	area under the plasma concentration vs. time curve
BCC	basal cell carcinoma
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
CEP	Certification of suitability of European Pharmacopoeia monographs
CI	confidence interval
CK	creatine phosphokinase
Cmax	maximum plasma concentration
Cmin	trough plasma concentration
CR	complete response
CRO	contact research organization
CRR	complete response rate
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	cytochrome P450 3A4
DoR	duration of objective response
EC	European Commission
EU	European Union
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FAS	full analysis set
FDA	Food and Drug Administration
FMI	final market image
GC	Gas chromatography
Hh	hedgehog
HPLC	High Performance Liquid Chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
IDMC	Independent Data Monitoring Committee
IR	Infrared
IRC	Independent Review Committee

KF	Karl Fischer titration
laBCC	locally advanced basal cell carcinoma
LDPE	Low density polyethylene
LoD	Loss on drying
MB	medulloblastoma
mBCC	metastatic basal cell carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
MPA	Medical Products Agency
mRECIST	modified Response Evaluation Criteria In Solid Tumors
MRI	magnetic resonance imaging
NMSC	non-melanoma skin cancer
NMR	Nuclear magnetic resonance
OD	once daily
ORR	objective response rate
OS	overall survival
PAR	Proven Acceptable Range
PCTFE	Polychlorotrifluoroethylene
pEAS	primary efficacy analysis set
PFS	progression-free survival
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetics
PPD	product of perpendicular diameters
PR	partial response
PVC	Polyvinyl chloride
QD	quaqe die (every day)
QoL	quality of life
RECIST	Response Evaluation Criteria In Solid Tumors
RH	Relative humidity
SAE	serious adverse event
SCC	squamous cell carcinoma
SMO	smoothened homologue
SmPC	Summary of product characteristics
SOC	system organ class

TTR	time to tumor response
TSE	Transmissible spongiform encephalopathy
uHPLC	ultra-high performance liquid chromatography
UV	Ultraviolet
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Ltd submitted on 5 May 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Odomzo, 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 13 December 2012.

The applicant applied for the following indication: Odomzo is indicated for the treatment of adult patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that sonidegib (as phosphate) was considered to be a new active substance.

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 CW/1/2011 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.

Applicant's request(s) for consideration

New active Substance status

The applicant requested the active substance sonidegib (as phosphate) 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 06 May 2010 for sonidegib diphosphate. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

Novartis Pharma GmbH
Roonstrasse 25
90429 Nuremberg
Germany

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Pieter de Graeff Co-Rapporteur: Daniela Melchiorri

- The application was received by the EMA on 5 May 2014.
- The procedure started on 28 May 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 August 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 11 August 2014.
- PRAC RMP advice and assessment overview adopted by PRAC on 11 September 2014.
- During the meeting on 25 September 2014, 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 26 September 2014.
- On 24 November 2014, the applicant submitted a request for an extension of the clock-stop. During the meeting on 18 December 2014, the CHMP agreed to a clock-stop extension of an additional two months.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 February 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 1 April 2015.
- PRAC RMP advice and assessment overview adopted by PRAC on 10 April 2015.
- During the CHMP meeting on 23 April 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant. The final List of outstanding issues was sent to the applicant on 24 April 2015.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 May 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of outstanding issues to all CHMP members on 10 June 2015.
- PRAC RMP advice and assessment overview adopted by PRAC on 11 June 2015.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant’s responses to

the List of outstanding issues to all CHMP members on 18 June 2015.

- During the meeting on 22-25 June 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Odomzo.

2. Scientific discussion

2.1. Introduction

Basal cell carcinoma and squamous cell carcinoma (SCC), are the most common subtypes of non-melanoma skin cancer (NMSC), with BCC accounting for approximately 80% of NMSCs[1]. Exact incidence of BCC is unclear due to lack of a cancer registry for this condition. However, a systematic review on the worldwide incidence of BCC reported studies that showed that the rates of BCC have increased at a similar rate over the past four decades, on average increasing by 20 /100 000 person-years every 15 years, a 5.5% increase per year, varying greatly between the different countries.[1].

There are at least 6 major histological variants of BCC, including nodular (classic), superficial, micronodular, morpheaform (sclerosing), infiltrating, and baso-squamous, with difference in behaviour (aggressive vs. less aggressive disease)[2]. Exposure to ultraviolet (UV) light, ionizing radiation, or to certain chemicals are known risk factors for developing basal cell carcinoma (BCC). Other risk factors for developing BCC are non- or hypo-coloured skin, old age, male gender, prior cancer of the skin, long-term or severe skin inflammation or injury, xeroderma pigmentosum, psoriasis and reduced immunity.

BCC is usually amenable to local therapy with recurrence rates varying from 5% to 14% after initial resection[3]. A small proportion of BCCs may progress to an advanced state with considerable morbidity from local tissue invasion and destruction particularly on the face, head, and neck, causing severe disfigurement[4]. The incidence of mBCC is extremely rare, with frequencies ranging from 0.0028% to 0.55% of all BCC cases[5], often involving regional lymph nodes (40-83%), lung (35-53%), bone (20-28%), skin (10-17%), and liver[6]. Based on a recent review of 100 mBCC cases, median survival after mBCC diagnosis was 54 months, with shorter survival in patients with distant metastases versus those with regional metastases (24 vs 87 months)[7].

BCC can be present as a sporadic as well as part of a rare inherited autosomal dominant condition, so-called Gorlin syndrome or nevoid basal cell carcinoma syndrome (NBCCS), caused by inactivating mutations in the Patched 1 gene (PTCH1). Loss of function of PTCH1 results in uncontrolled Hedgehog (Hh) signal transduction, which is linked with the development of BCC. Most cases of sporadic BCCs are also considered to harbour activating mutations in either PTCH (90%) or Smoothened (10%, SMO)

[1] Lomas A, Leonardi-Bee J, Bath-Hextall F (2012) A systematic review of worldwide incidence of nonmelanoma skin cancer Br J Dermatol; 166:1069-80.
[2] Goldenberg G, Hamid O (2013) Understanding BCC pathogenesis: treatment advancements and challenges. J Drugs Dermatol; 12(10):1110-20.
[3] Sartore L, Lancerotto L, Salmaso M, et al (2011) Facial basal cell carcinoma: Analysis of recurrence and follow-up strategies. Oncol Rep; 26:1423-9.
[4] Wong CSM, Strange RC, Lear JT (2003) Basal cell carcinoma. Br Med J; 327:794-8.
[5] Wadhera A, Fazio M, Bricca G, et al (2006) Metastatic basal cell carcinoma: a case report and literature review. How accurate is our incidence data? Dermatol Online J; 12(5):7.
[6] Aldhaban S, Marc S, Eshki M, et al (2011) Giant basal cell carcinoma with regional lymph node and distant lung metastases. Eur J Dermatol; 21: 972-5.
[7] McCusker M, Basset-Seguin N, Dummer R, et al (2014) Metastatic basal cell carcinoma: prognosis dependent on anatomic site and spread of disease. Eur J Cancer; 50:774-83.

genes. As a consequence most BCCs are expected to be dependent on this Hh signalling for growth and progression. The Hedgehog (Hh) signaling pathway is one of the key regulators of development and morphogenesis in mammals. Hh signaling is strictly controlled during cellular proliferation, differentiation and embryonic pattern formation. Mutations that constitutively activate the pathway, such as Smoothened (Smo), are linked to tumour formation. During the G0-phase (resting phase) of the cell replication cycle, the activity of Smo is blocked by Patched (Ptch), the Hh-ligand specific cell surface receptor. Aberrant activation of Smo as a consequence of loss-of-function mutations of Ptch or gain-of-function mutations of Smo is associated with development of several tumour types, including non-melanoma skin cancers such as basal cell carcinoma (BCC).

Treatment options available for BCC include surgery (including Mohs micrographic surgery), photodynamic therapy, Imiquimod, 5-fluorouracil (5-FU), radiotherapy. Treatment of metastatic disease has been mainly palliative since regimens using radiation, surgery, and chemotherapy have typically been ineffective. Vismodegib (Erivedge), an orally available small-molecule inhibitor of the Hedgehog pathway, was recently approved for the treatment of “patients with symptomatic metastatic basal cell carcinoma or locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy”.

Sonidegib is an orally bioavailable inhibitor of the Hh signalling pathway. It binds to Smoothened (Smo), a G protein coupled receptor like molecule that positively regulates the Hh pathway and eventually activates and releases glioma associated oncogene (GLI) transcription factors which induces the transcription of Hh target genes involved in proliferation, differentiation and survival. Aberrant Hh signalling has been linked to the pathogenesis of several types of cancer, including basal cell carcinoma (BCC). Sonidegib binding to Smo will inhibit Hh signalling and consequently block signal transduction.

The applicant applied for a marketing authorisation for the following indication:

Odomzo is indicated for the treatment of adult patients with:
- Locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy.
- Metastatic BCC.

The final indication following CHMP review of this application is: Odomzo is indicated for the treatment of adult patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy.

Odomzo should only be prescribed by or under the supervision of a specialist physician experienced in the management of the approved indication.

The recommended dose is 200 mg sonidegib taken orally once daily at least two hours after a meal and at least one hour before the following meal, at the same time each day.

Treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity develops.

Dose modifications for creatine phosphokinase (CK) elevations and muscle related adverse events are presented in section 4.2 of the SmPC

Management of severe or intolerable adverse reactions may require temporary dose interruption (with or without a subsequent dose reduction) or discontinuation.

When dose interruption is required, consider resuming Odomzo at the same dose after resolution of the adverse reaction to ≤ grade 1.

If dose reduction is required, then the dose should be reduced to 200 mg every other day. If the same adverse drug reaction occurs following the switch to alternate daily dosing and does not improve, consider discontinuing treatment with Odomzo.

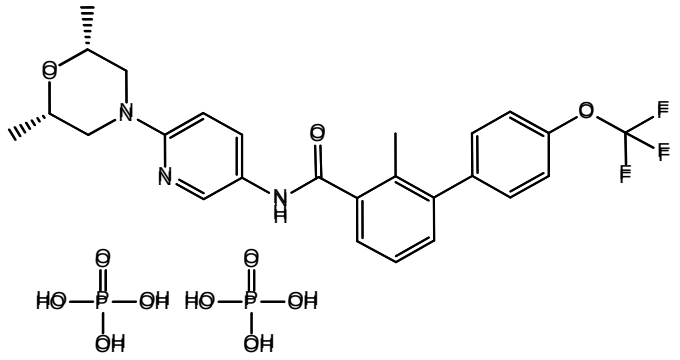
Due to the long half-life of sonidegib the full effect of a dose interruption or dose adjustment of sonidegib on several adverse events is expected to generally occur after a few weeks (see section 5.2).

2.2. Quality aspects

2.2.1. Introduction

General information

The chemical name of sonidegib diphosphate is *N*-[6-(*cis*-2,6-dimethylmorpholin-4-yl)pyridine-3-yl]-2-methyl-4'-(trifluoromethoxy)-[1,1'- biphenyl]-3-carboxamide diphosphate, and it has the following structure and properties:



Formula: $C_{26}H_{26}F_3N_3O_3.2H_3PO_4$; Molecular weight: 681.49

The chemical structure of sonidegib diphosphate was inferred from the synthetic route and confirmed by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, mass spectrometry, UV spectroscopy, elemental analysis and XRPD.

Sonidegib diphosphate is a white to slightly yellow crystalline, non-hygroscopic powder, practically insoluble in aqueous media from pH 1 to 7.5, slightly soluble in acetone, and sparingly soluble in alcohols. Control of particle size by milling is required for adequate dissolution due to the low aqueous solubility.

The active substance is achiral. Multiple polymorphic forms have been identified. Crystallographic data indicate that the proposed commercial polymorph is a co-crystal of sonidegib monophosphate and phosphoric acid. It is the thermodynamically stable form, but does interconvert with a second form in which the co-crystallised phosphoric acid molecule is removed in the presence of water. This conversion occurs during the wet granulation step employed in finished product manufacture. However, since the solubility of both polymorphic forms in physiologically relevant media is equivalent, there is no impact on product performance. In addition, the applicant has demonstrated methods to characterise and distinguish between the two forms in the isolated active substance.

Sonidegib diphosphate is considered to be a new active substance. It is neither an active metabolite, nor a pro-drug of any other active substance authorised within a medicinal product in the EU.

2.2.2. Active Substance

Manufacture, characterisation and process controls

Sonidegib diphosphate is synthesized convergently in four main steps by five manufacturers using well-defined starting materials with acceptable specifications. The starting materials were re-defined during the procedure in order to resolve a major objection. Several genotoxic compounds are produced during manufacture and these are limited below the threshold of toxicological concern in the intermediates, and shown to be purged by the process conditions. The crystallisation conditions ensure the correct polymorphic form of the co-crystal active substance is produced and subsequent micronisation affords sonidegib diphosphate with the required particle size distribution.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Specification

The active substance specification includes tests for appearance (visual examination), identity (IR, XRPD), assay (HPLC), impurities (HPLC), residual solvents (GC), loss on drying (Ph. Eur.), heavy metals (ICP-MS), microbial enumeration (Ph. Eur.), phosphoric acid assay (titration), particle size (laser diffraction), as well as clarity and colour of solution (both Ph. Eur.).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data on 25 batches of the active substance manufactured on pilot to commercial scale and used in clinical and stability studies is provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on three pilot scale batches of active substance from one of the proposed manufacturers stored in a range of packaging materials was provided. This included data on active substance stored in the intended commercial package (very tight packaging to exclude moisture – LDPE bag inside quadruple laminated foil pouch) for up to 18 months under long term conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines. In addition, active substance was stored in less tight (more permeable brown glass bottles) packaging under long term and accelerated conditions, as well as at 5 ºC. The following parameters were tested: appearance; identity, impurities, assay, loss on drying, clarity and colour of solution, and microbial limits (skip testing). Particle size was measured during the stability studies but since no changes were observed, this test is not listed in the re-test specifications. All parameters remained within specifications and no significant trends were observed.

Photostability testing following the ICH guideline Q1B was performed on one batch, but in a sealed container rather than a petri dish given the hygroscopicity of sonidegib diphosphate. Other than the observation that the colour of an aqueous solution intensified, there were no changes to any of the parameters.

Stress tests were carried out in the solid state at high temperatures at different humidities, and in the presence of oxygen. Studies were also carried out in hot aqueous solution without additive, with acid or with base and at ambient temperature with oxidant. Small amounts of degradation were observed at high temperature. Some degradation was observed in base and with oxidant, whilst significant degradation occurred under acidic conditions. The analytical methods used were the same as for release and were shown to be stability indicating.

The applicant provided a commitment to continue the stability studies up to the re-test date, and also, to carry out equivalent stability studies on batches of sonidegib diphosphate from the other manufacturer. Given that the manufacturing processes are the same, irrespective of the site of manufacture, this was considered acceptable.

The stability results indicate that the drug substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The aim of development was to produce an immediate release oral formulation of sonidegib diphosphate. The active substance has low density and poor flow properties and so a densification method was sought in order to produce a dosage form able to deliver the high doses required in early clinical studies. Direct compression and roller compaction methods were not suitable due to the poor flow properties and inherent low solubility of the active substance. Thus, a wet granulation process was investigated. The active substance converts to a different polymorphic form in the presence of water, losing the co-former phosphoric acid molecule from the crystal lattice in the process and thus being converted to sonidegib phosphate. This conversion was shown to occur during wet granulation, but does not impact on the dissolution of the active moiety. Sonidegib diphosphate also exhibits poor wettability and stuck to the vessel walls during granulation unless two surfactants (poloxamer and sodium lauryl sulfate) were added to the blend. Crospovidone was also incorporated to aid disintegration of the granules *in vivo*. Magnesium stearate (lubricant) and colloidal anhydrous silica (glidant) were added following granulation in order to improve the flow properties of the granules for encapsulation. Compatibility of the active substance and excipients was demonstrated by stability studies using binary mixtures at various temperatures. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

During studies into the granulation process, amount of water, addition rate, and mixing time were found to impact the fines content and polymorphic form of the active substance. These parameters were optimised in order to maximise dissolution rate and improve the flow properties for encapsulation. The batch size for the encapsulation process was optimised in order to combat the stickiness of the bulk powder blend.

Various formulations were used throughout the clinical programme including a powder for oral suspension, tablets, a solution for oral suspension and the final hard gelatin capsule formulation. Pivotal clinical studies were carried out using the same hard gelatin capsule formulation intended for marketing.

The discriminatory power of the dissolution method has been demonstrated by comparison of typical batches with those containing less disintegrant, manufactured using different granulation processes, or with active substance of a larger particle size. A two tier method is used for the dissolution test at

shelf-life due to the impact of gelatin cross-linking, a well-known phenomenon which occurs on storage over time.

The primary packaging is PCTFE/PVC/Alu blisters. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of four main steps: wet granulation of the active substance with intra-granular excipients and drying; milling and blending with extra-granular excipients; encapsulation; packaging. Holding times for final blend (up to 6 weeks) and bulk capsules (up to 12 months) have been justified with the appropriate stability data. The process is considered to be a standard manufacturing process. The in-process controls are considered adequate for production of hard gelatin capsules.

The manufacturing process will be validated on full production scale before commercialisation. The validation protocol is considered adequate.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form and comprise tests for appearance of capsule and contents (visual inspection), identification (UV, uHPLC), water content (KF), dissolution (Ph. Eur.), uniformity of dosage units (Ph. Eur.), degradation products (uHPLC), polymorphic content (XRPD), assay (uHPLC) and microbiological contamination (Ph. Eur.).

Batch analysis results are provided for nine commercial scale (and higher) batches used in clinical and stability studies, and for registration, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data on three production scale batches of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH), for up to 24 months under intermediate conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The stability batches were identical (including primary packaging) to those proposed for marketing proposed for marketing. Samples were tested for appearance of capsule and contents, water content, dissolution, degradation products, polymorphic content, assay and microbiological contamination. The analytical procedures used are stability indicating.

In addition one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant changes to any of the tested parameters were observed indicating that the product is photostable.

Based on available stability data, the shelf-life of 24 months stored below 30 ^{o}C as stated in the SmPC is acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the

Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Gelatin obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

The magnesium stearate is of vegetable origin.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical pharmacology studies were carried out *in vitro* and *in vivo* in compliance with GLP. Dose range finding studies do not all claim GLP compliance but were conducted in a GLP-compliant facility. The inhibition of signal transduction induced by Hh agonists was studied in several cell lines. The pharmacokinetic studies were performed in animal models of the rat, minipig, rabbit and dog using 14C radiolabeled drug substance. The toxicokinetic measurements were performed as part of toxicity studies in rats, rabbits, and dogs. The plasma protein binding and blood distribution was investigated in the mouse, rat, dog, minipig and human.

2.3.2. Pharmacology

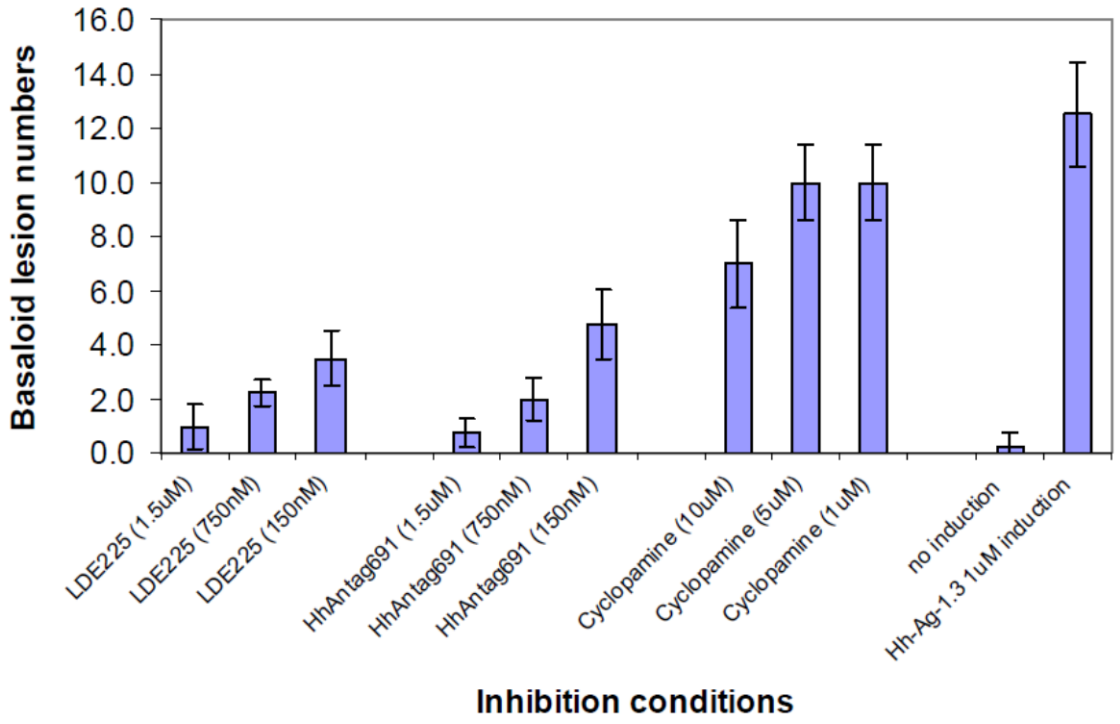
Primary pharmacodynamic studies

In a competition binding assay, the IC50 in an agonist displacement assay was 11nM using human Smo and 7 nM in an antagonist displacement assay (**RD-2007-50686**). Using a cell-based reporter gene assay (RGA) in which mouse Leydig cells were transfected with luciferase cDNA under the control of Gli regulatory sequences, the IC50 was 4 nM and 37 nM compared to the reference antagonist compound NVP-BFQ150 (cyclopamine), used at the same concentrations, with an IC50 of 46 and 4757 nM (**RD-2007-50689**).

Sonidegib was assessed for the ability to inhibit the proliferation of cells freshly isolated from mouse medulloblastoma as a biological effect model of Smo antagonism in cancers with a known relationship with Hh signalling. Allografts were generated in nude mice by injection of cells obtained from spontaneous tumours of transgenic mice with heterozygous deletion of Patched (Ptc) in combination with either homozygous deletion of p53 or heterozygous deletion of hypermethylated in cancer (Hic). *Ex vivo* cell proliferation was inhibited with an IC_{50} ranging from 6 to 9 nM (**RD-2007-50807**). Sonidegib also blocked Gli-1 expression in a human cell line from fetal mesenchymal origin with an IC50 of 12.7 nM (**RD-2007-50858**).

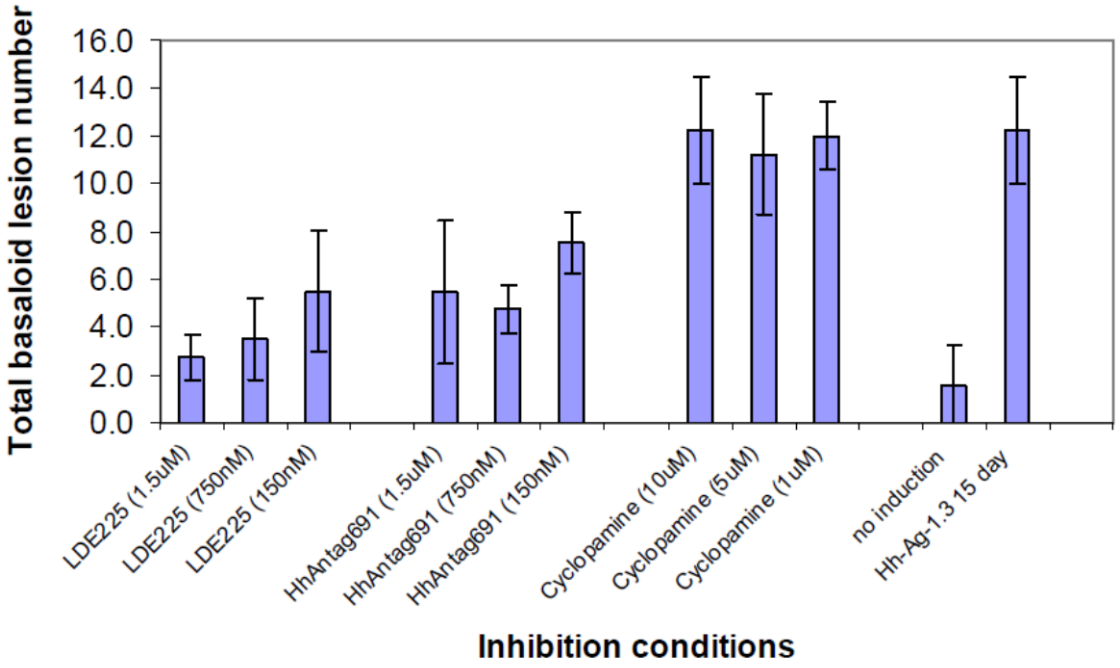
The effect of sonidegib (batch NVP-SONIDEGIB-NX3) was also assessed in ex vivo cultures of skin punch biopsies taken from 17.5 day Ptc+/- LacZ mouse embryos or newborn mice, exposed to the Smo agonist Hh-Ag-1.3 (1 µM), which give rise to basaloid nests similar to human basal cell carcinoma. Both Hh signal, assessed by X-gal staining, and basaloid nest formation were dose-dependently inhibited by 0.15-1.5 µM sonidegib and by Curis Hh-Antag691, a known Smo antagonists. By contrast, cyclopamine effect, a vegetable alkaloid able to inhibit Hh signal, was found to be less active. Results are showed in the figure below.

Figure 1: Inhibition of basaloid lesion formation by sonidegib, Curis Hh-Antag691 and cyclopamine in embryonic day 17.5 *Ptch+/--LacZ* mouse skin punches stimulated with Hh-Ag-1.3 (1 micromolar)



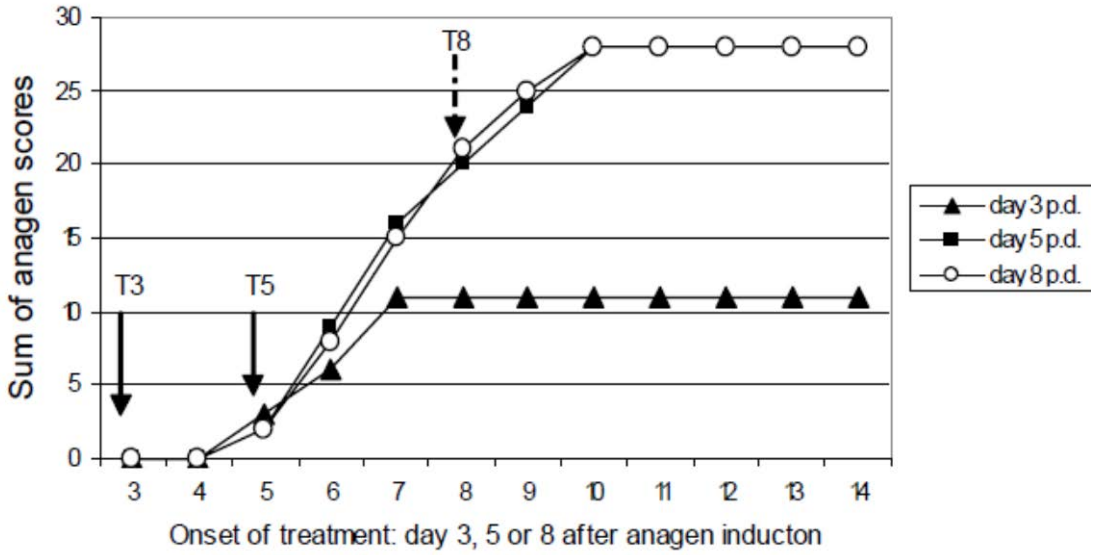
Sonidegib also inhibited Hh signalling and induced regression of basaloid nests when skin punch cultures were exposed to the drug 7 days after induction with Hh-Ag-1.3. Also in this case a dose-dependent activity similar to Curis Hh-Antag691 was observed, whereas cyclopamine showed very low potency (see figure below).

Figure 2: Regression of basaloid lesion by sonidegib, Curis Hh-Antag691 and cyclopamine in embryonic day 17.5 *Ptch+/--LacZ* mouse skin punches pre-stimulated with Hh-Ag-1.3 (1 micromolar)



Hh signalling plays a pivotal role in the development and maturation of mouse hair follicle during embryogenesis and in anagen phase of hair follicles in the adult. For this reason the ability of sonidegib to interfere *in vivo* with Hh signaling was evaluated in a model of hair growth after depilation in C57BL/6 mice. One-hundred-fifty µL of 1 or 0.1 % solution of the drug, was topically administered in the depilated area, for up to 14 days. Results indicated that sonidegib effectively blocked anagen entrance only when given 3 days after the induction of the anagen phase by depilation (study 253-07). A later administration induced the recovery with a kinetic similar to that observed in the previous experiments after treatment with vehicle.

Figure 3: Anagen development in C57BL7/6 mice treated from days 3, 5 or 8 on after depilation with 150 µl 1% sonidegib (Study # 253-07)



Inhibition of hair re-growth and follicle associated Hh-target gene expression can thus serve as surrogate PD model for LDE225 (**RD-2007-01671**). Skin samples of mice treated with LDE225 had reduced cyclin D1 immunohistochemistry staining (**RD-2007-50956**).

Secondary pharmacodynamic studies

Study report RD-2007-50628

The potential effects of sonidegib were tested *in vitro* on a panel of about 150 off-targets including G protein-coupled receptors (GPCR), ion channels, transporters and nuclear receptors. Different methods, such as ligand displacement or enzymatic assays, were used, depending on the target analysed. A panel of 68 potential off-targets was initially tested. None of them was inhibited for more than 50% with sonidegib concentration up to 10 µM.

Sonidegib showed low activity in most off-targets in a panel of 150 G-protein-coupled receptors (GPCRs), transporters, ion channels, nuclear receptors and enzymes, linked to potential side effects. Activities of ≥50% inhibition at 10 µM were found in 4 assays: melatonin MT1 (Ki = 0.55 µM; EC50 = 1.75 µM), CB2 (Ki = 6.5 µM), rat brain sodium channel type II (Ki = 0.75 µM) and rabbit monoamine transporter VMAT2 (IC50 = ~10 µM). These IC50's and Ki's are well above the free fraction Cmax of 0.053 µM in humans.

A further evaluation was performed on 82 additional off-targets. Only in four of them (Cannabinoid CB2, Melatonin MT1, Sodium channel Site 2, Monoamine transporter), sonidegib 10 µM induced a binding and/or activity inhibition higher than 50%.

The effect of different sonidegib concentrations was assessed; for the monoamine transporter the IC_{50} was around 10µM, for cannabinoid CB2 receptor the Ki was 6.5µM, for the melatonin MT1 receptor Ki was 0.55 µM and for the sodium channel Ki was 0.75 µM. Functional evaluation on MT1 showed a full agonist activity (EC_{50} 1.75 µM) in inducing the binding of radiolabeled GTP whereas no effect was observed in the rat caudal artery ring contraction assay up to 30 µM.

NVP-LGE899 (M48) was assessed for its off-target activity in a panel of 58 GPCRs, transporters, ion channels, nuclear receptors and enzymes. The compound did not show an activity of greater than 50% inhibition or activation at 10 µM on any of the targets. The compound was tested up to 30 µM on 35 targets and activities of greater than 50% inhibition or activation were also not found at this concentration.

Safety pharmacology programme

The safety pharmacology in the central nervous system (CNS), cardiovascular and respiratory systems has been investigated. Functional Observational Battery (FOB) was used to evaluate sonidegib effects on the central nervous system (CNS), in a study complying with GLP [Study Report 0770728]. No mortality was observed and no effect was reported regarding clinical signs, body weight variations and FOB. The effect of sonidegib on the cardiovascular system was evaluated in vitro [Study Reports 0718501] in heart samples and in transfected HEK293 cells [Study report 0770726]. A concentration-dependent reduction of the conduction velocity and of the coronary perfusion rate was observed. Sonidegib decreased hERG channel activity when used 0.5 µM (0.24 µg/ml) by 20.7 %. The total plasma steady-state Cmax in humans at 200 mg QD is 2.1 µM (Study sonidegib-A2201), and the free fraction in human plasma is 2.5%, so the free Cmax is 0.053 µM. Therefore, since the lowest potential exposure in the hERG assay of 0.5 µM is used to calculate multiple exposure, there is a 9-fold multiple exposure for hERG inhibition of 20% at a dose of 200 mg QD. The IC50 could not be assessed due to the solubility problems encountered. In vivo studies further evaluated the effect on the cardiac activity performed by telemetry recording of electrocardiogram (ECG) in two beagle dogs [Study report 0670734 and 0770734]. RR interval was prolonged and heart rate was reduced; by contrast other parameters and morphology and rythm of the ECG were not modified. Cardiovascular data from repeat dose toxicology studies showed no effects on cardiovascular parameters were seen in dogs in the 2-week oral dose range-finding study (**0770601**) at doses of 100, 300 and 1000 mg/kg, in the 4-

week study (**0770733**) at doses of 3, 12.5 and 50 mg/kg/day and in the 13-week study (**0870705**) at doses of 0.1, 1 and 10 mg/kg/day. However, in the 26-week dog study at doses of 0.1, 0.5, 10 and 50 mg/kg/day (**1070055**) minimal effects on cardiovascular parameters were seen at 50 mg/kg/day in both sexes.

Pharmacodynamic drug interactions

No non-clinical pharmacodynamic drug interaction studies were submitted (see non-clinical discussion).

2.3.3. Pharmacokinetics

Non-clinical pharmacokinetics was investigated in the rat, dog, and minipig. Intravenous pharmacokinetics was examined in all three pre-clinical species; oral pharmacokinetics was examined in the rat and dog, and dermal pharmacokinetics was investigated in the mini-pig.
The oral absorption and bioavailability of sonidegib were investigated in the rat [Studies R0700684-01 and R1100109] and dog [Study R1100218].

Table 1: Mean pharmacokinetic parameters of [^{14}C] sonidegib related radioactivity in plasma in rats and dogs

Species	Route of administration	Dose mg/kg	Tmax h	Cmax ngEq/mL	Cmax µM	AUClast ngEq•h/mL	AUClast µM•h	Apparent $T_{½}$ h	Absorption --
Rat [DMPK R0700684-01]	Intravenous	2	48	2950	6.08	378000	779	97 ± 20	
[DMPK R0700684-01]	Oral	25	64	28400	58.6	3690000	7600	--	78%
[DMPK R1100109]	Oral	25	48-72	15200	31	4260000	8770	~140-200	--
Dog [DMPK R1100218]	Intravenous	1	0.083	723	1.49	40800	84	76 ± 16	
[DMPK R1100218]	Oral	10	48	1040	2.13	151000	310	89-107	37.9%

Table 2: Mean pharmacokinetic parameters of sonidegib in plasma in rats and dogs

Species	Route of administration	Dose mg/kg	Tmax h	Cmax ng/mL	Cmax µM	AUClast ng•h/mL	AUClast µM•h	Bioavailability (%)	Apparent $T_{½}$ h
Rat	Intravenous	2	0.033[a]	673	1.39	1740	3.59		3.2
[DMPK R0700684-01]	Oral	25	4[a]	6680	13.8	118000	243	Not calculated	
Dog	Intravenous	1	0.083[a]	601	1.24	2030	4.19		25.3
[DMPK R1100218]	Oralb	10	48	218	0.450	10500	21.6	45.5	

[a]first sampling time

[b]mean of 2.

In rats, comparison of blood levels of radioactivity and the AUCs following oral or intravenous dosing (2 minute bolus) shows that absorption was 78%. In this study, after oral administration of [^{14}C]sonidegib, the AUC for sonidegib was <1% of the total radioactivity exposure, with LGE899 contributing >95% of the exposure. Clearance of sonidegib was moderate (1.08 L/h/kg) and the volume of distribution was large (4.8 L/kg).

In dogs, after intravenous administration of [^{14}C]sonidegib, radioactivity was measureable up to 504 h in plasma and up to 672 h (last sampling) in blood [Study R1100218]. The C_{max} of total radiolabeled components occurred at 0.083 h (first time point) after dosing. The apparent terminal half-life was of 76.4 ± 15.8 h in plasma and 189 ± 10.1 h in blood.

Sonidegib was measurable up to 168 h post-dose in plasma. C_{max} occurred at the first timepoint (0.083 h) post-dose and the apparent terminal half-life was 25.3 ± 8.70 h. Sonidegib had a large

volume of distribution (Vss) of 10.8 ± 4.5 L/kg. The plasma clearance was 0.476 ± 0.121 L/h/kg, and based on the in-vitro blood/plasma concentration ratio [Study R0700955-03], a blood clearance of 0.865 ± 0.220 L/h/kg was estimated, ~50% of the liver blood flow.

The ratio of the mean AUCs of sonidegib and its metabolite, LGE899, suggests that ~95% of total radioactivity in the systemic circulation is attributable to the carboxylic acid metabolite LGE899.

Following oral administration of [^{14}C]sonidegib, radioactivity was detectable in blood and plasma up to 336-504 h post-dose. The C_{max} for radioactivity was observed at 48 h post-dose. The terminal T½ was 97.9 h in plasma and 124 h in blood, in the same range as after intravenous administration. Following oral administration of [^{14}C]sonidegib, the parent compound was determined in plasma up to 336 h post-dose. The C_{max} in plasma occurred at 48 h post-dose and the apparent terminal elimination half-life of 30 h was similar to the value derived after intravenous administration (25.3 ± 8.70 h). The AUC_{last} value was 21.6 h·µM.

The tissue distribution of [^{14}C] sonidegib-derived radioactivity was investigated in two studies using whole body autoradiography in pigmented male Long Evans Hooded (LEH) rats and in Hanover Wistar (HW) male rats.

In the study R0700684, performed in rats, no information on LCS LOD is available, whereas in the study R1100218, performed in dogs, LOD was defined as 1.8 times the background value; the following values are provided: 14C-LOD (RA plasma): 10.9 nM (i.v.) and 154 nM (p.o.); 14C-LOD (RA blood): 12.9 nM (i.v.) and 145 nM (p.o.).

Drug-derived radioactivity was associated with the melanin-containing tissues in the eye and pigmented skin. Affinity for melanin containing structures was shown by 8.9 fold higher concentration of total labelled components in the eye choroid of a LEH rat at 168 h post-dose when compared with an albino rat (R0700684-01). In the second study (R1100109), the concentrations of total radiolabeled components in the eye choroid, dropped from 29.7 µmol/kg at 168 h to 9.19 µmol/kg at 840 h, indicating that the uptake into melanin rich tissues is at least partially reversible.

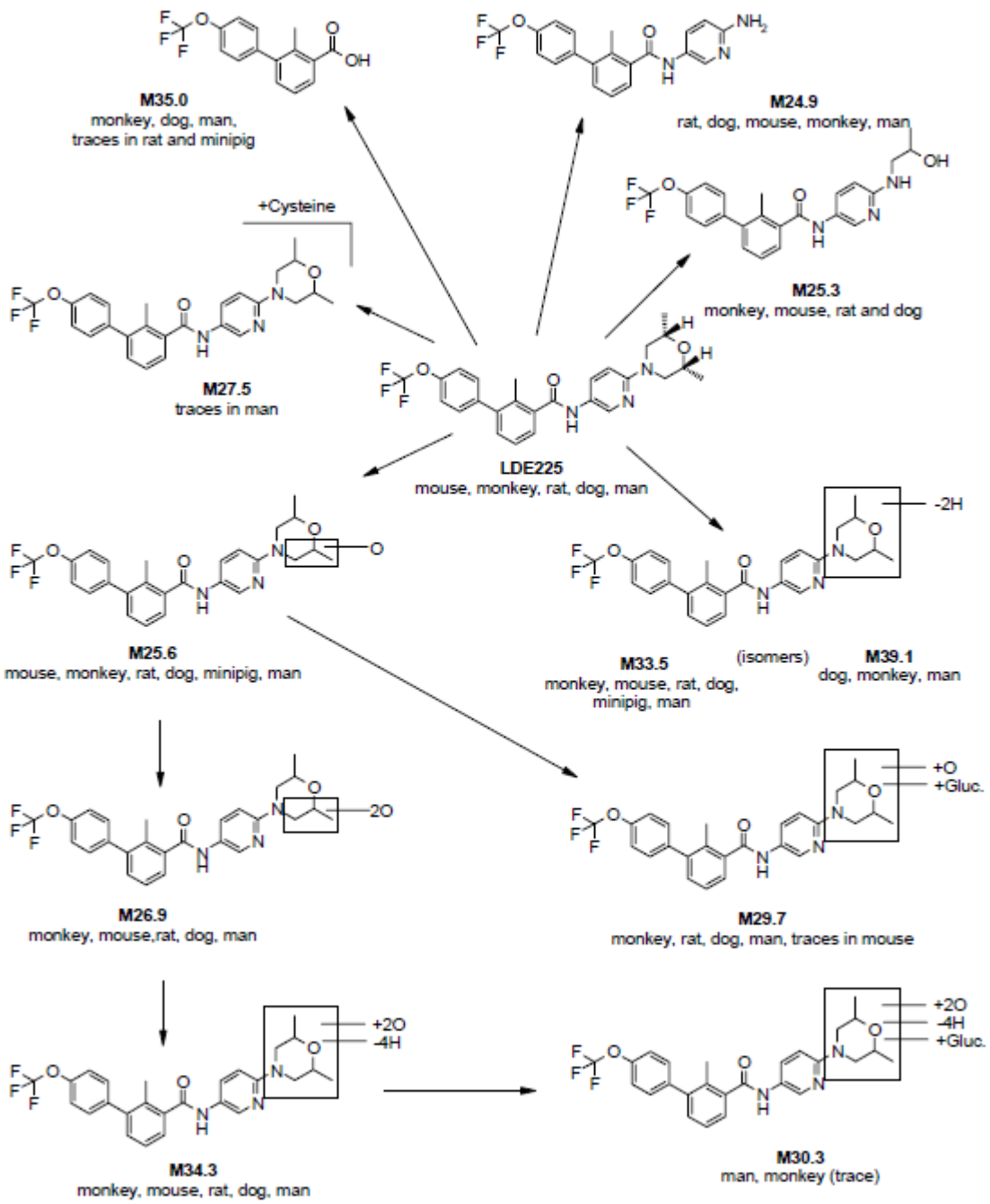
Measurable radioactivity concentrations in brain and spinal cord were observed through 7-days post-dose with an approximate tissue/blood AUC value of 0.2, suggesting drug-derived radioactivity crossed the blood:brain barrier (Study R0700684-01). The radioactivity was also detected in testis of males through 168 hours post-dose with a tissue/blood AUC value of 0.34.

The mean percent (%) of the plasma protein binding was high (97-99%) in the mouse, rat, dog, minipig and human, and there was no difference between the species tested. The binding was independent of concentration in all species tested.

Following i.v. and oral administration, [^{14}C]sonidegib was well absorbed and extensively metabolized such that only low levels of unchanged sonidegib were detected in excreta from rat, dog, and mini-pig (only i.v.). Thus, sonidegib was primarily eliminated via metabolism in nonclinical species and excretion of radioactivity occurred predominantly via feces (~75-90% of the dose in rat and dog; ~49% of the dose in mini-pig). Only ≤ 3% of dose was recovered in urine from rat and dog, and ~29% of the dose in urine from mini-pig.

The metabolic profiles in plasma, feces, bile (only rat), and urine from rat, dog, minipig and human are described below.

Figure 6: Proposed in vitro metabolic pathways of sonidegib



Following i.v. and/or oral administration, the metabolites were primarily excreted in feces and/or bile from rat, dog and mini-pig (i.v. only).

The urinary excretion of radioactivity was limited, accounting for < 2% of the dose in most species with the exception of mini-pig (~29% of the dose; i.v.). The major metabolites were M48 (LGE899) and M47e (acyl glucuronide) in urine from mini-pig, total accounting for ~13% of the i.v. dose.

Table 3: Metabolites of sonidegib identified in biological matrices following oral administration to rat, dog and human

Metabolite	Rat	Dog	Human
LDE225	P, U, B, F[a]	P, U, F	P, F
M4	ND[b]	ND	U, F
M6	U, B	U	ND
M7	U, B	U	ND
M14 (M24.1)[c]	U, B, F	P, U, F	U, F
M16 (M24.9, LNC119)[c]	P, U, B, F	P, U, F	P, U, F
M18	U, B	ND	ND
M21	ND[b]	F	ND
M22	U, B, F	ND	F
M23 (M25.3,LMT323)[c]	P, U, B, F	P, U, F	P, U, F
M24	B	ND	F
M24.8	F	ND	ND
M25 (M25.6, LMT326)[c]	P, U,B, F	P, U, F	P, U, F
M26 (M26.0, LMR550)[c]	U, B	P, U, F	ND
M26.2	F(trace)	ND	ND
M26.5	F(trace)	ND	ND
M27	B	ND	ND
M29 (M27.4)[c]	U, B, F(trace)	P, F	ND
M29.1	F	ND	ND
M30	ND	ND	P
M31 (M26.9)[c]	P, U, B, F	P, U, F	P, U, F
M32 (M27.5)[c]	ND	ND	F
M33	ND	ND	P, F
M34 (M30.5)[c]	P, B, F	P, F	P
M35 (M29.7)[c]	U, B	ND	P, U
M37 (M31.7)[c]	U, B, F	P, U, F	F
M41 (M34.3)[c]	P, U, B, F	P, F	P, F
M43 (LNM147)[c]	B, F	ND	F
M47e (CMN964)[c]	U, B	P, U	P, U
M48 (M35.0, LGE899)[c]	P, U, B	P, U, F	P, U, F
M49	F	ND	ND
M50 (M33.5)[c]	P, U, B, F	P, U, F	P, F
M51 (M39.1)	U, B, F	P, F	P, F
M52	B	ND	ND
M53 (M28.8)[c]	ND	F	F
M54	ND	P, U, F	ND
M56	B	P, F	P, F
M57	ND	P, F	P, F
M58	ND	P, F	ND
M59	B	F	ND
M60	ND	P, F	ND
M61 (M30.3)[c]	U, B	U	ND
M63	B	ND	ND
M64	B	ND	ND
M65	B	ND	ND
M66 (M22.7)[c]	B	ND	ND
M67	B	ND	ND
M69	ND	ND	P, F
M70	ND	ND	P, F

[a]P, U, B, F represent plasma, urine, bile and feces, respectively.

[b]ND: not detected.

[c]Details of nomenclature of metabolites are presented in [DMPK R1200697]. The codes inside the parenthesis are previous codes used in reports [DMPK R0700684-01], [DMPK R0800034] and [DMPK R0700977-01].

***In vitro* assessment of covalent protein binding potential for sonidegib in rat and human liver microsomes and human hepatocytes**

The objective of this study was to determine if [14C]sonidegib has the potential to bind covalently to protein when incubated with rat and human liver microsomes or human hepatocytes. The results show that sonidegib is poor at binding proteins.

Excretion of sonidegib was assessed using radiolabelled sonidegib in the rat, mini-pig, dog, and human. In all species most of the radioactivity was excreted as parent compound in the faeces.

It is concluded that the signal for covalent binding of LDE225 observed in this study is weak and as liver has not been identified as a target organ, no further follow-up is requested. Metabolite NVP-LGE899 (M48) does not show off-target activity in a panel of 58 GPCRs, transporters, ion channels, nuclear receptors and enzymes.

2.3.4 Toxicology

Single dose toxicity

The results of a single dose toxicity study are presented in Table 4.

Table 4: Single dose toxicity studies with sonidegib

Study ID	Species/ Sex/Number/ Group	Dose/Route	Approx. lethal dose / observed max non-lethal dose	Major findings
0970683 GLP	**Rat** (Wistar) F/6	2000 mg/kg Oral	>2000 mg/kg	One animal died, but probably not because of test item.

Repeat dose toxicity

The results of studies evaluating repeat dose toxicity are presented in Table 5 and 6.

Table 5: Non-pivotal repeat-dose toxicity studies with sonidegib

Species/ Study ID	Duration Sex/ Number/ Group	Dose (mg/kg/ day) /Route	Major findings
Rat (Wistar) 0670733 Dose range-finding Non-GLP	2 weeks M/5	0, 50, 100, 200 Oral	**≥50**: ↓Body weight, food consumption. Changes to femur/tibia and in lymphoid tissue and/or bone marrow. **200**: Focal fibrosis and focally prominent endosteal osteoblasts. **NOAEL**: ND

Species/ Study ID	Duration Sex/ Number/ Group	Dose (mg/kg/ day) /Route	Major findings
Rat (Wistar) 0770715 Pilot toxicity Non-GLP	2 weeks M/5	0, 300, 600, 1000 Oral	**≥300**: ↓ Body weight gain and thin femoral growth plates and dentin dysplasia. **≥600**: ↓ mucus in GI tract. **1000**: Pale and thin appearance, cold to touch, unkempt coat, ↓ locomotor activity, muscle tremors, absent feces, red urine, and perineal staining. ↓ serum urea, creatinine and triglycerides, ↑ kidney, thyroid, adrenal, and liver weight, enlarged kidneys, enlarged/ discoloured adrenals, distended urinary bladder, diffuse minimal hepatocellular hypertrophy, gastric mucosal necrosis, renal tubular mineralization, degeneration, and dilatation, pelvic hemorrhage, hemorrhagic inflammation of the prostate/ seminal vesicle and urinary bladder, vacuolation of seminiferous tubules, thin bone in the head, osteochondrosis, and lymphocytolysis and/or lymphoid depletion in lymphoid tissues. Clinical signs, gross- and histo-pathological findings were often noted in single animals. **NOAEL**: ND
Dog (Beagle) 0770601 Dose range-finding Non-GLP	2 weeks M+F/1-2	0, 100, 300, 1000 Oral (0, 100, 300: 1M, 1F. 1000: 2M, 2F)	**≥100**: ↑ cholesterol levels (F), ribs, sternum, and femur consisting of slight to marked ↓ in proliferating/ prehypertrophic and hypertrophic chondrocytes (generally more marked in F) and closure of the growth plate (F) and moderate to marked ↓ in anagen hairs. **300**: ↓ ovarian follicular development (F). **≥300**: ↑cholesterol levels (M), minimal lymphocytolysis/ lymphopha-gocytosis in germinal centers of lymph nodes and GALT, minimal to slight lymphoid depletion in thymus (M), and minimal to slight single cell denegeration of fundic glands of the gastric mucosa. **1000**: Histopathological findings of closure of the growth plate in the femurs (M). There were no treatment-related effects in ECG. **NOAE**: ND
Dog (Beagle) 0870112 (a) Pilot toxicity Non-GLP	2 weeks M+F/1-2	0, 3, 12.5, 50 Oral (0: 1 M/F, 3, 12.5, 50: 2M/F)	**≥3**: soft diarrhea and/or mucoid, a minimal to marked ↓ in the number/height of proliferating/ prehypertrophic chondrocytes and hypertrophic chondrocytes in the costochondral junctions of the ribs resulting in a ↓ in the formation of primary spongiosa. **12.5**: emesis with feed (M). **≥12.5**: emesis with test material (F) ↓ in ALP activity. **50**: minimal to mild ↑ in cholesterol concentration and histopathological findings of an ↑ in lymphocytolysis/lymphophagocytosis (minimal) in mesenteric and retropharyngeal lymph nodes. No treatment-related effects were noted in ECG. **TK**: After 14 days of dosing, exposure increased over-proportionally with increasing dose (levels were ~ 3-and 30-fold higher than was seen after a single dose at the 3 and 50 mg/kg dose levels). **NOAEL**: 3 mg/kg/day

Species/ Study ID	Duration Sex/ Number/ Group	Dose (mg/kg/ day) /Route	Major findings
Dog (Beagle) 0870112 (b) Pilot toxicity Non-GLP	13 days (5 doses) M+F/1-2	0, 50, 200, 1000 Oral, once/day **every 4th day** (0: 1 M/F, 50, 200, 1000: 2 M/F	**≥50**: ↓ in ALP activities, a minimal to marked ↓ in the number/height of proliferating/prehypertrophic chondrocytes and hypertrophic chondrocytes in the costochondral junctions of ribs resulting in a ↓ in the formation of primary spongiosa and a minimal ↑ in lymphocytolysis/ lymphophagocytosis in retropharyngeal lymph nodes (F). **≥200**: diarrhea, feces with apparent compound (M), and emesis with or without apparent compound (F), minimal to mild ↑ in cholesterol concentrations, and minimal ↑ in lymphocytolysis/ lymphophagocytosis in retropharyngeal lymph nodes (M). **TK:** ↑ in exposure was ~ proportional with the ↑ in dose following single and multiple doses. Exposure after 13 days (i.e., 5 total doses) was ~ 4-fold higher than the single dose exposure. **NOAEL**: ND

Table 6: Pivotal repeat-dose toxicity studies with sonidegib

Species/ Study ID	Duration Sex/ Number/ Group	Dose (mg/kg /day)/ Route	Major findings
Rat (Wistar) 0770732 GLP	4 weeks +4 weeks recovery M+F/10	0, 20, 100, 600 Oral	**≥20:** abnormal teeth. Pale appearance, thin, hunched posture (F). ↓Body weight, food consumption, ↓ thymus weights,↓ uterus weights, microscopic changes in teeth, bones, nasal cavity, female reproductive tract, lungs, thymus and other lymphoid tissues, lymphoid depletion, infiltrates or aggregates of foamy macrophages in the lungs **≥100**: Pale appearance, thin, hunched posture (F), marked uterine atrophy **600:** Dead: 6M+6F. Cold to touch, pale, thin, dehydration, hunched, reddened skin, muscle tremors, ↓ locomotor activity. minimally ↑ cholesterol, compromised renal function, renal tubular necrosis and mineralization or hydronephrosis, hepatocellular damage (↑ASAT, ALT, ALP, bilirubin) and cholestasis, mild inflammation, ↓ reticulocyte counts, ALP activity and triglyceride, adrenal cortical hypertrophy and vacuolation, ↓ovary weights, distention of stomach with watery contents, haemorrhage in stomach, distension or thick wall in duodenum, ↑adrenal glands, small uterus, microscopic changes in stomach, kidneys and adrenals, gastric irritation, tubular necrosis, adrenal cortical hypertrophy and vacuolation **NOAEL**: ND
Rat (Wistar) 0870704 GLP	13 weeks +8 weeks recovery M+F/10	0, 0.2, 2, 20 Oral	**20**: broken teeth, loss of teeth, loss of whiskers (F), swollen muzzle, lower jaw, salivation, malocclusion, fur thin on lower jaw, tremors, dry skin and, dehydration. ↓body weight/gain, food consumption, ↑neutrophils, fibrinogen (M), ↓albumin, ALP, histopathology findings in bones, teeth, skin, mandibular lymph nodes and the uterus **NOAEL**: 2 mg/kg/day
Rat (Wistar) 1070056 GLP	26 weeks M+F/20	0, 0.5, 3, 10 Oral	**10**: Dead by early sacrifice: 2M+1F Teeth-related abnormalities, few feces, and/or thin appearance; severe ↓body weight and food consumption, alopecia, thin appearance, tremors, thinning/closure of growth plates and decreases in trabeculae/status spongiosa in bones, inflammation of glands/crypts in gastrointestinal tract, focal or multifocal acute inflammation of prostate, depletion of lymphocytes in spleen and lymph nodes, infiltrates of macrophages and erythrocytes in sinuses in lymph nodes **NOAEL**: 3 mg/kg/day

Species / Study ID	Duration Sex / Number / Group	Dose (mg/kg/day) / Route	Major findings
Dog (Beagle) 0770733 GLP	4 weeks + 4 weeks recovery M+F/3	0, 3, 12.5, 50 Oral	**≥3**: ↓ovary and uterus weight, ↓thyroid weight, changes in sternum, femur and rib **≥12.5**: ↓bone-ALP, ↓bone formation, ↓proliferating and prehypertrophic chondrocytes and decreased trabeculae/primary spongiosa **50**: ↓testis and prostate weight, hair loss, ↓spermatogenesis, atrophy or delayed development of prostate, atresia or degeneration of ovarian follicles, immaturity of uterus **NOAEL**: ND
Dog (Beagle) 0870705 GLP	13 weeks + 8 weeks recovery M+F/3	0, 0.1, 1, 10 Oral	**≥1**: ↓bone-ALP, minimal to marked closure of growth plate in sternum, thinning of bony trabeculae(M) **10**: thinning or missing fur, ↑cholesterol, ↑triglycerides(M), thinning of bony trabeculae(F), marked closure of the growth plate of rib, enlargements of various joints of forepaws, alopecia, single cell necrosis of epithelial cells of villi in ileum **NOAEL**: 0.1 mg/kg/day
Dog (Beagle) 1070055 GLP	26 weeks High dose suspended after 14 weeks M+F/4	0, 0.1, 0.5, 10, 50	**≥0.5**: ↓body weight(M), thinner mucosa in stomach **≥10**: Abnormal feces, emesis, excessive shedding, alopecia, warm to touch, dry or red skin, ↓body weight(F), ↑QRS(F), ↑cholesterol, absent rib growth plates, degeneration/necrosis and/or increased mitotic activity in mucosal epithelium of small intestine, changes in lymphoid tissue(M) **50**: Dead by early sacrifice: 2M+2F Tremors, ataxia, hypersalivation, severe ↓body weight and food consumption, ↑QRS, ↑QTc(M), degeneration/necrosis of mucosal epithelium in stomach, changes in lymphoid tissue(F), vacuolation of adrenal cortex **NOAEL**: 0.5 mg/kg/day

Genotoxicity

The results of genotoxicity studies are presented in Table 7.

Table 7: Genotoxicity studies performed with sonidegib

Type of test / study ID / GLP	Test system	Concentrations / Concentration range / Metabolising system	Results Positive / negative / equivocal
0770725 Gene mutations in bacteria GLP	Salmonella strains TA 1535, TA97a, TA98, TA100 and TA102	0.32, 1.6, 8, 40, 200 µg/plate +/- S9 (plate incorporation) 6.25, 12.5, 25, 50, 100, 200 µg/plate +/- S9 (preincubation)	Negative
0770727 Chromosomal aberrations in mammalian cells GLP	Human peripheral blood lymphocytes	1.0 – 64 µg/ml +/- S9	Negative
0614112 Chromosomal aberrations in mammalian cells Non-GLP	TK6 human lymphoblastoid cells (micronucleus)	6.3 – 131.0 µg/ml +/- S9	Negative
1070158 Chromosomal aberrations in vivo GLP	Rat, micronuclei in bone marrow	0, 200, 632, 2000 mg/kg	Negative

In the Ames test, treatment with sonidegib did not increase the revertant numbers of any of the bacterial tester strains used. In conclusion, sonidegib was not mutagenic.

Sonidegib did not induce chromosome aberrations in cultured human peripheral blood lymphocytes, when tested to the maximum practicable concentration limited by precipitation in both the absence and presence of S-9.

Sonidegib did not increase the number of cells containing micronuclei after 20-hour treatment ± S9, therefore sonidegib was not clastogenic or aneugenic.

In the in vivo rat bone marrow micronucleus test by the oral route, sonidegib did not induce micronuclei in bone marrow cells of rats up to the maximum tested dose (2000 mg/kg/day). This indicates that the test item has no clastogenic and/or aneugenic potential in vivo under the test conditions used.

Carcinogenicity

The applicant did not submit carcinogenicity studies (see non-clinical discussion).

Reproduction and development Toxicity

The results of reproductive and developmental toxicity are presented in Table 8.

Table 8: Overview of reproductive toxicity studies with sonidegib

Study type/ Study ID / GLP	Species; Number/ group	Route & dose	Dosing period	Major findings	NOAEL (mg/kg &AUC)
0970632 Male and female fertility GLP	Wistar rat 25/sex/dose	Oral gavage 0, 0.2, 2.0, 20 mg/kg/day	M: D50 pre-mating – 2wks after F: 5 wks pre-mating – GD 6	**M:=20**: ↓ BW, fc **F:≥2.0**: ↓ pregnancies, ↑ early resorptions, post-implantation loss, ↓ viable foetuses **=20**: no pregnancies	NOAEL for fertility: M: 20 F: 0.2
0970151 Embryo-fœtal development Non-GLP	NZW rabbit 3-6 F/dose	Oral gavage 5*, 10*, 20*, 25, 50, 100, 200 mg/kg/day	GD 7-20	**F0: ≥5**: resorptions, pre-post implantation loss, ↓ viable foetuses **≥10**: ↓ BW gain, no viable foetuses **≥25**: abortions **≥100**: Mortalities, ↓ fc **F1: ≥5**: severely malformed foetuses, ↓ foetal BW	N.D.
0970631 Embryo-fœtal development GLP	NZW rabbit 20 F/dose	Oral gavage 0, 0.01, 0.1, 5 mg/kg/day	GD 7-20	**F1: ≥0.01**: metacarpal incomplete ossification/unossified, forepaw phalanx incomplete ossification **≥0.1**: frontal incomplete ossification **=0.5**:hyoid/interparietal/ cervical centrum/thoracic centrum incomplete ossification	F0: 5 AUC: 1080 ng.h/ml F1: N.D.

*Groups 5, 10, and 20 mg/kg/day were erroneously dosed with 17.8, 35.65, and 71.5 mg/kg/day respectively on GD 7-9, due to calculation error.

Fertility and early embryonic development

In the fertility study in rats, LDE225 administered to female rats at 20 mg/kg resulted in a complete lack of fertility even though estrous cycling was within normal ranges and the precoital interval was comparable to concurrent controls. There was also a reduction of the number of pregnant females and a decrease in the number of viable fetuses at 2 mg/kg/day. The no observed effect level (NOEL) for female fertility was 0.2 mg/kg. For LDE225-treated males, the 20 mg/kg/day (high) dose did not impact the ability of the male rat to impregnate the untreated females and therefore, the 20 mg/kg/day dose is considered the NOEL for fertility and reproduction in the male rat.

Embryofoetal development

In pregnant rabbits (gestation days 7-20) receiving daily oral doses of LDE225 10 mg/kg/day were not tolerated by pregnant rabbits as evidenced by abortion, moribundity and/or complete resorption of embryos/foetuses. The 5 mg/kg/day dose was not overtly toxic to the maternal animal, but resulted in resorptions and severely malformed foetuses. Teratogenic effects included severe craniofacial malformations (varying degrees of holoprosencephaly), vertebral, distal limb and digit malformations, anophthalmia and gastroschisis (open perineum). Embryofetal loss growth retardation and variations were also observed.

In the pivotal study with lower doses, skeletal variations occurred at statistically increased fetal and/or litter incidences in all dose groups and included incomplete ossification of the frontal bone, metacarpals, cervical centrum, hyoid and interparietals. Unossified metacarpals and dumbbell ossification of the thoracic centrum also occurred at statistically increased fetal and/or litter incidences in the high dose group. Fetal drug concentration could be consistently measured in the high dose group, but not in the mid and low dose groups. However, the dose-dependent incidence of skeletal variations in the fetuses confirmed drug administration.

The lowest dose of 5 mg/kg/day was without maternal toxicity and produced foetuses with numerous malformations, as well as reduced number of viable foetuses. Therefore, 5 mg/kg/day was chosen as the high dose in the pivotal study. The 5 mg/kg/day dose of LDE225 is considered the NOAEL for the maternal animal. LDE225 caused embryo-fetal toxicity (skeletal variations) at all doses, therefore a NOAEL for the foetus was not established in this study.

Prenatal and post-natal development

The results of juvenile toxicity studies are presented in Table 9.

Table 9: Juvenile toxicity studies with sonidegib

Species/ Study ID	**Duration Sex/ Number/ Group**	**Dose (mg/kg/day)/ Route**	**Major findings**
Rat (Wistar) 0770836 Dose range-	20 days (D14-34 post partum)	0, 50, 150, 355 Oral (Gavage)	**≥50:** ↓Body weight **≥150**: Mortality. Distended abdomens, rales and tremors **355:** Distended stomachs, gas and/or fluid filled intestines,

Species/ Study ID	Duration Sex/ Number/ Group	Dose (mg/kg /day)/ Route	Major findings
finding Non-GLP	M+F/12		impacted intestine(M) **NOAEL**: ND
Rat (Wistar) 0770903 GLP	5 weeks (D14-49 post partum) + 8 weeks recovery M+F/12 (8 in H)	0, 1, 3, 10, 30 Oral (Gavage)	**≥3**: Teeth abnormalities, epididymal oligo/aspermia **≥10**: Abdominal distension, fecal changes, diarrhea, tremors, uncoordination, pallor, decreased activity, abnormal gait, ↓food consumption and body weight, ↑ day of physical (sexual) development. ↑Neutrophils, monocytes, reticulocytes, red cell distribution width, platelets. ↓ ALP, triglycerides, creatine kinase, total protein, albumin. ↓Liver, thymus, ovaries, testes and uterus weights. ↓Longitudinal bone growth (i.e., femoral and tibial bone lengths) and femoral and tibial shaft widths, without recovery. Small testes, uteri, ovaries and thymuses (for testes without reversibility). <u>Histopathological:</u> polyostotic findings (thinning/closure of the growth plates, decreased cancellous bone, chondrodysplasia and periosteal hyperostosis) and dental findings (atrophy of the incisor roots, fracture of the exteriorized incisors, and secondary oral changes). Degeneration of nerve fibers was found in the sciatic nerve and, less commonly, in the thoracic spinal cord. Intestinal cryptal necrosis, cutaneous changes (atrophy of hair follicles, squamous cyst), thymic lymphoid depletion and extramedullary hematopoiesis in spleen. Reproductive tract changes (degeneration/atrophy of the testicular seminiferous tubules, epididymal inflammation, partial glandular development of the seminal vesicles and prostate; endometrial/ myometrial atrophy in the uterus, epithelial atrophy/mucification and/or exudate in the vagina). Dental and cutaneous changes, most of the skeletal changes, nerve findings and epididymal oligo/aspermia showed no reversibility. **30**: 10 Dead (5M+5F) ↓Glucose (F) Degeneration/necrosis of the ovarian granulosa cells **PK**: Exposures at 30 mg/kg in juvenile rats at the end of week 5 were similar to adult rats dosed at 20 mg/kg on Day 29 indicating

Species/ Study ID	Duration Sex/ Number/ Group	Dose (mg/kg /day)/ Route	Major findings
			similar PK in adult and juvenile rats. **NOAEL**: 1 mg/kg/day

In the juvenile toxicity study, similar findings have been seen as in adult rats, with the exception of the effect on the sciatic nerve and spinal cord. In juvenile rats these sciatic nerve and spinal cord findings may have been due to the early bone growth plate closure resulting in growth cessation causing compression on the still growing nerves and spinal cord.

Toxicokinetic data

Toxicokinetic measurements were performed as part of toxicity studies in rats, rabbits, and dogs.

Rat

The toxicokinetics of sonidegib have been investigated in male rats (2 week studies) [Study 0670733] and [Study 0770715], and male and female rats (4, 13, and 26 week studies) [Study 0770732], [Study 0870704], and [Study 1070056]. In all studies, the exposure increased with dose, there was also evidence of sonidegib accumulation following repeated dosing. This increase showed a trend towards under-proportionality with increasing dose, but this was variable. In the 4 week rat study [Study 0770732] there was evidence of a sex difference, with females having higher exposure, but there was no evidence of a sex difference in either the 13 [Study 0870704] or 26 [Study 1070056] week studies.

Dog

The toxicokinetics in the dog (4, 13, and 26 week studies) [Study 0770733], [Study 0870705], and [Study 1070055] were similar to the rat. Increasing doses showed under-proportional increases in exposure in the 4 week toxicology study [Study 0770733], and over-proportional exposure in the 13 [Study 0870705] and 26 week [Study 1070055] studies. There was no difference in exposure between male and female dogs, and there was evidence of accumulation (2- to 46-fold) following repeated dosing.

Rabbit

In the rabbit, toxicokinetic parameters were determined following oral dosing in pregnant female rabbits [Study 0970631]. Exposures in the maternal animal at the lowest dose could not be determined. Between the mid-dose (0.1 mg/kg) and the high dose (5 mg/kg) the exposure increased in an over proportional manner. Exposure of sonidegib in the fetus could only be demonstrated consistently from the high dose group, where the fetuses at 24h post dose were on average exposed twice more than the mean concentration found in plasma of the maternal animal.

Local Tolerance and phototoxicity

Local tolerance was assessed in several studies using topical application of sonidegib [study 0770162, 0970682 and 0970680]. Two local lymph node assays, were performed in mice. No effect on lymph

nodes was observed in either study, and no effect of UVA radiation was observed in the non-GLP study assessing photo-allergic potential. A slight increase in ear weight was seen in the non-GLP study at 30% sonidegib, indicating a potential for skin irritation. However, no such effect was seen at up 62.5% sonidegib in the GLP assay. No clinical signs or local irritation were observed.

Other toxicity studies

The four genotoxic impurities 2-chloro-5-nitropyridine (C1), cis-2,6-dimethyl-4-(5-nitro-2-pyridinyl)morpholine (C3), 4-(trifluoromethoxy) phenylboronic acid (Y4c), and 3,3'-(1,3-diazenediyl)bis[2- methylbenzoic acid] (501-11) are below the threshold of toxicological concern of 1.5 µg/day.

The impurity triphenyl phosphine oxide has shown transient neural toxicity in dogs and limits were set based on a toxicological evaluation (TPPO limit 2012) at not more than 18 ppm in the final intermediate, sonidegib free base.

Sonidegib exacerbated the severity of muscle toxicity induced by simvastatin in rats, but by itself had no effect on muscle. Sonidegib does not show synergistic toxic effects in cultures of human skeletal muscle cells after co-treatment combinations with simvastatin or pravastatin.

Concurrent treatment with human parathyroid hormone (PTH) had some limited effects mitigating complete bone growth plate closure. These studies were for proof of concept only to suggest a possible intervention if pediatric patients were to receive sonidegib. This is not relevant for the adult BCC patient population.

2.3.4. Ecotoxicity / environmental risk assessment

Table 10: Summary of main study results

Substance (INN/Invented Name): sonidegib					
CAS-number (if available): 1218778-77-8					
PBT screening		Result			**Conclusion**
Bioaccumulation potential – log K_{ow}	OECD123	log K_{ow} 5.70 at pH 5 log K_{ow} 5.78 at pH 7 log K_{ow} 5.83 at pH 9			see below
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	5.83 (pH 9)			
	BCF_{kLg}	821 and 1022 L/kg			not B
Persistence	ready biodegradability	not readily biodegradable			
	DT50	324 and 618 d at 12°C forms a persistent metabolite M1			vP
Toxicity	NOEC				cannot be concluded
	CMR				potentially T
PBT-statement	Sonidegib is considered not PBT, nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surface\ water}$, default F_{pen}	0.71	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)	not investigated				
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 12659 L/kg (sludge) 10271 L/kg (sludge) 13133 L/kg (soil) 14783 L/kg (soil) 21849 L/kg (soil)			
Ready Biodegradability Test	OECD 301B	not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50\ water}$ 3.0 and 2.2 d $DT_{50\ sediment}$ 152 and 291 d $DT_{50\ system}$ 44 and 175 d Sediment shifting: >10%			at 20°C Forms a persistent metabolite (R1)
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test / *P. subcapitata*	OECD 201	NA	N.A.		test unreliable. Test substance present in control
Daphnia magna Reproduction Test	OECD 211	NOEC	≥14.9	µg/L	mortality, reproduction,
Fish, Early Life Stage Toxicity Test / *Danio rerio*	OECD 210	NOEC	≥10.5	µg/L	mortality, hatching, growth
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥1000	mg/L	loading rate
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF_{kLg}	821 1022	L/kg L/kg	total radioactivity, lipid normalised
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$	N.A.		
Sediment dwelling organism	OECD 218	NOEC	N.A.		
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect	N.A.		
Terrestrial Plants, Growth Test / Species	OECD 208	NOEC	N.A.		
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	N.A.		
Collembola, Reproduction Test	OECD 232/ISO 11267	NOEC	N.A.		

Sonidegib is considered not PBT, nor vPvB.

The ERA submitted is considered incomplete. The Applicant committed to revise the ERA and perform a number of environmental risk assessment studies (see non-clinical conclusions).

2.3.5. Discussion on non-clinical aspects

The pharmacodynamic studies showed regression of tumour growth by inhibiting the Hh pathway in *in vitro* (mouse skin punches) and *in vivo* models (medulloblastoma tumour model). Results from animal models suggest that for efficacy, sonidegib should achieve at least 80% Gli1 inhibition in the clinic.

Sonidegib and main metabolite NVP-LGE899 (M48) do not show off-target activity in GPCRs, transporters, ion channels, nuclear receptors and enzymes at relevant concentrations in rat, dog and human. Sonidegib did not show important toxic effects on the central nervous-, respiratory- and cardiac systems of animals in safety pharmacology studies in rats and dogs.

Non-clinical pharmacokinetics was investigated in the rat, dog, and minipig. Intravenous pharmacokinetics was examined in all three pre-clinical species; oral pharmacokinetics was examined in the rat and dog, and dermal pharmacokinetics was investigated in the mini-pig.

In general, oral absorption appeared high in the rat (up to 78%) but was about half that in the dog (37.9%). The rate of absorption was moderate to low in the rat and dog with T_{max} occurring at 4-48h following a single oral dose in ADME studies. Bioavailability in the dog was comparable to absorption, demonstrating little or no first pass metabolism.

In the dog, plasma levels of sonidegib could be measured up to one week post dosing, and in the rat, elimination was more rapid with only very low concentrations measurable after 24 hours (T½ in rat 3.2 h; in dog 25.3 h). The volume of distribution was large in both species: 10.8 L/kg (dog); 4.8 L/kg (rat). Following oral administration of radiolabeled sonidegib, drug related radioactivity was widely distributed to most tissues in rat. The highest tissue distribution was observed in the uveal tract, followed by the harderian gland, fat, liver, small intestine, adrenal cortex, and adrenal medulla. Drug-derived radioactivity was associated with the melanin-containing tissues in the eye and pigmented skin. Uptake into melanin rich tissues was found to be at least partially reversible. Therefore, corneal disorders have been included as important potential risks.

Measurable radioactivity concentrations in brain and spinal cord were observed through 7- days post-dose, suggesting drug-derived radioactivity crossed the blood:brain barrier.

The in vitro plasma protein binding of sonidegib ranged from ~97%-99% in all species tested and independent of the concentration. Sonidegib showed little or no affinity for blood cells.

In all of the animals investigated, sonidegib was cleared primarily by metabolism with a preference for elimination in the faeces. Oxidations and oxidative cleavages (N/O dealkylation) in the morpholine ring appear to be the major metabolic pathways of sonidegib in all species. M48 (LGE899) was the prominent circulating metabolite with a long T½ in non-clinical species studied, and may account for the much longer T½ of radioactivity as compared to the T½ for the parent compound sonidegib. Especially in the rat almost all of the plasma radioactivity 24 hours after a single dose of radiolabeled sonidegib is traced as LGE899. This metabolite was not found to be pharmacologically active in vitro. In all species tested, the circulating levels of radioactivity were higher and measurable for longer than parent sonidegib.

In rats and dogs most of [^{14}C]-associated radioactivity was excreted in the faeces. Both after oral and after intravenous administration. After iv dosing very little of the radioactivity was recovered as parent drug. Very low percentage of radioactivity was recovered from urine. After 168 hour relatively high

percentage of radioactivity (10-15%) was still present in the carcass of rats, reflecting the long elimination time from tissues.

No non-clinical pharmacodynamic drug interaction studies were submitted. This is acceptable as drug interaction studies were performed using biomaterials (see clinical pharmacology section).

The majority of adverse effects of sonidegib can be attributed to its pharmacological mechanism of action on developmental pathways and effects in rats and dogs were similar. Most effects occurred close to the intended human exposures. These effects observed at clinically relevant exposures include closure of bone growth plates, effects on growing teeth, effects on the male and female reproductive tract, atrophy of the hair follicles with alopecia, gastrointestinal toxicity with body weight loss and effects on lymph nodes. At exposures well above the clinical exposure, an additional target organ was the kidney. The toxic effects occur at relatively low concentrations and are probably related to the pharmacological mechanism of sonidegib by Hh pathway inhibition. Effects on bone growth plates and teeth are not relevant for adult human patients, but the other target organs may be affected at the intended human exposure. However, only minimal decreases in platelet counts showed in a few animals, and there were no clinical or anatomic pathological findings attributable to this. The platelet decrease was attributed partially to bone marrow hypocellularity in two males, linked to poor body condition resulting e.g. from broken teeth.

Sonidegib exacerbated the severity of muscle toxicity induced by simvastatin in rats, but by itself had no effect on muscle; however, skeletal muscle effects was a main dose limiting toxicity in humans, (see also Clinical Safety). These findings were not observed in animals and the mechanism of this effect is not presently known.

The applicant submitted genotoxicity studies which showed no mutagenic findings in the in vitro assays used (SmPC section 5.3).

Another Smo inhibitor, compound vismodegib (Erivedge) induces pilomatricoma, hypothesized to be related to pharmacologically mediated disruption of hair follicle morphogenesis. Sonidegib induces irreversible hair follicle atrophy and this possibility should therefore to be taken into account. The applicant did not submit carcinogenicity studies, as per ICH S9 Guideline on nonclinical evaluation for anticancer pharmaceuticals. However, the proposed indication concerns patients which in most cases do not have a life-threatening disease, according to ICH S 9. Thus, carcinogenicity studies would be considered necessary and have been identified as missing information in the RMP. A meaningful exposure of sonidegib cannot be reached in rodents due to adverse effects on teeth, which reduced food consumption and hamper interpretation of any potential tumour findings. Therefore, the CHMP has imposed a post-authorisation measure to evaluate a subset of tissues from the 6 month rat study using KI-67 immunohistochemistry and to quantify cell proliferation. The results from the investigations on the 6 month rat study should be submitted by December 2016.

In the 4-week dog study, in males effects in the testes and atrophy or delayed development of the prostate, and in females atresia or degeneration of ovarian follicles and immaturity of the uterus or delayed/arrested maturation were seen at doses of 50 mg/kg/day. These effects were not seen in the 26-week dog study at the same dosage, while in the 4-week study the AUC0-24h were 26500-47900 ng.h/ml and in the 26-week study were much higher, namely 350000-399000 ng.h/ml at day 22/23. Probably, this difference is caused by the younger age (6 months old) of the dogs in the 4-week study at the initiation of dosing than in the 26 week study (10-11 months old). In both 4- and 13-week studies including recovery investigations, the toxic effects were not reverted. Impaired fertility has been identified as an important potential risk. Small effects seen in animals on cardiovascular system, kidney and liver do not seem to be relevant for humans.

Prenatal and postnatal development studies have not been conducted with sonidegib as per the ICH S9 Guidelines for the development of oncology drugs for use in advanced cancers. However, Hh inhibitors are known to have teratogenic potential and there is a risk of developmental toxicity. Exposure of sonidegib in the foetus could only be demonstrated consistently from the high dose group (and was twice that than what was found in the plasma of the maternal animal). Sonidegib was shown to be foetotoxic in rabbits, as evidenced by abortion and/or complete resorption of foetuses and teratogenic resulting in severe malformations at very low exposure. Teratogenic effects included vertebral, distal limb and digit malformations, severe craniofacial malformations and other severe midline defects. Foetotoxicity in rabbits was also seen at very low maternal exposure. There was reduced fertility at low exposure in female rats. For sonidegib treated male rats, exposure at approx. 2 fold the clinical exposure did not impact male fertility (SmPC Section 5.3).This is expected considering the fundamental role of Hh signalling pathway in embryonic development. Post-natal development defects have been identified as important potential risks. This has been properly stated in the SmPC sections 4.4 and 4.6.

Local tolerance and photoxicity were evaluated in mice and rabbits, respectively. A treatment-related effect was not observed in either species. Tests in rabbits revealed that sonidegib is not a skin or eye irritant. Sonidegib has no phototoxic potential as tested in the 3T3 assay. It can be concluded that sonidegib is not considered to have contact (photo) allergenic potential and is not a lymph node.

2.3.6. Conclusion on the non-clinical aspects

In conclusion, the non-clinical studies (pharmacology, pharmacokinetics and toxicology), submitted for the marketing authorisation application for sonidegib, were considered adequate and acceptable for the assessment of non-clinical aspects. However, considering that BCC is - in the great majority of cases - not life threatening, carcinogenicity studies should be performed.

Non-clinical studies have confirmed that there is a risk of developmental toxicity and teratogenicity to the foetus following administration of sonidegib in animals. The risk of developmental toxicity and teratogenicity are adequately addressed in the SmPC and RMP. In addition, based on the results from the non-clinical toxicity studies, the CHMP has imposed the implementation of educational material in order to ensure that patients and HCPs are aware of the potential risks to the foetus and the requirement to use effective contraception while using sonidegib.

The CHMP considers the following post-authorisation measures necessary to address the non-clinical issues:

1. A carcinogenicity study to perform an evaluation of a subset of tissues from the 6-month rat study using KI-67 immunohistochemistry and to quantify cell proliferation.

The CHMP recommends the following measures necessary to address the non-clinical issues:

1. The applicant is recommended to revise the ERA, including terrestrial and sediment assessment, based on the studies listed below, by December 2016.
    - Effects on a sediment dwelling organism should be investigated and compared to the PECsediment. Applicable tests are those with Hyalella sp; Lumbriculus sp. (OECD 225) or Chironomus sp. (OECD 218).
    - Aerobic and anaerobic transformation in soil (OECD 307),

- Soil Micro organisms: Nitrogen Transformation Test (OECD 216),
- Terrestrial plants, growth test (OECD 208, use version 2006),
- Earthworm, acute toxicity tests (OECD 207),
- Collembola, reproduction test (OECD 232).

2. The applicant is recommended to repeat the Freshwater Alga, Growth Inhibition Test (OECD 201) and submit the report during the ERA update of December 2016.
3. The applicant is recommended to perform an appropriate reproduction study (fish full life cycle study) in order to address the long term effects on aquatic vertebrates. A draft protocol should be submitted by October 2015.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 11: Phase I clinical studies providing PK data for sonidegib in healthy subjects

Study	Objectives	Sonidegib dose	No. of subjects dosed with sonidegib
[A1102]	Ethnic PK, safety, tolerability, (Japanese subjects)	200 mg, 400 mg, 800 mg single dose	36[a] (M)
[A2108]	PK (DDI), safety, tolerability	800 mg single dose	47[b] (M/F)
[A2110]	PK, ADME, safety, tolerability	800 mg single dose	6[c] (M)
[A2114]	PK (food effect and relative bioavailability), safety	200 mg, 600 mg, 800 mg, 1200 mg, or 1400 mg single dose	146[d] (M/F)

PK=pharmacokinetics; DDI=drug-drug interaction; ADME=absorption, distribution, metabolism, and excretion; M=male; F=female

Table 12: Summary of Phase I and Phase II clinical studies with PK and PK/PD components for sonidegib in patients

Study	Objectives	Sonidegib dose	No. of patients dosed
[A2201] (Phase II - pivotal)	Efficacy, safety, PK-ECG (Patients with laBCC or mBCC)	200 or 800 mg qd	229[a] (143 M, 86 F)
[X2101] (Phase I)	MTD, safety, tolerability, PK, preliminary anti-tumor activity, PD (Patients with advanced solid tumors)	100, 200, 400, 800, 1000, 1500, or 3000 mg qd, or 250, 400, or 750 mg bid	103[b] (63 M, 40 F)
[X1101] (Phase I)	MTD, safety, tolerability, PK, preliminary anti-tumor activity, PD (Patients with advanced solid tumors)	400, 600 mg qd; 800 mg qd in Group 2 only	21 Japanese patients in Group 1 included in submission[c] (8 M, 13 F)
[B2209] (Phase II)	Efficacy, safety, PK (Patients with NBCCS)	400 mg qd or placebo qd	8 on active[d] (4 M, 4 F); 2 on placebo (2 M)

PK=pharmacokinetics; MTD=Maximum tolerated dose; PD=Pharmacodynamics; laBCC=locally advanced Basal Cell Carcinoma; mBCC=metastatic Basal Cell Carcinoma; NBCCS=Nevoid Basal Cell Carcinoma Syndrome; M=male; F=female

2.4.2. Pharmacokinetics

The clinical pharmacology program for sonidegib consists of basic pharmacokinetic (PK) studies conducted in healthy subjects (absorption, distribution, metabolism, and excretion, drug-drug interaction, food effect and relative bioavailability, and PK in Japanese subjects). Single- and multiple-dose properties of sonidegib have been evaluated in patients with advanced solid tumours or BCC. Further across study analyses have been performed: population PK analysis, exposure-efficacy and exposure-creatine phosphokinase (CK) relationships in patients, PK-QTc relationships in patients and healthy subjects.

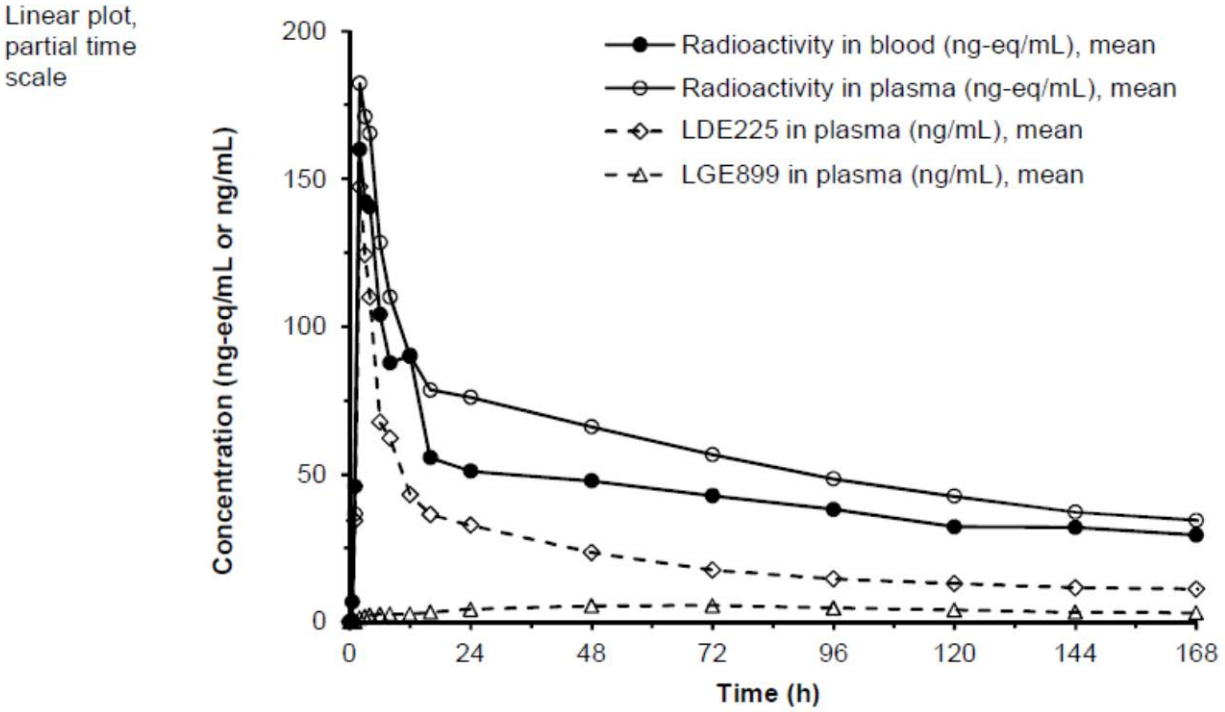
Additionally, in vitro studies with human biomaterials were performed in order to assess the potential of sonidegib to act either as a substrate, inhibitor, or inducer of drug metabolizing enzymes and drug transporters.

Descriptive statistics of pharmacokinetic parameters included mean, SD, %CV, geometric mean, %CV of geometric mean, minimum and maximum. When a geometric mean was presented it was stated as such. For Tmax, median values and ranges were given.

Absorption

Study A2110, was a single-dose study to determine the absorption, distribution, metabolism, and excretion (ADME) of sonidegib in healthy subjects after an 800 mg oral dose containing a tracer amount of [14C]sonidegib (~74kBq). Figure 7 shows that sonidegib is rapidly absorbed showing a median Tmax of 2 hours (range 2 to 4 hours). Cmax of sonidegib after an 800 mg dose was 154 ± 33 ng/ml. After peak plasma concentration, sonidegib concentration declined rapidly by factor of ~5 till 24 hours, followed by a slow terminal phase with a mean T1/2 of 319 hours (~13 days).

Figure 7: Mean concentration-time profiles (partial time scale) of total radiolabeled components (radioactivity; blood and plasma), sonidegib (LDE225 plasma) and metabolite LGE899 (plasma) after a single oral dose of 800 mg [14C]sonidegib in 6 male subjects (study A2110)



- **Bioavailability**

Sonidegib is poorly water soluble at pH>2 solubility is <0.0002 mg/ml. In the absence of an intravenous formulation for human use due to the poor aqueous solubility, the absolute bioavailability of sonidegib could not be determined.

An oral absorption of 5% was estimated by the percentage of metabolites recovered in urine and faeces in Study A2110.

Based on low solubility and low absorption under fasted conditions and moderate permeability in vitro, sonidegib can be classified as a Biopharmaceutics Classification System (BCS) class II compound.

- **Influence of food**

Study A2114 investigated the effect of a high fat meal on the PK of sonidegib 800 mg capsule in healthy subjects. Subjects in the fasted arm underwent overnight fasting for at least 10 hours before dosing and fasting for additional 4 hours post-dose. Subjects in the fed arm also underwent overnight fasting for at least 10 hours before receiving a high-fat breakfast (approximately 1000 calories, with 50% of calories from fat). Within 30 minutes of the start of meal, the subjects in the fed arm received an 800 mg sonidegib dose and remained fasted for 4 hours post-dose.

Absorption of sonidegib was delayed by 3 hours (median Tmax, fasted 2 hours vs Tmax, fed 5 hours) after a high-fat breakfast. Table 13 shows that the mean systemic availability of sonidegib is increased when given with a high fat meal (7.78-fold and 7.38-fold increase in Cmax and AUCinf). Elimination half-life was not affected by food intake. Administration of sonidegib after a high-fat meal also reduced

the inter-individual variability of Cmax and AUClast, 23% vs 60% and 43% vs 65%, respectively.

Table 13: Effect of food on the pharmacokinetics of sonidegib 800 mg (study A2114)

PK Parameter (unit)	Treatment 800 mg	n*	Adjusted Geo-mean	Comparison	Treatment Comparison 90% CI Geo-mean Ratio	Lower	Upper
AUCinf (ng·h/mL)	fasted	12	10739.44				
	high fat meal	12	79296.03	high fat/fasted	7.38	4.94	11.04
AUClast (ng·h/mL)	fasted	11	10348.35				
	high fat meal	12	77691.84	high fat/fasted	7.51	5.34	10.56
Cmax (ng/mL)	fasted	13	216.49				
	high fat meal	12	1684.89	high fat/fasted	7.78	5.13	11.81

Model is a linear model of the log-transformed PK parameters. Included in the model was treatment as a fixed effect. Results were back transformed to get adjusted geometric mean, geometric mean ratio and 90% CI.

n* = number of subjects with evaluable PK data.

Distribution

The apparent volume of distribution at steady state (Vss/F) based on a population PK analysis was 9170 L.

The fraction of sonidegib bound to human plasma proteins in vitro is approximately 97.5% and is independent of concentration from 1 ng/mL to 2500 ng/mL. Sonidegib binds to serum albumin and α1-acid glycoprotein. Binding of [14C]sonidegib to α1-acid glycoprotein was dependent on the protein concentration and resulted in the mean unbound fractions of 7.64%,3.58%, and 0.810% at the AGP concentrations of 0.5, 1 and 5 g/L, respectively.

Sonidegib showed little affinity for blood cells.

Sonidegib accumulated in skin tissue over time: skin/plasma ratio increased from 3 to 6-fold comparing day 29 to day 85 (study B2209).

Elimination

Apparent clearance (CL/F) in cancer patients was 10 L/h (90% prediction interval: 3.6, 27.5 L/h) as predicted by popPK. The geometric mean T1/2 in cancer patients was estimated 28.3 days (90% prediction interval: 7.0, 120 days).

Following single dose administration in healthy volunteers, CL/F measured by non-compartmental methods was 45-76 L/h for the 200 mg dose (studies A1102 and A2114) and a terminal elimination half-life of 7-10 days. PopPK analysis estimated a CL/F of 35 L/h and an elimination half-life of 8.7 days.

Excretion

Study A2110 was a single-dose study to determine the absorption, distribution, metabolism, and excretion (ADME) of sonidegib in healthy subjects after an 800 mg oral dose containing a tracer amount of [14C]sonidegib (~74kBq).

On average less than 2% of the administered dose was excreted in the urine. Sonidegib was not detected in urine. Unchanged sonidegib in faeces 0-504 hours accounted for 88.7% of dose. Recovery of radioactivity across the 0-504 hour time interval amounted to 93.3% of dose (when excluding both urine and feces of Subject 00003). In the period of 0-504 hours, 3.3% and 1.2% of the administered dose was excreted in faeces and urine in the form of metabolites.

Metabolism

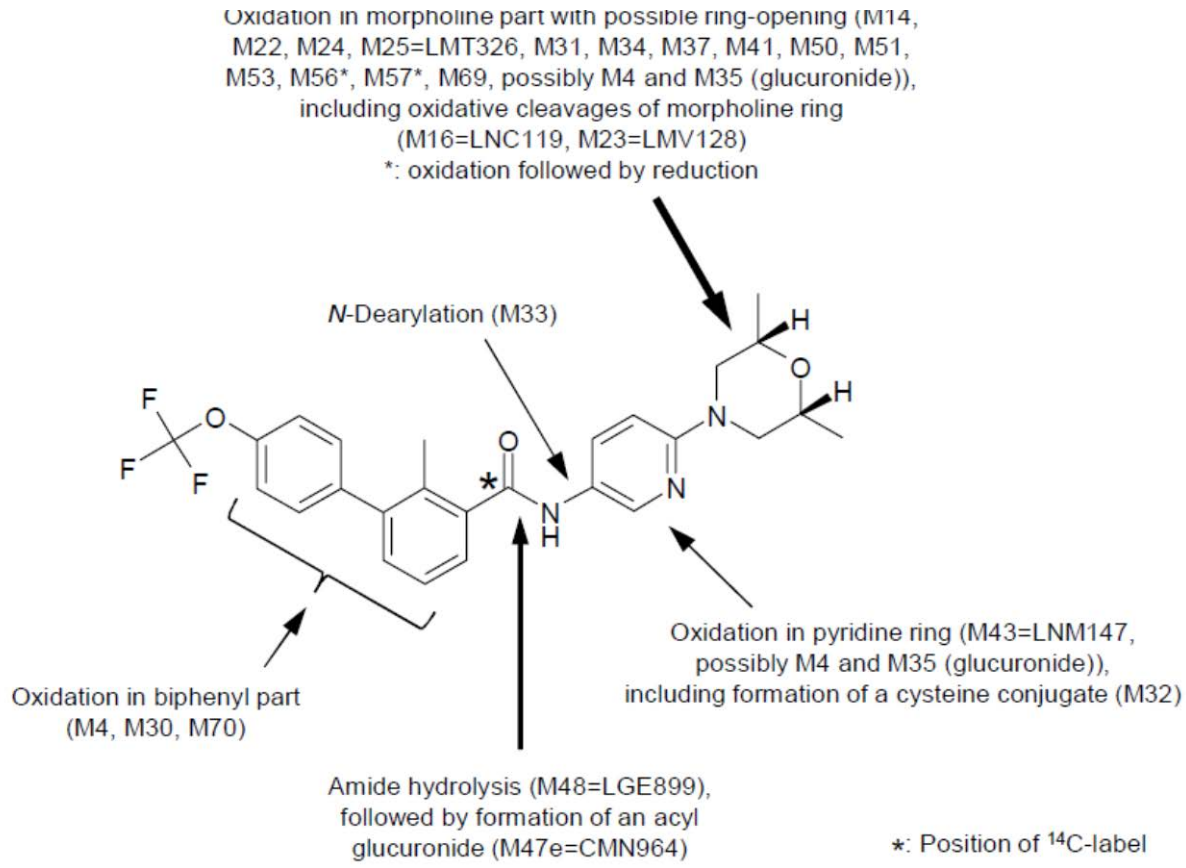
In vitro

The metabolic profile of sonidegib was determined in human liver microsomes and contributions of the individual cytochrome P450 enzymes and flavin monooxygenase (FMO) enzymes to sonidegib metabolism were evaluated using recombinant human enzymes. Selective inhibitors of CYP enzymes were used to identify the major metabolic enzymes in human liver microsomes (study DMPK R0800034).

The predominant metabolic pathways of sonidegib metabolism in human liver microsomes (HLM) were formation of the metabolites: M50, M51, M53, and M25 [DMPK R0800034]. No direct or secondary glucuronidation was observed in HLM in the presence of the co-factors for glucuronidation (UDPGA) and CYP enzyme mediated metabolism (NADPH). Evaluation of sonidegib metabolism by fifteen individual recombinant human CYP enzymes and three flavin monooxygenase (FMO) enzymes found only the CYP enzymes, CYP3A4 and CYP3A5 capable of metabolizing sonidegib. Ketoconazole and azamulin (inhibitors of CYP3A) inhibited total sonidegib metabolism in HLM by a maximum of 89-96% with IC50 values in-line with the median reported Ki or IC50 values for inhibition of CYP3A by these compounds. Other CYP selective inhibitors did not inhibit sonidegib metabolism to the reported IC50 values for that specific CYP inhibition.

The proposed metabolic pathway of sonidegib is presented in Figure 8.

Figure 8: Overview of identified metabolic pathways for sonidegib



In vivo

In mass balance study A2110, Cmax of sonidegib amounted to 76.6±4.4% (mean±SD) of Cmax of total radioactivity in plasma and AUCinf of sonidegib accounted for 34.9±6.6% (mean±SD) of the AUCinf of total radioactivity in plasma.

Metabolite profiles (14C-chromatograms) in plasma were determined in pools across all six subjects at four selected time points (4, 16, 120 and 504 hours). The recovery of radioactivity after sample preparation was essentially complete (estimated at 96.2-104%). Seventeen metabolites, amounting for 88.9% of the total radioactivity, were identified in plasma. Four metabolites of sonidegib were determined in more detail: the amide hydrolysis product LGE899 (metabolite M48), its acyl glucuronide CMN964 (M47e) and the oxidative morpholine cleavage products LMV128 (M23) and LNC119 (M16). All metabolites found in plasma were approximately 4- to 90-fold less potent than sonidegib and represented less than 40% of sonidegib exposure in plasma.

Dose proportionality and time dependencies

After a single oral dose of the sonidegib capsule intended for commercial use in the range of 200 to 1200 mg in healthy subjects in Study A1102 (Japanese), Study A2108, and Study A2114, the Tmax was approximately 2 hours (Table 14). Exposures as represented by maximum plasma concentration (Cmax) and various areas under the plasma concentration-time curve (AUCs) generally increased less than dose proportionally in the tested dose range.

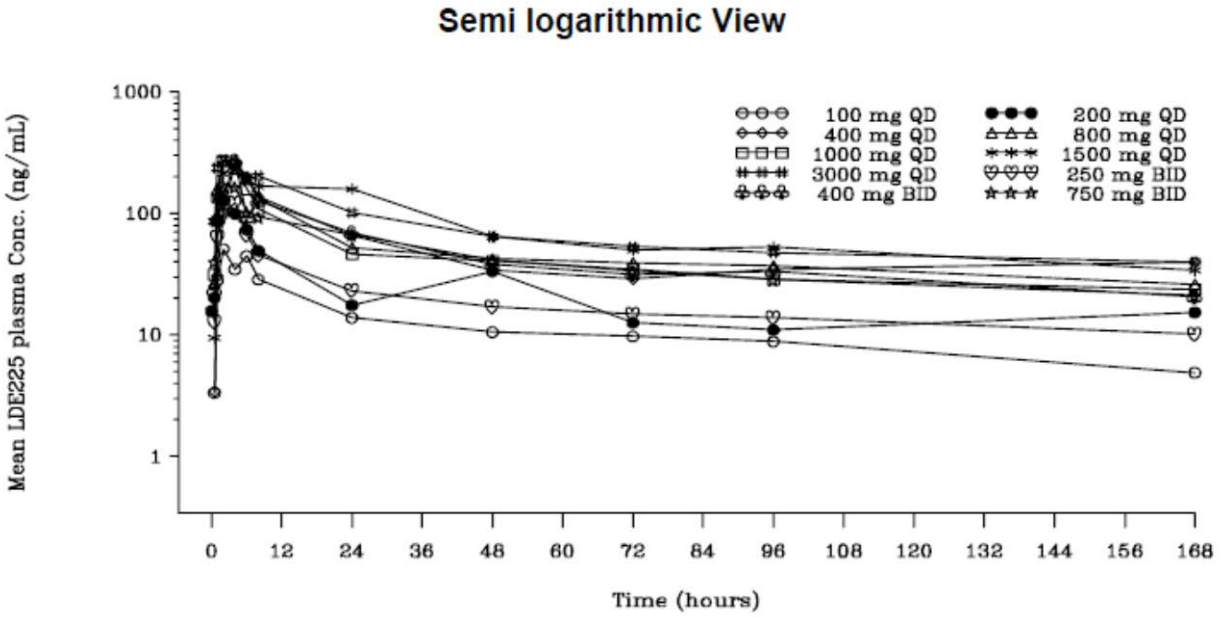
Table 14: Summary of PK parameters after a single dose of 200 to 1200 mg sonidegib (capsule) in healthy subjects by study (CLDE225A1102, CLDE225A2108, CLDE225A2110, CLDE225A2114)

Study	Dose (mg)	N	Tmax (h)	Cmax (ng/mL)	AUCinf (ng·h/mL)	AUC0-10d (ng·h/mL)	AUC0-14d (ng·h/mL)	CL/F (L/h)	Vss/F (L)	T1/2 (h)
A1102	200	12	2.00	136.17	4423.8	NA	NA	45.21	12727.0	233.0
			(1.00-5.00)	(45.43)	(46.62)			(46.62)	(59.24)	(42.13)
	400	12	2.00	172.98	5980.3	NA	NA	66.89	15884.1	191.8
			(1.00-4.00)	(41.91)	(53.41)			(53.41)	(63.29)	(32.61)
	800	12	2.00	275.44	12605.7	NA	NA	63.46	20075.1	241.1
			(1.00-6.00)	(36.37)	(40.66)			(40.66)	(32.20)	(24.74)
A2108	800	16	2.04	212	NA	5620	6570	NA	NA	NA
			(1.00-4.00)	(56.3)		(42.0)	(41.8)			
A2110[a]	800	6	2.00	151	8780	NA	NA	89.9	33300	310
			(2.00-4.00)	(20.8)	(30.5)			(30.1)	(20.7)	(26.1)
A2114[b]	200	11	2.01	87.05	2626.8	NA	2056.3	76.14	13904.0	163.03
			(1.02-5.00)	(99.6)	(130.3)		(118.6)	(130.3)	(107.7)	(49.7)
	800	12	2.10	216.49	10739.4	NA	6681.5	74.49	22259.3	234.22
			(1.02-5.00)	(71.1)	(59.6)		(45.7)	(59.6)	(55.3)	(61.7)
	1200	12	2.01	250.61	NA	NA	7125.5	NA	NA	NA
			(1.13-3.03)	(42.0)			(46.2)			

NA: not applicable
Data are presented as geometric mean (CV% geo mean) for all parameters except Tmax which is presented as median (range).
[a]Data after administration of a capsule formulation made by dry blending.
[b]N for 200 mg Tmax and Cmax was 12; N for 800 mg Tmax and Cmax was 13; N for 1200 mg AUC0-14d was 11.

In study X2101, after a single oral dose of 100 mg to 3000 mg in the PK run-in period, the median Tmax occurred at 2 to 4 hours. After repeated dosing for 2 weeks, the median Tmax occurred at 2 to 13 hours. Mean plasma exposure to sonidegib appeared to increase approximately dose-proportionally up to 400 mg, but less than proportionally above 400 mg Twice-daily dosing with 400- and 750-mg bid dosing resulted in AUC was 18-30% higher than with the equivalent once-daily dose. Figure 9 shows that elimination half-life was independent of dose as illustrated by parallel decline in plasma concentration for all doses.

Figure 9: Dose dependent pharmacokinetics of sonidegib (first dose) in the PK run in part of study X2101 in patients with solid tumours



Time dependency

The pharmacokinetics of sonidegib is not time-dependent in the popPK model.

In Study A2201, the mean plasma concentrations of sonidegib and LGE899 continued to rise until Week 13 to Week 17 following daily administration of sonidegib 200 mg and 800 mg. An approximate steady state appeared to be reached by approximately three months of starting sonidegib for both dose levels, which can be expected for a drug with a terminal elimination half-life of 28 days.

Pharmacokinetics in the target population

A population PK model was developed to characterize the PK of sonidegib after multiple doses in cancer patients, also including the full PK profiles from healthy subjects. The popPK structural model for sonidegib was a two-compartment disposition model with first order absorption with a lag. Dose-dependent bioavailability was included. PopPK model estimated a 3 fold larger apparent clearance among healthy subjects compared to cancer patients 35 L/h vs 10 L/h, respectively. The terminal elimination half-life was estimated 8.7 days days in healthy volunteers vs 28 days in cancer patients. The comparison between healthy volunteers and patients may be confounded as pharmacokinetics in healthy volunteers were conducted following single dose administration only while most information in patients was obtained following multiple dosing, the conditions with regard to meals was different (fasted or high fat meal conditions in healthy subjects, rather than 2 hours after a light breakfast as was instructed in the pivotal study), and most covariate categories (age, hepatic and renal function, intake of anti-acid drugs) were not equally distributed in healthy subjects and patients.

The PK parameters for cancer patients are summarized in Table 15. The mean steady-state Cmax for 200 mg QD was predicted as 1030 ng/mL, in good agreement with the mean Cmax concentration of 1031 ng/mL on Week 17 for 200 mg QD that occurred 2 hours post-dose.

Table 15: Population PK model-based PK parameter estimates for sonidegib in cancer patients

Dose	Day	AUC0-24h (ng*h/mL)	Cmax (ng/mL)	Cmin (ng/mL)
200 mg qd	Day 1	1122 (249, 2575)	125 (23.6, 321)	20.9 (5.21, 52.1)
	Steady state	22348 (5967, 53263)	1030 (317, 2351)	890 (224, 2170)
800 mg qd	Day 1	2724 (695, 5958)	303 (60.9, 769)	48.0 (14.4, 112)
	Steady state	51982 (12889, 125322)	2405 (652, 5396)	2065 (491, 5097)

Values are presented as mean (90% prediction intervals).

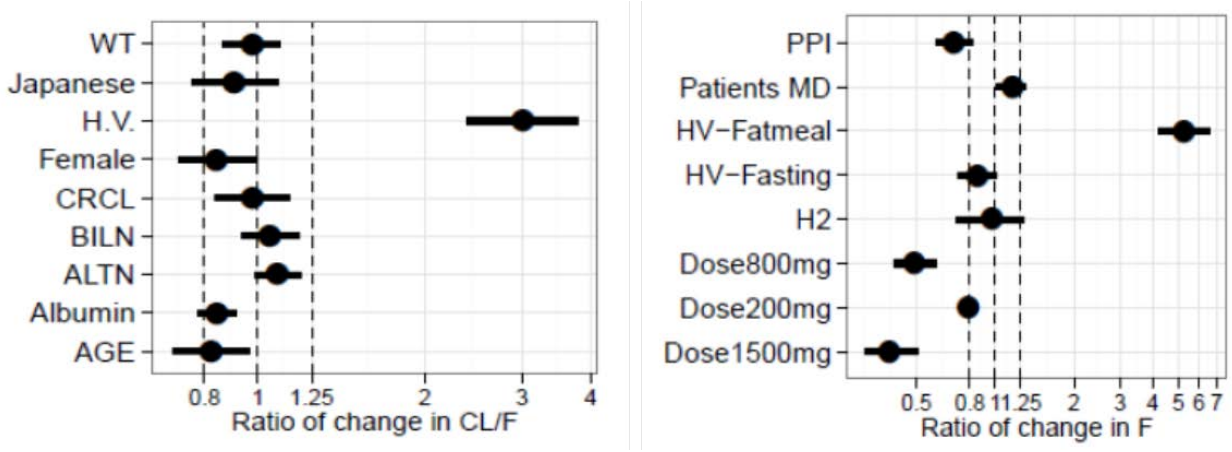
Parameters	Geometric Mean	%CV	5%	Median	95%
CL/F (L/h)	10.0	73.6	3.57	9.92	27.5
Vss/F (L)	9166	71.1	3166	9152	27881
Accumulation ratio	19.4	109	4.57	19.3	91.3
T1/2 (days)	28.3	108	6.98	27.7	120

The accumulation ratio is calculated by taking the ratio of AUC0-24h at steady state to AUC0-24h on Day 1

Special populations

A population PK analysis was conducted to estimate the impact of covariates on the apparent oral clearance of sonidegib. Incorporation of covariates in the popPK model led to a reduction in the inter-individual variability of CL/F from 106% to 64.5%. Figure 10 displays the confidence intervals of the ratio for the covariates on clearance and on absorption.

Figure 10: Effect of covariates on apparent clearance (CL/F) and on relative absorption factor (F) (considering BCC patients with 100 mg F=1)



Impaired renal function

Among 351 cancer patients included in the population PK analysis, 161 patients had normal renal function (CrCL ≥ 90 mL/min), while 129 patients had mild impairment at baseline (CrCL 60 to <90 mL/min), 60 patients had moderate impairment (CrCL 30 to <60 mL/min), and 1 patient had severe (CrCL 15 to <30 mL/min) impairment. Baseline CrCL with range of 27.3 to 290 mL/min had no statistically significant effect on CL/F of sonidegib. The ratio of the apparent clearance at 118 mL/min (75th percentile of CrCL) to the apparent clearance at 71 mL/min (25th percentile of CrCL) was estimated to be 0.98 (95% CI: 0.84, 1.1) when other covariates are held fixed at their typical values.

Impaired hepatic function

Based on the popPK analysis, the apparent oral clearance for sonidegib was estimated to decrease with increasing baseline albumin levels. The ratio of the apparent clearance at 46 g/L (75th percentile for baseline albumin) to the apparent clearance at 40 g/L (25th percentile of baseline albumin) was estimated to be 0.84 (95% CI: 0.78, 0.91) when other covariates were fixed at their typical values. Baseline ALT and baseline total bilirubin had no significant effect on the apparent clearance of sonidegib.

Pharmacokinetic interaction studies

Drug interaction with ketoconazole and rifampicin

Study A2108 was a single-dose, parallel group, drug-drug interaction study to assess the effects of 200 mg twice daily (bid) oral dose of ketoconazole and the effect of 600 mg once daily (qd) oral dose of rifampicin on the PK of a single 800 mg oral dose of sonidegib in healthy subjects. Ketoconazole and rifampicin were dosed from day 1 through day 14. At day 5 a single dose sonidegib 800 mg was administered.

Table 16: Effect of ketoconazole (200 mg bid) and rifampicin (600 mg qd) on pharmacokinetics of a single dose sonidegib 800 mg (Study A2108)

PK Parameter (unit)	Treatment	n *	Adjusted Geo-mean	Comparison	Treatment comparison Geo-mean Ratio	90% CI Lower	90% CI Upper
AUC0-240h (ng*h/mL)	sonidegib	16	5620				
	sonidegib+keto	15	12700	sonidegib+keto/ sonidegib	2.25	1.78	2.86
	sonidegib+rifam	16	1550	sonidegib+rifam/ sonidegib	0.276	0.219	0.349
Cmax (ng/mL)	sonidegib	16	212				
	sonidegib+keto	15	316	sonidegib +keto/ sonidegib	1.49	1.11	1.99
	sonidegib+rifam	16	97.7	sonidegib +rifam/ sonidegib	0.461	0.346	0.613

Model is a linear model of the log-transformed PK parameters. Included in the model is treatment as a fixed effect. Results were back transformed to get adjusted geo-mean, geometric mean ratio, and 90% CI.
n* = number of subjects with non-missing values.
keto = ketoconazole. rifam = rifampicin
Source: [Study A2108 – Table 11-3]

Drug interaction with contraceptives

Steady-state exposure following 200 mg sonidegib based on popPK analysis is AUC0-τ 22 µg.h/ml, Cmax,ss 1.0 µg/ml, Ctrough 0.89 µg/ml, t1/2 28 days. Based on an embryo-fetal development toxicity study in rabbits, the safe plasma concentration was set to 3 pg/mL. As estimated by popPK analysis, more than 95% of female patients of childbearing age are expected to have sonidegib levels below the threshold of 3 pg/mL at 20 months after ending treatment and after six months of condom use post drug discontinuation by male patients, less than 5% of healthy female partners are exposed to sonidegib concentrations above the safety threshold of 3 pg/mL.

Pharmacokinetics using human biomaterials

In vitro studies with human biomaterials were performed in order to assess the potential of sonidegib to act either as a substrate, inhibitor, or inducer of drug metabolizing enzymes and drug transporters.

Sonidegib as substrate of enzymes (study DMPK R0800034)

Evaluation of sonidegib metabolism by fifteen individual recombinant human CYP enzymes and three flavin monooxygenase (FMO) enzymes found only the CYP enzymes, CYP3A4 and CYP3A5 capable of metabolizing sonidegib. Ketoconazole and azamulin (inhibitors of CYP3A) inhibited total sonidegib metabolism in HLM by a maximum of 89-96% with IC50 values in-line with the median reported Ki or IC50 values for inhibition of CYP3A by these compounds. Other CYP selective inhibitors did not inhibit sonidegib metabolism to the reported IC50 values for that specific CYP inhibition.

Sonidegib as inhibitor of enzymes (study DMPK R0700986)

Sonidegib showed potent inhibition of CYP2B6 (unbound Ki = 0.007 µM) and CYP2C9 (unbound Ki = 0.237 µM). For other CYP activities (1A2, 2A6, 2C8, 2C19, 2D6, 2E1, 3A4/5), very little or no inhibition was observed up to 100 µM sonidegib.

Sonidegib as inducer (study DMPK R1200636)

The potential for sonidegib to act as an inducer of CYP1A2, CYP2B6, CYP2C9, and/or CYP3A4 enzymes was evaluated in primary human hepatocytes of three individual donors using both mRNA quantification and CYP activity measurements. Human hepatocytes were treated with sonidegib at a concentration range of 0.5- 25 µM (approximate therapeutic Cmax and a range of 2 orders of magnitude) for 48 h in addition to positive control inducers (rifampicin, phenobarbital and omeprazole). Sonidegib (0.5-25 µM) did not induce CYP2C9 or CYP3A mRNA and activities (levels were < 2-fold) in the three donor hepatocytes. In the induction study in hepatocytes from 1 liver a ~2-fold increase in mRNA was observed but increase in activity of CYP1A2 was <1.5-fold. These effects were < 20% of the positive control inducer responses.

Table 17: DMPK R1200636 in vitro evaluation of sonidegib as inducer of CYP enzymes in hepatocytes

Sonidegib Conc µM	CYP1A2			CYP2B6			CYP2C9			CYP3A4		
liver	1	2	3	1	2	3	1	2	3	1	2	3
0.5 µM	1.2	1.2	1.2	1.02	1.16	0.88	1.00	1.16	1.00	1.17	1.20	1.07
5 µM	1.9	1.5	1.5	0.93	0.77	0.77	0.94	0.84	1.05	0.95	0.44	1.27
10 µM	2.0	1.1	1.5	0.66	0.49	0.59	0.79	0.64	0.74	0.44	0.17	0.56
25 µM	1.9	1.1	0.75	0.55	0.38	0.37	0.72	0.57	0.42	0.43	0.15	0.11
Rif 10 µM	0.78	0.75	0.85	6.3	9.0	6.3	1.51	2.39	1.74	37	71	34
PB 1000 µM	1.3	1.4	1.3	8.6	11.4	11.6	1.61	2.67	2.20	35	91	48
Ome 50 µM	18.2	14.7	13.5	5.0	4.1	3.7	0.95	1.35	0.76	9.7	22	14

Sonidegib as substrate/inhibitor of transporter

In vitro studies using various cell lines were conducted to investigate substrate or inhibitor affinity of sonidegib for transporters. The results of these studies are summarized in Table 18.

Table 18: Sonidegib potential transporter interactions

transporter	cell system	Sonidegib Concentration µM	substrate	inhibitor	study	
Pglycoprotein	Caco-2 LLC-PK1-MDR1 MDA435 T0.3	5, 25[2] 2.5, 12.5[2] 0.01 - 50[3]	No no	 no	R0700984 R0700984 R0700988	
MRP-2	Caco-2 MDCKII-MRP2	5, 25[2] 5, 25	no	 no	R0700984 R0800540	
BCRP	Caco-2 CBBe1-Pgp/MRP2-KO (IGROV1)T8	5, 25[2] 0.82, 7.7[2] 0.01 - 50[3]	No no	 Yes EC50 =1.5µM	R0700984 R1300665 R0800323	
OATP1B1	HEK296 cells-OATP1B1 HEK293-OATP1B1	1.3 and 5.7 [1] 0.007-6.6[1]	no	 no	R1500333 R1200563	
OATP1B3	HEK296 cells-OATP1B3 HEK293-OATP1B3	1.3 and 5.7 [1] 0.007-6.6[1]	no	 Not consistent[4]	R1500333 R1200563	
OAT1	HEK293-OAT1	0.007-6.6[1]		no	R1200564	
OAT2	Hepatocyte suspension	0.2, 0.8[1]	no		R1200562	
OAT3	HEK293-OAT3	0.007-6.6[1]		no	R1200564	
OCT1	Hepatocyte suspension HEK293-OCT1	0.2, 0.8[1] 0.007-6.6[1]	no	 no	R1200562 R1200565	
OCT2	HEK293-OCT2	0.007-6.6[1]		no	R1200565	

[1]Unbound concentration
[2]In presence of 0.1%-0.5% human serum albumin
[3]In presence of 2% FCS

2.4.3. Pharmacodynamics

In clinical studies, Smo inhibition by sonidegib was studied by inhibition of the downstream Gli-1 mRNA expression in skin/tumour tissue in dose finding study X2101, study B2209 in patients with Gorlin syndrome and in a subgroup of patients with BCC in the pivotal study A2201.

The exposure-efficacy and exposure-safety relationships for sonidegib were evaluated to support the dose decision for advanced BCC.

- An exposure-efficacy analysis was performed for laBCC and mBCC from the pivotal Study A2201.
- An exposure-CK analysis was performed for four patient studies A2201, B2209, X1101, X2101.

- The risk of QTc prolongation was evaluated in the PK/ECG subgroup in the pivotal study, in a PK-QTc analysis using a pool of healthy subjects in Studies A1102, A2108, A2110, and A2114 and a separate pool of patients in studies A2201, B2209, X1101, and X2101.

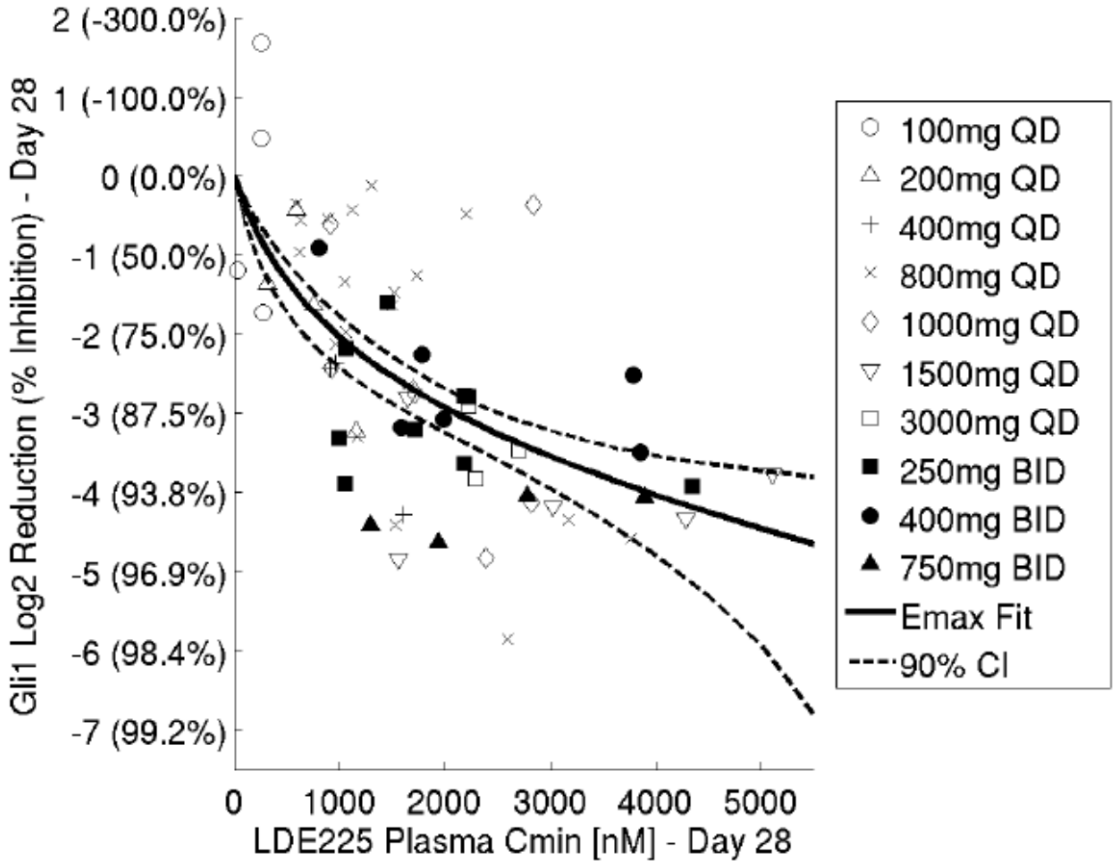
Mechanism of action

The applicant did not submit studies on mechanism of action (see non-clinical pharmacology).

Primary and Secondary pharmacology

Study X2101, a Phase I dose-escalation study, change in Gli1 mRNA expression from baseline in normal skin was the primary pharmacodynamics marker of sonidegib activity measured during the study. Skin tissues were collected at baseline and at Cycle 1 Day 28. Skin Gli1 expression was decreased by sonidegib treatment, and the magnitude of decrease correlated with sonidegib exposure as represented by Ctrough at Cycle 2 Day 1 (Figure 11). At 800 mg qd, 200 mg qd and 100 mg qd, mean Gli1 inhibition was 74%, 68%, and 29%, respectively. Paired tumour and skin biopsies available from 11 patients demonstrate that Gli1 inhibition in the tumour is similar to or more pronounced than that in the skin.

Figure 11: Reduction in skin Gli-1 mRNA expression relationship with sonidegib Ctrough concentration after 28 days treatment in patients with solid tumours (study X2101)

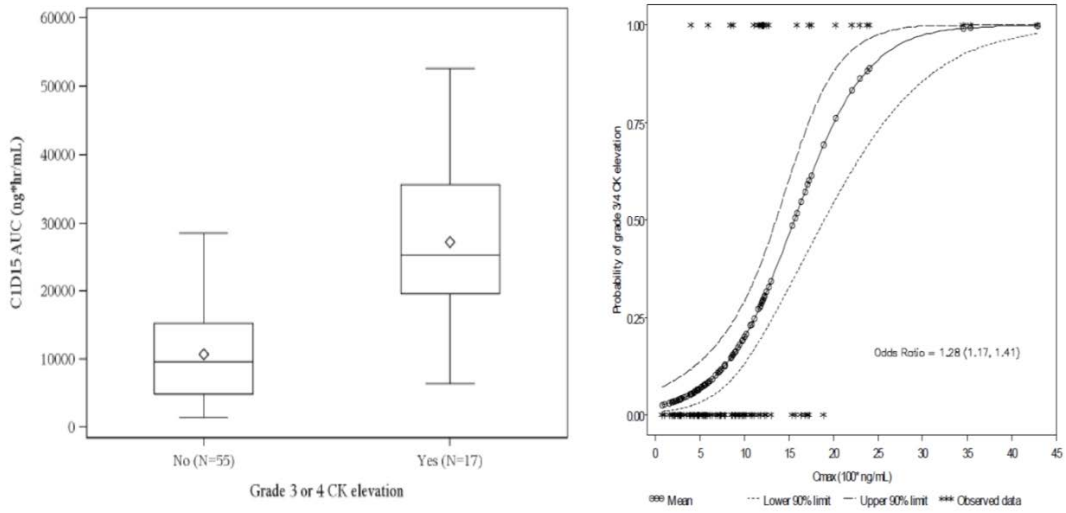


Exposure-CK relationship

An analysis of exposure-CK relationship was performed on pooled data for four studies in cancer patients included in the current submission (Studies A2201, X2101, X1101, and B2209). Figure 12

shows that patients with grade 3 or 4 CK elevations had significantly higher exposure to sonidegib. PKPD modeling showed that sonidegib exposure evaluated by AUC, Cmax or Ctrough at Cycle 1 Day 15 were all significantly correlated with the risk of grade-3 or -4 CK elevation, with increasing exposure associated with an increased risk of grade-3 or -4 CK elevation. The estimated mean (90% CI) probability of grade 3 or 4 CK elevation at the median Cmax for 200 mg qd was 0.039 (0.015, 0.097) and at the median Cmax for 800 mg qd was 0.112 (0.063, 0.192). Similar results were observed for AUC and Cmin.

Figure 12: Relationships between sonidegib exposure and grade 3 or 4 CK elevation (PK/CK set)



Exposure-QTc prolongation

Non-clinical cardiovascular safety pharmacology studies did not show an increase in QTc or an increase in cardiovascular toxicity at clinically relevant plasma concentrations. No dedicated QTc prolongation study was conducted because steady-state concentration of sonidegib are higher than can be achieved by single dose administration. The PK-QTc analysis included the patient studies [Study A2201], [Study X2101], [Study X1101], [Study B2209] and separately, the healthy subject studies [Study A1102], [Study A2108], [Study A2110], [Study A2114].

The analyses indicated that sonidegib does not produce a prolongation of QTcF; the 90% two-sided (95% one-sided) upper confidence limit never exceeded 10 msec at any time point. There was no correlation between sonidegib plasma concentrations and QTcF increase.

2.4.4. Discussion on clinical pharmacology

Study X2101 was a Phase I dose-escalation study of sonidegib to determine the maximum tolerated dose (MTD) when administered QD (100mg -3000mg) and bid (250, 400 and 750 mg) in a 28-day cycle to adult patients with advanced solid tumours that had progressed despite standard therapy or for which no standard therapy existed. The MTD was determined to be 800 mg for the once daily regimen and 250 mg for the twice daily regimen. The most common DLT was increased CK. Grade 3 and 4 CK elevations were not observed at dose levels below 800 mg on the QD schedule or 250 mg on the bid schedule in study X2101. Twice-daily dosing with 400- and 750-mg bid dosing resulted in AUC

was 18-30% higher than with the equivalent once-daily dose but an increased tendency to cause grade 3 or 4 CK elevations.

The 200-mg once-daily regimen was selected for evaluation on the basis that it represented the lowest dose level tested that demonstrated preliminary evidence of anti-tumour activity and Gli-1 inhibition.

Following the administration of a single dose of Odomzo (100 mg to 3000 mg) without food in patients with cancer, the median time-to-peak concentration (T_{max}) was 2 to 4 hours. Sonidegib exhibited dose-proportional increases in AUC and C_{max} over the dose range from 100 mg to 400 mg, but less than dose-proportional increases above 400 mg. There was no evidence of clearance change with repeated dosing based on the population pharmacokinetic analysis and estimated accumulation at steady state was 19-fold irrespective of dose. Steady state was reached approximately 4 months after starting sonidegib. The average steady state C_{trough} for 200 mg was 830 ng/ml (range 200 to 2400 ng/ml) in cancer patients. Compared to the fasted state, the C_{max} and AUC of Odomzo 800 mg was increased 7.8- and 7.4-fold, respectively when the dose was given with a high-fat meal.

Sonidegib has a long half-life (2-4 weeks). A profound food effect was observed for sonidegib exposure, sonidegib Cmax and AUCinf were increased 7.78- and 7.38-fold, respectively, when a single 800 mg dose of sonidegib capsule was administered with a high-fat meal compared to a fasted state indicating that this type of meal affected the absorption but not the elimination of sonidegib. Findings from the study also revealed that patients have a 3-fold higher exposure of sonidegib compared to healthy subjects (tested under fasting conditions). The current recommendation is that sonidegib capsules should be taken on an empty stomach at least 1 hour before or 2 hours after a meal to avoid overexposure to sonidegib (section 4.2 SmPC). The current dosing recommendations in the SmPC section 4.2 reflect the dosing conditions applied in the pivotal study. Food interactions have been identified as important identified risks in the RMP. Further, the CHMP has imposed a post-authorisation measure to perform a comparative bioavailability study to evaluate timing of meal relative to dose and fasting conditions and effect of light meal (low fat meal).

Based on a population pharmacokinetic analysis of 351 patients who received oral doses of Odomzo in the dose range of 100 mg to 3000 mg, the apparent steady-state volume of distribution (Vss/F) was 9170 litres. Steady-state level of sonidegib in the skin was 6-fold higher than in plasma.

Sonidegib was highly bound to human plasma proteins (human serum albumin and alpha-1 acid glycoprotein) *in vitro* (>97%), and binding was not concentration-dependent from 1 ng/ml to 2500 ng/ml.

Sonidegib and its metabolites are eliminated primarily by the hepatic route with 93.4% of the administered dose recovered in the faeces and 1.95% recovered in urine. Unchanged sonidegib in faeces represented 88.7% of the administered dose and was not detectable in urine. The elimination half-life (t1/2) of sonidegib estimated from population pharmacokinetic modeling was approximately 28 days. As sonidegib is mainly eliminated by metabolism, therefore, reduced hepatic function may affect the exposure of sonidegib (SmPC section 5.2). Results of the interim report of study A2113 showed that there is no substantial increase in the sonidegib exposure in the mild and moderate hepatic impairment group compared to the normal group. Therefore, no dose adjustment is necessary in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. The recommendations in section 4.2 of the SmPC for hepatic impaired patients is acceptable. The results of a study in severe impaired patients are awaited and in the meantime patients with severe hepatic impairment has been identified as missing information in the RMP. Further, the CHMP has imposed a post-authorisation measure to the applicant to evaluate the pharmacokinetics and protein binding of sonidegib in healthy subjects with normal hepatic function and subjects with impaired hepatic function.

Population pharmacokinetic analyses showed that there are no clinically relevant effects of age (range tested from 20 to 93 years, mean 61 years), body weight (range tested 42 to 181 kg, mean 77 kg), gender, or creatinine clearance (range tested 27.3 to 290 ml/min 290 ml/min, mean 92.9 ml/min) on the systemic exposure of sonidegib. The covariate effects of age, gender, and albumin levels were statistically significant, but the effects were <20% and were not considered clinically relevant for dose adjustment. Body weight and creatinine clearance had no effect on the pharmacokinetics of sonidegib.

The effect of renal impairment on the systemic exposure of sonidegib has not been studied. Since sonidegib is not renally excreted, no change in systemic exposure is anticipated in patients with renal impairment. A population pharmacokinetic analysis did not find significant influence of renal function (creatinine clearance >27 ml/min) on the apparent clearance (CL/F) of sonidegib suggesting that dose adjustment is not necessary in patients with renal impairment. The absence of data in severe renal impairment has been identified as missing information and is adequately addressed in the SmPC sections 4.2 and 5.2.

The C_{max} and AUC_{inf} of sonidegib in Japanese healthy subjects were 1.56 and 1.68-fold higher, respectively, than those seen in Western healthy subjects for a single dose of 200 mg. Therefore, a dose adjustment based on ethnicity is not required but races other than Caucasians has been identified as missing information in the RMP.

Overall the investigation for the potential of pharmacokinetic drug interaction has been reasonably well conducted. In vitro findings have been adequately followed-up by in vivo studies. Based upon the in vitro data, metabolism of sonidegib is mediated primarily by CYP3A4. Unchanged sonidegib represented 36% of circulating radioactivity and the major circulating metabolite (45% of parent exposure) identified in plasma is the hydrolysis product of sonidegib and is pharmacologically inactive. All the metabolites were deemed 4 to 90 times less potent than sonidegib. A drug-drug interaction study with CYP3A4 inhibitor ketoconazole increased sonidegib exposure by 2.3 fold (90% CI 1.8-2.9 fold). A drug-drug interaction study with rifampicin reduced sonidegib exposure by 72% (90%CI 65%-78%). The magnitude of the effects of CYP3A4 inhibitors and inducers could not be fully estimated as the effect of ketoconazole and rifampicin was determined up to 14 days, which is only a half of the elimination half-life and was conducted in healthy volunteers. Further, the simulations estimated a 2-fold increase in sonidegib exposure for short term concomitant use of strong CYP3A4 inhibitors, i.e. 2 weeks. Co-medication with strong CYP3A4 inhibitors or inducers were excluded in the pivotal study as a drug-drug interaction study A2108 showed that these drugs affected the exposure of sonidegib to a potentially clinical significant effect. Therefore, interactions with strong CYP3A4 inhibitors and CYP3A4 inducers have been identified as important identified risks. Dose recommendations for sonidegib when co-administered with strong CYP3A4 inhibitors have been introduced in the SmPC in section 4.5.

Based upon the *in vitro* data, sonidegib is a potentially strong inhibitor of CYP2C9 and CYP2B6. Therefore, co-medication of drugs metabolized by CYP2B6 or CYP2C9 that have narrow therapeutic index was excluded from study A2201. This potential interaction has been adequately described in the SmPC in section 4.5. However, *in vivo* drug interaction has not been submitted. Therefore, the CHMP has imposed a post-authorisation measure on the submission of the Study LDE225A2112. A Phase Ib, multicenter, two parallel group, open label, drug-drug interaction study to assess the effect of sonidegib on the PK of bupropion (CYP2B6) and warfarin (CYP2C9) in patients with advanced solid tumours. Sonidegib is an inhibitor of BCRP transporter. The potential interaction has been described adequately in the SmPC in section 4.5 and 5.2. Sonidegib was not a substrate for OATP1B1 and OATP1B3. This information has been adequately described in the SmPC in section 5.2. Sonidegib has shown pH-dependent solubility and dose-dependent bioavailability and therefore, a potential exists for differential effect of proton pump inhibitors depending on sonidegib dose. In the popPK model, a 30% lower exposure was predicted for patients taking PPIs as co-medication while co-medication with H2

receptor antagonist was predicted not to affect the exposure of sonidegib. Therefore, a warning has been included in section 4.5 on the potential to alter the solubility of sonidegib and potentially reduce its bioavailability. In addition, the CHMP has imposed a post-authorisation measure to investigate the potential interaction of esomeprazole on the PK of sonidegib. Interactions with sensitive CYP2B6, CYP2C9, and BCRP substrates with low therapeutic index and interaction with proton-pump inhibitors have been identified as important potential risks in the RMP.

Sonidegib treatment is associated with creatine kinase elevations. Temporary dose interruptions are proposed for CK elevations and muscle related AEs or an increase in sonidegib dose if CYP3A4 inducers are coadministered (SmPC section 4.2). In study A2201, co-medication of HMG-CoA reductase inhibitors (statins), clofibrate, and gemfibrozil, which are also associated with muscle-related toxicity/rhabdomyolysis was excluded from the study or if it was essential that the patient stayed on a statin to control hyperlipidemia, only pravastatin was allowed to be used. Therefore, limited safety data are available for co-medication with statins and the available data is restricted to pravastatin. This is reflected in the SmPC in section 4.4 and 4.5. Muscle –related events have been included as important identified risks in the RMP.

The sonidegib plasma concentration-QTc analysis showed that the upper bound of one-sided 95% confidence interval for QTc increase was below 5 msec at steady-state C_{max} for 800 mg daily doses, which provide 2.3-fold plasma exposure compared with the recommended 200 mg dose. Therefore, therapeutic doses of Odomzo are not expected to cause clinically significant QTc prolongation. Further, sonidegib plasma concentrations above those achieved with the therapeutic doses were not associated with life-threatening arrhythmias or torsades de pointes. Tumour response was independent of Odomzo dose or plasma concentration in the dose range of 200 mg to 800 mg.

Studies in animals have shown reproductive, foetal and developmental toxicity (see non-clinical discussion). A drug interaction study with contraceptives will be difficult to conduct as the use of effective contraception has been recommended in the SmPC in section 4.4 and 4.6. Female patients of childbearing potential taking concomitant oral contraceptives have been identified as missing information in the RMP. Based on the non-clinical studies, the safe plasma concentration was set to 3 pg/mL. As estimated by popPK analysis, more than 95% of female patients of childbearing age are expected to have sonidegib levels below the threshold of 3 pg/mL at 20 months after ending treatment and after six months of condom use post drug discontinuation by male patients, less than 5% of healthy female partners are exposed to sonidegib concentrations above the safety threshold of 3 pg/mL. This has been communicated in the SmPC as well as in the educational material.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology of sonidegib has been adequately characterised. The dose has been justified based on PK data and correlative data with the PD biomarker Gli expression, which is considered acceptable. In addition, the current dosing recommendation of taking sonidegib without food has been justified as it reflects the dosing conditions in the pivotal trial. However, the unexplained 3-fold difference in apparent clearance between cancer patients and healthy subjects and the high unexplained variability in sonidegib pharmacokinetics in patients is still of concern. Further, there is an uncertainty regarding the timing to food intake of sonidegib exposure. It is uncertain if patients not following the dosing recommendations as applied in the pivotal study are at risk of overdosing when taking sonidegib with a meal or at risk of underdosing when taken under fasted. Therefore, and to provide more guidance for the dosing recommendations in the SmPC, the CHMP has imposed further investigation of how the exposure of sonidegib following the dosing recommendations in study A2201 relate to the exposure under fasting conditions and fed conditions.

The CHMP considers the following measures necessary to address the issues related to pharmacology (see also RMP):

1. A comparative bioavailability study to evaluate timing of meal relative to dose and fasting conditions and effect of light meal (low fat meal).
2. Study LDE225A2112 A Phase Ib, multicenter, two parallel group, open label, drug-drug interaction study to assess the effect of sonidegib on the PK of bupropion and warfarin in patients with advanced solid tumours.
3. Investigation the potential interaction of sonidegib with esomeprazole (Study LDE225A2118).
4. Study LDE225A2113 A phase I, open label, multi-center, single dose study to evaluate the pharmacokinetics and protein binding of sonidegib in healthy subjects with normal hepatic function and subjects with impaired hepatic function.

2.5. Clinical efficacy

2.5.1. Dose response study

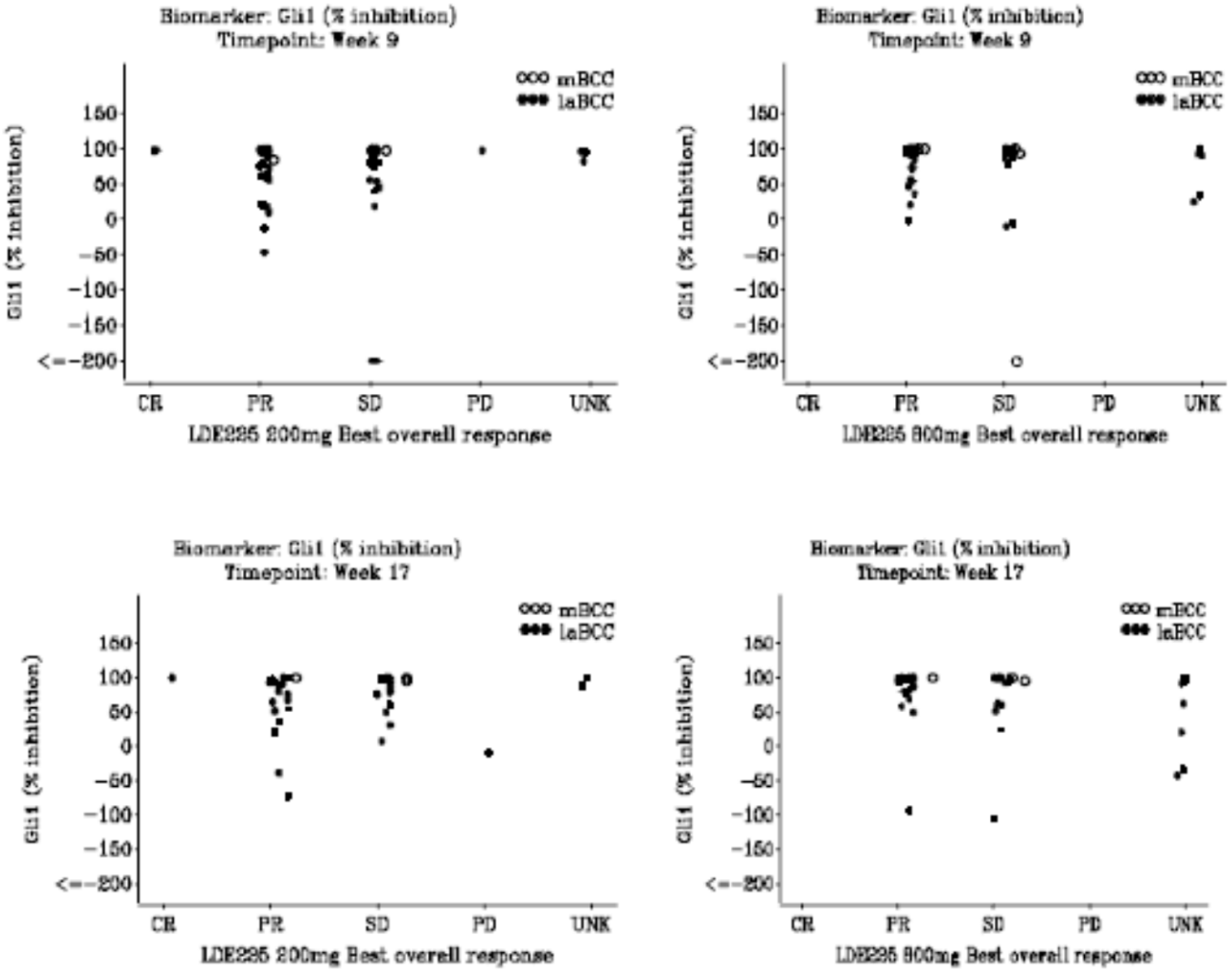
In the phase I X2101 trial conducted in patients with advanced solid tumours (103 pts) (median treatment duration: 50 days), sonidegib doses ranging from 100 mg to 3000 mg QD (100, 200, 400, 800, 1000, 1500, 3000 mg), and from 250 to 750 mg BID (250, 400, 750 mg) or tablets (120, 160, 220 mg) were administered.

The MTD was determined to be 800 mg for the once daily regimen and 250 mg for the twice daily regimen. The most common DLT was increased CK. Grade 3 and 4 CK elevations were not observed at dose levels below 800 mg on the qd schedule or 250 mg on the bid schedule in study X2101. Preliminary evidence of anti-tumour activity (CR or PR) was observed in 6/16 patients with advanced BCC or 2/9 patients with medulloblastoma. There was no clear correlation with dose and anti-tumour activity.

At the once daily MTD of 800 mg, mean Gli-1 inhibition (the primary pharmacodynamic marker chosen to assess the activity of the substance) was 74%, and at the once daily dose of 200 mg mean Gli-1 inhibition was 68%.

Figure 13 shows the individual change from baseline in Gli1 levels versus best overall response by treatment arm and BCC stage, in study A2201. For the 200-mg arm, median inhibition ranged from 81.9% to 92.8% for patients with laBCC. In the 800-mg arm, the median inhibition across visits was >95%. The intersubject variability in change of Gli1 expression was very high.

Figure 13: Strip plot of change from baseline in Gli1 levels versus best overall response by treatment arm and BCC stage (FAS) study A2201



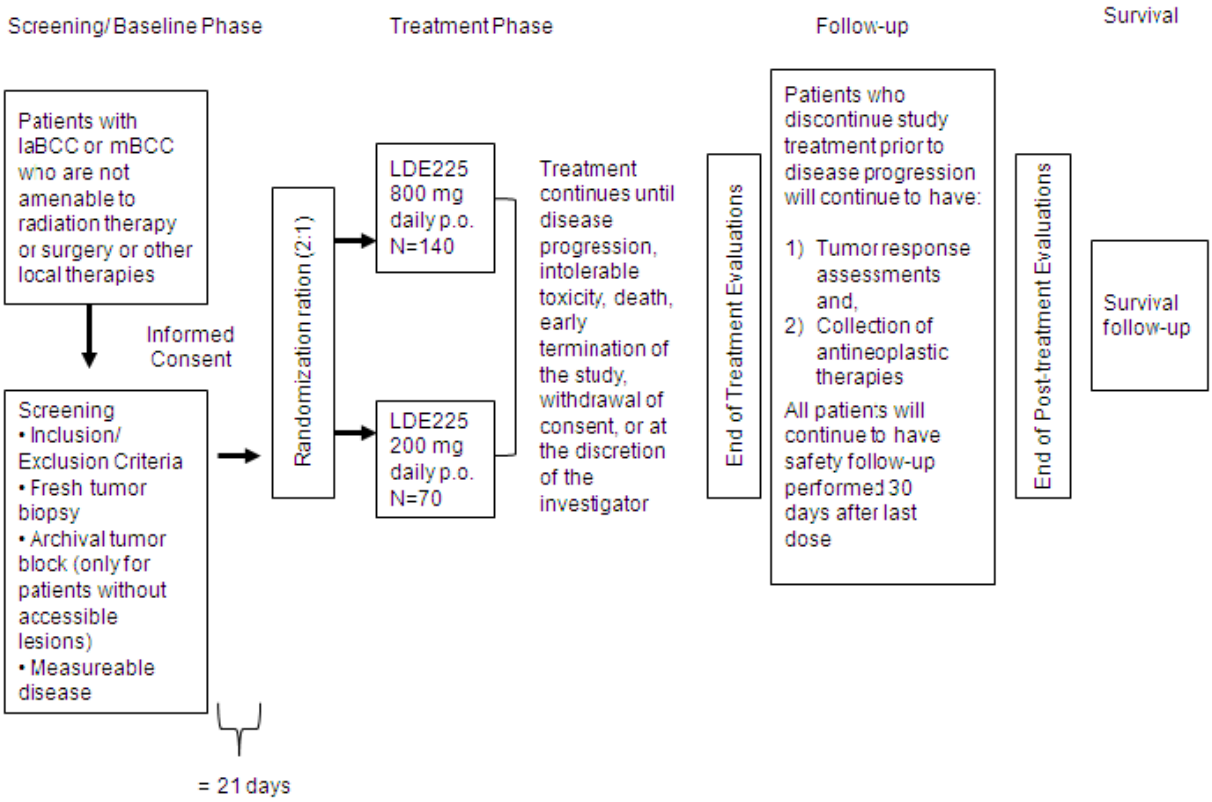
The 800 mg QD dose corresponded to the MTD observed in the X2101 study. However, based on preliminary anti-tumour activity with reported exposures in the predicted efficacious range in the great majority of patients and on the basis also of Gli-1 inhibition data, no further anti-tumour activity was found compared to the 200 mg QD dose. Therefore, the dose of 200 mg was chosen for the main study.

2.5.2. Main study

CLDE225A2201: A phase II, randomized, double-blind study of efficacy and safety of two dose levels of LDE225 in patients with locally advanced or metastatic basal cell carcinoma (BOLT)

Methods

Figure 14: Study design for A2201



Study Participants

The main inclusion criteria were:

- Age 18 years or older
- Patients with locally advanced BCC (laBCC) or metastatic BCC (mBCC):
    - Patients with a histologically confirmed diagnosis of laBCC that is not amenable to radiation therapy, curative surgery, or other local therapies. Histological confirmation of diagnosis must be based on the fresh tumour biopsy obtained at screening. Patients who do not have accessible BCC lesion(s) must provide an archival tumour specimen for this purpose. Patients with laBCC must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension as ≥ 10 mm with magnetic resonance imaging (MRI) scan or on color photographs.

- Patients with a histologically confirmed diagnosis of mBCC. Histological confirmation of diagnosis must be based on the screening fresh tumour biopsy (if feasible) or archival tumour specimen. Patients with mBCC must have measurable disease, defined as at least one non-nodal lesion that can be accurately measured in at least one dimension as no less than double the slice thickness or 10 mm, whichever is greater with spiral computed tomography (CT) or MRI scan or one nodal lesion (i.e. lymph node) ≥ 15 mm in short axis with spiral CT scan or MRI scan (irrespective of slice thickness). Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by CT/MRI can be considered as measurable lesions. Lesions in previously irradiated areas can only be considered measurable if they have shown clear evidence of progression since the radiotherapy, as documented in the medical records.

- World Health Organization (WHO) performance status ≤ 2
- Patients with adequate bone marrow, liver and renal function, as specified below:
    - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
    - Hemoglobin (Hgb) ≥ 9 g/dL
    - Platelets ≥ 100 x 10^9/L
    - Serum total bilirubin ≤ 1.5 x ULN (upper limit of normal)
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN or ≤ 5 x ULN if liver metastases are present
    - Serum CK <1.5 x ULN
    - Serum creatinine ≤ 1.5 x ULN or 24-hour clearance ≥ 50 mL/min

The main exclusion criteria were:

- Patients who have had major surgery within 4 weeks of initiation of study medication
- Patients with concurrent uncontrolled medical conditions that may interfere with their participation in the study or potentially affect the interpretation of the study data
- Patients unable to take oral drugs or with lack of physical integrity of the upper gastrointestinal tract or known malabsorption syndromes
- Patients who have previously been treated with systemic sonidegib or with other Hh pathway inhibitors
- a) Patients who have neuromuscular disorders (e.g. inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis and spinal muscular atrophy) or are on concomitant treatment with drugs that are recognized to cause rhabdomyolysis, such as HMG-CoA reductase inhibitors (statins), clofibrate, and gemfibrozil, and that cannot be discontinued at least 2 weeks prior to starting sonidegib treatment. If it is essential that the patient stays on a statin to control hyperlipidemia, only pravastatin may be used with extra caution.

  b) Patients who are planning on embarking on a new strenuous exercise regimen after initiation of study treatment. NB: Muscular activities, such as strenuous exercise, that can result in significant increases in plasma CK levels should be avoided while on sonidegib treatment.
- Patients who have taken part in an experimental drug study within 4 weeks of initiating treatment with sonidegib.

- Patients who are receiving other anti-neoplastic therapy (e.g. chemotherapy, targeted therapy or radiotherapy) concurrently or within 4 weeks of starting treatment with sonidegib. All toxicity from prior therapy must be ≤ grade 1 prior to initiation of study treatment.
- Patients who are receiving treatment with medications known to be moderate and strong inhibitors or inducers of cytochrome P450 (CYP) 3A4/5 or drugs metabolized by CYP2B6 or CYP2C9 that have narrow therapeutic index, and that cannot be discontinued before starting treatment with sonidegib . Medications that are strong CYP3A4/5 inhibitors should be discontinued at least 7 days and strong CYP3A/5 inducers for at least 2 weeks prior to starting treatment with sonidegib.
- Pregnant or nursing (lactating) women, confirmed by a positive hCG laboratory
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, UNLESS they were using two forms of highly effective contraception, throughout the study and for 6 months after the last treatment.
- Sexually-active males must use a condom during intercourse while taking the drug and for 6 months after stopping sonidegib treatment and should not father a child in this period. A condom was required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

Treatments

Sonidegib was administered orally, on a continuous once-daily schedule, at a dose of either 200 mg or 800 mg. Sonidegib was supplied as 200-mg hard-gelatin capsules. The 200- mg arm received 1 sonidegib capsule+3 placebo capsules and the 800-mg arm received 4 capsules of sonidegib. Placebo (batch number: X338MG) was formulated to be indistinguishable from the sonidegib capsules.

All eligible, enrolled patients were randomized in a 1:2 ratio to treatment with either sonidegib 200 mg or sonidegib 800 mg on a continuous once-daily dosing schedule.

Duration of treatment: Patients are to continue study treatment until documented disease progression (as confirmed by central review), discontinuation attributable to intolerable toxicity, withdrawal of consent, death, at the discretion of the investigator, or upon early termination of the study.

Dose adjustments were permitted for patients who were unable to tolerate the protocol specified dosing schedule to keep the patient on treatment. In addition, dosing modifications were allowed in the event of toxicities suspected to be related to the study drug.

For patients randomized to the 800-mg dose, a maximum of two dose-reduction steps were allowed. Patients taking 200 mg QD who required a dose reduction received placebo only as first reduction and discontinued from treatment if a second reduction was necessary. The following table describes the dose reduction steps.

Table 19: Dose reduction steps for sonidegib

		Dose reduction[a]	
	Starting dose level 0	Dose level -1	Dose level -2
Sonidegib dose (mg)	800	400	200
Sonidegib dose (mg)	200	placebo	n/a

[a] Dose reduction was based on the worst toxicity demonstrated.

For patients who underwent dose interruptions (delays), if the same toxicity returned after reinitiation of treatment, irrespective of duration, the second re-initiation was resumed at a lower dose. If the

patient required a dose interruption of >21 days from the previous dose, then the patient was discontinued from study treatment.

Medications required to treat AEs and manage cancer symptoms, concurrent stable disease (e.g. controlled hypertension) and supportive care agents such as erythropoietin, granulocyte growth factors, or blood transfusion, and pain medications were allowed (although use of growth factors, erythropoietin, blood transfusion or granulocyte colony-stimulating factor [GCSF] was not permitted, until the patients had developed dose-limiting anemia or neutropenia).

Sonidegib (200 mg hard-gelatin capsule or matching placebo, either 1 sonidegib capsule + 3 placebo capsules or 4 capsules of sonidegib) was to be taken with a glass of water over as short time as possible (e.g. 1 capsule every 2 minutes) approximately 2 hours after a light breakfast (e.g. consisting of juice, toast, and jam). Food intake was to be avoided for at least 1 hour after study drug administration. Patients were requested to avoid grapefruit, pomegranate, star fruit, and Seville (sour) oranges or relative juices during the study.

Objectives

The primary objective was to evaluate the efficacy of sonidegib as measured by ORR assessed by central review (for mBCC) and Independent Review Committee (IRC) (for laBCC) according to:

- mRECIST in patients with laBCC
- RECIST 1.1 in patients with mBCC

Key secondary objectives were:

- To determine the DoR as assessed by central review according to mRECIST in patients with laBCC and to RECIST 1.1 in patients with mBCC
- To determine the rate of complete response (CR) as assessed by central review according to mRECIST in patients with laBCC and to RECIST 1.1 in patients with mBCC

Other secondary objectives were:

- To evaluate the effect of sonidegib therapy on progression-free survival (PFS) as assessed by central review according to mRECIST in patients with laBCC and to RECIST 1.1 in patients with mBCC
- To evaluate the time to tumour response (TTR), i.e. complete response (CR) or partial response (PR) as assessed by central review according to mRECIST in patients with laBCC and to RECIST 1.1 in patients with mBCC
- To evaluate the effect of sonidegib therapy on ORR, CRR, DoR, PFS, TTR as assessed by investigator according to mRECIST in patients with laBCC and to RECIST 1.1 in patients with mBCC
- To further characterize the safety of sonidegib therapy
- To further characterize the pharmacokinetics (PK) of sonidegib by measuring trough (Cmin) plasma concentrations of sonidegib
- To assess the effect of sonidegib therapy on overall survival (OS)

Outcomes/endpoints

The primary efficacy endpoint was ORR determined by the IRC according to mRECIST for patients with laBCC and by central review according to RECIST 1.1 for patients with mBCC. All patients with laBCC were assessed with MRI scans and clinical photography, as appropriate. Patients with certain disease features, such as laBCC in difficult anatomical locations (e.g. auditory canal), may not have been suited for color photography. Also, some laBCC lesions were not suitable for MRI evaluation (as confirmed by central review). Patients with mBCC were assessed with either CT or MRI scans (and color clinical photography for skin lesions, if any) at baseline and subsequent time points per the tumour assessment schedule (the same imaging modality should have been used within patients).

Modified RECIST were developed to adequately assess response in patients with laBCC that were associated with features which were not adequately covered by RECIST 1.1, such as scarring/fibrosis and ulceration.

The underlying principles of the composite overall response as per mRECIST criteria, are as follows:

- Patients who achieve any shrinkage or morphological change in tumor (e.g. development of scars/fibrosis) that is potentially consistent with treatment effect will be biopsied to confirm the presence or absence of tumor.
    - Patients with post-treatment scar/fibrosis formation will be considered to have achieved CR if biopsies of the residual lesion(s) confirm the absence of tumor.
    - PR or SD with scar/fibrosis formation will be considered to be CR if histology confirms the absence of tumor.
- Missing biopsy data, e.g. if not taken (UNKNOWN), will be considered as POSITIVE histology for the purposes of composite overall response determination per m- RECIST with the following exception: Following determination of CR a biopsy sample is not required at any subsequent time-point unless visual (photograph) or radiologic evidence indicates progression of disease. In such cases, a missing biopsy data will be considered as NEGATIVE histology and the composite overall response will continue to be assessed as complete response (CR).

If the disease is not assessable by MRI scan at baseline (e.g. disease is not measurable or MRI is contraindicated for the patient due to metal implants), the composite overall response will be based on photograph(s) along with histology of the lesion(s). MRI scans at post-baseline time-points are not required and will not be used in response determination. Similarly, if the disease is not assessable by photo at baseline, MRI scan along with histology will be used to determine the composite overall response. Post-baseline photographs will not be used in response determination.

If the disease is assessable by MRI scan at baseline but an MRI scan is missing at any postbaseline assessment, then the composite overall response at that assessment will be “UNKNOWN”. Similarly, if the disease is evaluable by photograph at baseline but a photograph is missing at any post-baseline assessment, then the composite overall response at that assessment will be “UNKNOWN”.

Table 20: Composite overall response assessment per mRECIST in patients in laBCC

Composite overall response	MRI	Clinical photography	Histopathology
CR	CR	CR, PR(s/f), SD(s/f), or NA[a]	Negative
CR	NA[b]	CR, PR(s/f), or SD(s/f)	Negative
PR	PR	CR, PR(s/f), or SD(s/f)	Negative
PR	SD	CR, PR(s/f), or SD(s/f)	Negative
PR	CR	CR, PR(s/f), NA[a]	Positive or unknown
PR	CR	PR	Any
PR	PR	CR, PR(s/f)	Positive or unknown
PR	PR	PR, NA[a]	Any
PR	SD	CR, PR(s/f)	Positive or unknown
PR	SD	PR	Any
PR	NA[b]	CR, PR(s/f)	Positive or unknown
PR	NA[b]	PR	Any
SD	CR	SD	Any
SD	CR	SD(s/f)	Positive or unknown
SD	PR	SD	Any
SD	PR	SD(s/f)	Positive or unknown
SD	SD	SD, NA[a]	Any
SD	SD	SD(s/f)	Positive or unknown
SD	NA[b]	SD	Any
SD	NA[b]	SD(s/f)	Positive or unknown
Unknown	Any (except PD)	Unknown[c]	Any
Unknown	Unknown[d]	Any (except PD)	Any
PD	PD	Any	Any
PD	Any	PD	Any

CR = complete response; NA = not available; PD = disease progression; PR = partial response; SD = disease stabilization; s/f = scar/fibrosis only

[a] Disease unevaluable by photography at baseline; also includes scenarios where photographic data are unavailable

[b] Disease unevaluable by MRI scan at baseline; also includes scenarios where MRI data are unavailable

[c] As a result of missing assessment or other reasons post-baseline while disease is evaluable by photography at baseline

[d] As a result of missing assessment or other reasons post-baseline while MRI scan at baseline was available.

Imaging methodologies used for tumour assessments per central review and investigator assessment were:

• Localized/soft tissue MRI scans and color clinical photography for patients with laBCC

• Chest/abdomen/pelvis CT or MRI for patients with mBCC (color clinical photography for skin lesions, if any)

In addition to localized/soft tissue MRI scans, for all patients with laBCC, all skin lesions (target and non-target) were required to be assessed by color photography per the tumour assessment schedule, except for lesions in difficult anatomical locations, e.g. auditory canal, that cannot be assessed by color photographs.

Baseline tumour assessments were performed ≤ 21 days prior to starting study treatment. After baseline (screening assessments), further tumour response evaluations were performed at Weeks 5, 9, and 17 (±3 days) and subsequently every 8 weeks (±3 days) during the first year and every 12 weeks (±3 days) thereafter until PD was confirmed, start of a new antineoplastic therapy, lost to follow-up, or 78 weeks from the date of enrollment of the last patient, whichever came first. The tumour response assessment at Week 5 was required for patients with laBCC and was recommended (optional) for patients with mBCC.

Biopsies for confirmation of the presence or absence of tumour (i.e. at confirmation of CR or PR, or when tumour response was uncertain) were to be taken from target lesions (≥ 10 mm in their longest dimension).

Considerations for patients with laBCC

Measurable lesions were those that could be accurately measured in at least one dimension as ≥ 10 mm with MRI scan or on color photographs.

Any lesion that was previously treated with radiotherapy was considered as a non-target lesion, unless it was measurable and had shown clear progression since the radiotherapy, in which case, it may have been considered as a target lesion.

Considerations for patients with mBCC

Measurable lesions were non-nodal lesions that could be accurately measured in at least one dimension as no less than double the slice thickness or 10 mm, whichever was greater, with spiral CT or MRI scan, or nodal lesions (i.e. lymph node) ≥ 15 mm in short axis with spiral CT or MRI scan (irrespective of slice thickness). Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that could be evaluated by CT/MRI could be considered as measurable lesions.

As with the laBCC cohort, any lesion that was previously treated with radiotherapy was considered as a non-target lesion, unless it was measurable and had shown clear progression since the radiotherapy, in which case, it may have been considered as a target lesion.

The key secondary endpoints included duration of response (DoR) and complete response rate (CRR), both determined per central review, according to mRECIST for patients with laBCC and RECIST 1.1 for patients with mBCC. Other secondary endpoints included the following: time to tumour response (TTR, i.e. complete response or partial response as assessed by central review and investigator according to mRECIST in patients with laBCC and to RECIST 1.1 in patients with mBCC); progression-free survival (PFS, as assessed by central review and investigator according to mRECIST in patients with laBCC and to RECIST 1.1 in patients with mBCC).PROs included evaluation of Health Related Quality of life (according to EORTC QLQ-C30 and its associated head and neck cancer-specific module [H&N35] and SF-36. However, no formal inferential statistical analysis was planned for PROs. Time to deterioration for PRO outcomes (defined as the first time from the date of randomization that the patient's score hit a threshold of 10 points or more worsening from their baseline score with no later improvement above this threshold) was evaluated.

Sample size

Study A2201 (BOLT) was planned to include approximately 210 patients to obtain 150 patients in the primary efficacy analysis set (pEAS) if the study was continued beyond the interim analysis.
The decision operating characteristics for the primary endpoint (ORR per mRECIST in laBCC patients and RECIST 1.1 in mBCC patients as determined by central review, in the pEAS) of the study design under different true ORR (note that this is not the same as the observed ORR) on each treatment arm is provided in the table below. The table is based on 150 patients eligible for the pEAS.

Table 21: Decision operating characteristics for the primary endpoint of A2201 study design

True ORR	Probability of observing an ORR ≥ 30%		
	800 mg arm with 100 patients in pEAS at the primary analysis	200 mg arm with 50 patients in pEAS at the primary analysis	200 mg arm with 100 patients in pEAS at the primary analysis
0.20	0.003	0.024	0.005
0.25	0.085	0.150	0.089
0.30	0.424	0.417	0.405
0.35	0.805	0.703	0.759
0.40	0.961	0.884	0.921
0.45	0.993	0.962	0.971

The design provides control of type I (false-positive) error rate with only a 0.3% for 800 mg arm and 2.4% for 200 mg arm if the true ORR on the respective arms is 20% or less. When 800 mg arm is terminated and 200 mg is continued to enroll 100 patients in the pEAS the type I error rate is only 0.5% if the true ORR for 200 mg arm is 20% or less.
For the purposes of calculating the probabilities, the pEAS and the set of patients used for the interim analysis are assumed to be mutually exclusive. Also it is assumed that a high degree of concordance between the primary endpoint for the interim analysis (ORR per RECIST 1.1 as determined by local investigators), and the primary endpoint of the study (ORR per mRECIST in laBCC patients and RECIST 1.1 in mBCC patients as determined by central review, in the pEAS) so the same true ORR is used when calculating the probabilities at interim analysis and at primary analysis.

Table 22: Decision operating characteristics for the secondary endpoint of A2201 study design

True ORR	Probability of observing an ORR ≥ 30%		
	800 mg arm with 140 patients in FAS at the primary analysis	200 mg arm with 70 patients in FAS at the primary analysis	200 mg arm with 120 patients in FAS at the primary analysis
0.20	0.003	0.025	0.005
0.25	0.090	0.169	0.101
0.30	0.475	0.473	0.449
0.35	0.852	0.761	0.793
0.40	0.971	0.913	0.928
0.45	0.994	0.969	0.972

Randomisation

Subjects were randomized in a 1:2 ratio to receive treatment with sonidegib 200 mg or 800 mg. Randomization was stratified across the two treatment arms according to the stage of disease (laBCC or mBCC), histological subtype (non-aggressive or aggressive for laBCC patients) and the regions (Australia, Europe, and North America).

Blinding (masking)

Patients, investigator staff, persons performing any assessments, all Novartis personnel, and individuals at central laboratories (including central imaging) were to remain blinded to the identity of the treatment from the time of randomization until database lock for the primary analysis

Statistical methods

The primary analysis of ORR was based on a central review according to mRECIST in patients with laBCC and RECIST 1.1 in patients with mBCC. The pEAS was used for the primary analysis. The FAS and Per Protocol Set (PPS) were used as supportive analyses.

Treatment with the 800-mg dose of sonidegib was hypothesized to be more efficacious than the 200-mg dose. No statistical testing comparing the two treatment arms was planned.

Treatment with sonidegib was to be considered sufficiently efficacious if the observed ORR on any treatment arm at the primary analysis was 30% or higher. The point estimate of ORR for each arm and the corresponding 95% exact confidence interval (CI) was provided. Per the study design characteristics, if the lower bound of the 95% CI exceeded 20%, it was further considered to be clinically meaningful.

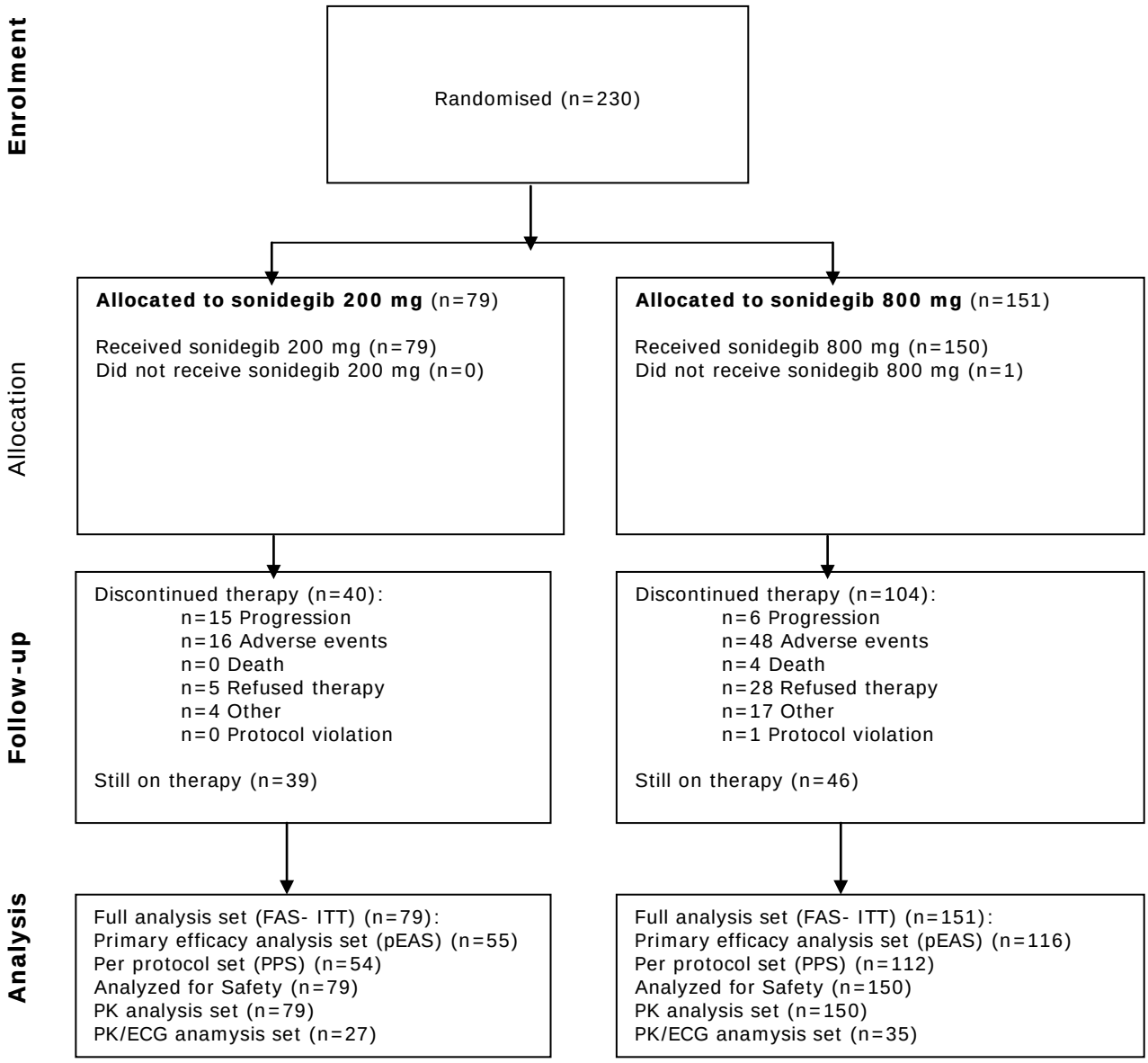
The difference in ORR between the two treatment arms was also summarized along with the 95% exact CI. The proportion of patients who underwent surgical resection after PR was also summarized along with the 95% exact CI, using the pEAS.

Interim analyses

The primary analysis of study data was performed when all patients had been treated for 24 weeks or discontinued treatment. One interim analysis of safety and efficacy data was performed when the first 48 patients randomized had completed 16 weeks of treatment or discontinued treatment; it was possible to terminate one or both treatment arms at the interim for lack of adequate efficacy, i.e. futility. The trial design was planned to be adaptively updated based on interim results. A final analysis of safety and efficacy was performed at 78 weeks following enrollment of the last patient.

Results

Participant flow



*Status as of 28 June 2013

The patient disposition for FAS and pEAS are shown in the following table:

Table 23: Patient disposition (FAS)

Disposition Reason	Primary analysis: 28-Jun-2013 data cut-off			12-month analysis: 31-Dec-2013 data cut-off			18-month analysis: 11-Jul-2014 data cut-off		
	Sonidegib 200 mg N=79 n (%)	Sonidegib 800 mg N=151 n (%)	All patients N=230 n (%)	Sonidegib 200 mg N=79 n (%)	Sonidegib 800 mg N=151 n (%)	All patients N=230 n (%)	Sonidegib 200 mg N=79 n (%)	Sonidegib 800 mg N=151 n (%)	All patients N=230 n (%)
Patients randomized									
Treated	79 (100.0)	150 (99.3)	229 (99.6)	79 (100.0)	150 (99.3)	229 (99.6)	79 (100.0)	150 (99.3)	229 (99.6)
Untreated	0	1 (0.7)	1 (0.4)	0	1 (0.7)	1 (0.4)	0	1 (0.7)	1 (0.4)
Patients treated									
Treatment ongoing	39 (49.4)	46 (30.5)	85 (37.0)	21 (26.6)	29 (19.2)	50 (21.7)	11 (13.9)	18 (11.9)	29 (12.6)
End of treatment	40 (50.6)	104 (68.9)	144 (62.6)	58 (73.4)	121 (80.1)	179 (77.8)	68 (86.1)	132 (87.4)	200 (87.0)
Primary reason for treatment discontinuation									
Adverse event(s)	16 (20.3)	48 (31.8)	64 (27.8)	20 (25.3)	52 (34.4)	72 (31.3)	22 (27.8)	56 (37.1)	78 (33.9)
Death	0	4 (2.6)	4 (1.7)	0	5 (3.3)	5 (2.2)	1 (1.3)	5 (3.3)	6 (2.6)
Lost to follow-up	1 (1.3)	4 (2.6)	5 (2.2)	1 (1.3)	4 (2.6)	5 (2.2)	2 (2.5)	4 (2.6)	6 (2.6)
Non-compliance with study treatment	0	3 (2.0)	3 (1.3)	0	4 (2.6)	4 (1.7)	0	4 (2.6)	4 (1.7)
Physician decision	3 (3.8)	10 (6.6)	13 (5.7)	7 (8.9)	11 (7.3)	18 (7.8)	9 (11.4)	13 (8.6)	22 (9.6)
Progressive disease	15 (19.0)	6 (4.0)	21 (9.1)	23 (29.1)	15 (9.9)	38 (16.5)	27 (34.2)	19 (12.6)	46 (20.0)
Protocol violation	0	1 (0.7)	1 (0.4)	0	1 (0.7)	1 (0.4)	0	1 (0.7)	1 (0.4)
Withdrawal by subject	5 (6.3)	28 (18.5)	33 (14.3)	7 (8.9)	29 (19.2)	36 (15.7)	7 (8.9)	30 (19.9)	37 (16.1)
Study evaluation after end of treatment phase									
Patients continued to the next phase of the trial:	27 (34.2)	57 (37.7)	84 (36.5)	42 (53.2)	72 (47.7)	114 (49.6)	48 (60.8)	79 (52.3)	127 (55.2)
Post-treatment follow-up	11 (13.9)	30 (19.9)	41 (17.8)	17 (21.5)	36 (23.8)	53 (23.0)	18 (22.8)	38 (25.2)	56 (24.3)
Survival follow-up	16 (20.3)	27 (17.9)	43 (18.7)	25 (31.6)	36 (23.8)	61 (26.5)	30 (38.0)	41 (27.2)	71 (30.9)

At the time of data cut-off (11-Jul-2014), 22 patients in the pEAS remained on study treatment: 9 (16.4%) and 13 (11.2%) in the 200-mg and 800-mg arms, respectively.

Table 24: Patient disposition (pEAS)

Disposition Reason	Primary analysis: 28-Jun-2013 data cut-off			12-month analysis: 31-Dec-2013 data cut-off			18-month analysis: 11-Jul-2014 data cut-off		
	Sonidegib 200 mg N=55 n (%)	Sonidegib 800 mg N=116 n (%)	All patients N=171 n (%)	Sonidegib 200 mg N=55 n (%)	Sonidegib 800 mg N=116 n (%)	All patients N=171 n (%)	Sonidegib 200 mg N=55 n (%)	Sonidegib 800 mg N=116 n (%)	All patients N=171 n (%)
Patients randomized									
Treated	55 (100.0)	115 (99.1)	170 (99.4)	55 (100.0)	115 (99.1)	170 (99.4)	55 (100.0)	115 (99.1)	170 (99.4)
Untreated	0	1 (0.9)	1 (0.6)	0	1 (0.9)	1 (0.6)	0	1 (0.9)	1 (0.6)
Patients treated									
Treatment ongoing	31 (56.4)	34 (29.3)	65 (38.0)	17 (30.9)	22 (19.0)	39 (22.8)	9 (16.4)	13 (11.2)	22 (12.9)
End of treatment	24 (43.6)	81 (69.8)	105 (61.4)	38 (69.1)	93 (80.2)	131 (76.6)	46 (83.6)	102 (87.9)	148 (86.5)
Primary reason for treatment discontinuation									
Adverse event(s)	9 (16.4)	38 (32.8)	47 (27.5)	13 (23.6)	42 (36.2)	55 (32.2)	15 (27.3)	46 (39.7)	61 (35.7)
Death	0	4 (3.4)	4 (2.3)	0	5 (4.3)	5 (2.9)	1 (1.8)	5 (4.3)	6 (3.5)
Lost to follow-up	0	2 (1.7)	2 (1.2)	0	2 (1.7)	2 (1.2)	0	2 (1.7)	2 (1.2)
Non-compliance with study treatment	0	3 (2.6)	3 (1.8)	0	4 (3.4)	4 (2.3)	0	4 (3.4)	4 (2.3)
Physician decision	3 (5.5)	9 (7.8)	12 (7.0)	5 (9.1)	9 (7.8)	14 (8.2)	6 (10.9)	11 (9.5)	17 (9.9)
Progressive disease	10 (18.2)	5 (4.3)	15 (8.8)	16 (29.1)	11 (9.5)	27 (15.8)	20 (36.4)	14 (12.1)	34 (19.9)
Protocol violation	0	1 (0.9)	1 (0.6)	0	1 (0.9)	1 (0.6)	0	1 (0.9)	1 (0.6)
Withdrawal by subject	2 (3.6)	19 (16.4)	21 (12.3)	4 (7.3)	19 (16.4)	23 (13.5)	4 (7.3)	19 (16.4)	23 (13.5)
Study evaluation after end of treatment phase									
Patients continued to the next phase of the trial:	18 (32.7)	47 (40.5)	65 (38.0)	29 (52.7)	57 (49.1)	86 (50.3)	34 (61.8)	63 (54.3)	97 (56.7)
Post-treatment follow-up	7 (12.7)	22 (19.0)	29 (17.0)	11 (20.0)	27 (23.3)	38 (22.2)	12 (21.8)	29 (25.0)	41 (24.0)
Survival follow-up	11 (20.0)	25 (21.6)	36 (21.1)	18 (32.7)	30 (25.9)	48 (28.1)	22 (40.0)	34 (29.3)	56 (32.7)

Recruitment

Enrollment started on 20 July 2011. The cut-off date for efficacy (defined as the date after all patients had reached the 24 week visit or had discontinued from the study) was 28 June 2013.

A total of 58 centers in 12 countries participated to the study: Australia (2 centers), Belgium (2 centers), Canada (2 centers), France (5 centers), Germany (10 centers), Greece (1 center), Hungary (2 centers), Italy (1 center), Spain (3 centers), Switzerland (3 centers), United Kingdom (7 centers), and United States (21 centers) (6 of 21 centers in US are USMO sites)

Conduct of the study

The protocol deviations are displayed in Table 25.

Table 25: Protocol deviations leading to exclusion from the pre-protocol set (pEAS)

	Sonidegib 200 mg N=55 n (%)	Sonidegib 800 mg N=116 n (%)	All patients N=171 n (%)
Any protocol deviation	1 (1.8)	4 (3.4)	5 (2.9)
Any eligibility criteria	0	3 (2.6)	3 (1.8)
No target or non-target lesions	0	2 (1.7)	2 (1.2)
Measurable disease <10 mm at baseline	0	1 (0.9)	1 (0.6)
Randomized prior to histological confirmation of BCC	0	1 (0.9)	1 (0.6)
Any other deviation	1 (1.8)	1 (0.9)	2 (1.2)
First dose taken >14 days after randomization	1 (1.8)	1 (0.9)	2 (1.2)

The original study protocol dated 28 February 2011 was subsequently amended 6 times.

Table 26: Rationale and justification for protocol amendments

Amendment no. (date) / no. of patients recruited	Summary of amendment	Rationale and justification
Amendment 1 (19-Apr-2011) 0 patients	Wording on contraceptive precautions updated	To ensure compliance with the UK Guideline of Prevention of Pregnancies in Participants in Clinical Trials
Amendment 2 (17-Nov-2011) 26 patients	Inclusion criteria modified to clarify eligible patient population	Reasons for ineligibility for local therapies or curative surgery to be collected
	Central histopathological analysis implemented	Initiated for confirmation of diagnosis and eligibility (NB: as a result, a majority of laBCC patients enrolled prior to this ineligible for analysis of ORR per mRECIST)
	Sample size increased from 80 to 100 in 800-mg arm and from 40 to 50 in the 200-mg arm	To collect additional safety and efficacy data
	Criteria for assessing ORR amended from RECIST 1.1 to mRECIST for patients with laBCC	Tumor response assessment in patients with laBCC when associated with ulceration, cysts, and scarring/fibrosis are not adequately covered by RECIST 1.1
	Implementation of central reading for determination of primary endpoint	To obtain more robust conclusions
Amendment 3 (23-Nov-2011) 29 patients	Patients experiencing asymptomatic treatment-emergent grade 1 CK elevation to undergo weekly monitoring until resolution	To satisfy local regulatory requirements in France
Amendment 4 (28-Jun-2012) 150 patients	Introduction of primary efficacy analysis set (pEAS)	mRECIST implemented in Amendment 2; consequently, a majority of patients with laBCC enrolled prior to this may not have been eligible for analysis of ORR per mRECIST. The pEAS defined a subset of the full analysis set (FAS) and excluded laBCC patients who were not eligible for tumor assessment per mRECIST.
	Sample size further expanded to approximately 210 patients	To ensure a sufficient number of patients in the pEAS (i.e. 50 patients on 200 mg and 100 patients on 800 mg)
Amendment 5 (03-Jun-2013) 230 patients	Statistical analysis for secondary endpoints updated	Allowed ORR according to RECIST 1.1 to be derived for central review data by MRI and photography independently without lesion matching between MRI/photograph and lesions
Amendment 6 (14-Nov-2013) 230 patients	Institution of Independent Review Committee to integrate MRI, photography, and histology data to assess composite overall response	To provide clarification on how the 3 methods of assessment per mRECIST (MRI, color photography, and histology) were to be integrated to determine the composite overall response for patients with laBCC (see

FAS = full analysis set; IRC = Independent Review Committee; laBCC = locally advanced basal cell carcinoma; mRECIST = modified RECIST; ORR = objective response rate; pEAS = primary efficacy analysis set.

Baseline data

Table 27: Baseline demographics (FAS and pEAS)

	FAS			pEAS		
Demographic variable	Sonidegib 200 mg N=79	Sonidegib 800 mg N=151	All patients N=230	Sonidegib 200 mg N=55	Sonidegib 800 mg N=116	All patients N=171
Age (years)						
Mean (SD)	65.6 (15.67)	63.6 (14.59)	64.3 (14.96)	67.1 (15.26)	64.9 (14.78)	65.6 (14.93)
Median	67.0	65.0	66.0	67.0	66.0	67.0
Min-max	25-92	24-93	24-93	25-88	24-93	24-93
Age category (years), n (%)						
<65	32 (40.5)	73 (48.3)	105 (45.7)	20 (36.4)	52 (44.8)	72 (42.1)
≥ 65	47 (59.5)	78 (51.7)	125 (54.3)	35 (63.6)	64 (55.2)	99 (57.9)
Gender, n (%)						
Male	48 (60.8)	96 (63.6)	144 (62.6)	32 (58.2)	73 (62.9)	105 (61.4)
Female	31 (39.2)	55 (36.4)	86 (37.4)	23 (41.8)	43 (37.1)	66 (38.6)
Race, n (%)						
White	71 (89.9)	145 (96.0)	216 (93.9)	52 (94.5)	112 (96.6)	164 (95.9)
Black	0	1 (0.7)	1 (0.4)	0	1 (0.9)	1 (0.6)
Other	8 (10.1)	5 (3.3)	13 (5.7)	3 (5.5)	3 (2.6)	6 (3.5)
ECOG performance status score, n (%)						
0	50 (63.3)	95 (62.9)	145 (63.0)	37 (67.3)	69 (59.5)	106 (62.0)
1	19 (24.1)	44 (29.1)	63 (27.4)	11 (20.0)	36 (31.0)	47 (27.5)
2	8 (10.1)	10 (6.6)	18 (7.8)	7 (12.7)	10 (8.6)	17 (9.9)
Unknown	2 (2.5)	2 (1.3)	4 (1.7)	0	1 (0.9)	1 (0.6)
Region, n (%)						
Europe	45 (57.0)	83 (55.0)	128 (55.7)	33 (60.0)	64 (55.2)	97 (56.7)
North America	29 (36.7)	61 (40.4)	90 (39.1)	18 (32.7)	47 (40.5)	65 (38.0)
Australia	5 (6.3)	7 (4.6)	12 (5.2)	4 (7.3)	5 (4.3)	9 (5.3)

ECOG = Eastern Cooperative Oncology Group; SD = standard deviation

Table 28: Lesion characteristics at baseline (FAS and pEAS)

	FAS			pEAS		
	Sonidegib 200 mg N=79	Sonidegib 800 mg N=151	All patients N=230	Sonidegib 200 mg N=55	Sonidegib 800 mg N=116	All patients N=171
Lesion characteristics	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Primary site of cancer						
Skin	31 (39.2)	68 (45.0)	99 (43.0)	19 (34.5)	51 (44.0)	70 (40.9)
Scalp	8 (10.1)	9 (6.0)	17 (7.4)	5 (9.1)	7 (6.0)	12 (7.0)
Forehead	7 (8.9)	9 (6.0)	16 (7.0)	6 (10.9)	7 (6.0)	13 (7.6)
Head	6 (7.6)	13 (8.6)	19 (8.3)	5 (9.1)	9 (7.8)	14 (8.2)
Lower extremities	4 (5.1)	3 (2.0)	7 (3.0)	4 (7.3)	1 (0.9)	5 (2.9)
Trunk	2 (2.5)	4 (2.6)	6 (2.6)	1 (1.8)	3 (2.6)	4 (2.3)
Upper extremities	2 (2.5)	1 (0.7)	3 (1.3)	2 (3.6)	1 (0.9)	3 (1.8)
Lips	2 (2.5)	0	2 (0.9)	2 (3.6)	0	2 (1.2)
Ears	1 (1.3)	7 (4.6)	8 (3.5)	1 (1.8)	6 (5.2)	7 (4.1)
Eyelids	1 (1.3)	4 (2.6)	5 (2.2)	1 (1.8)	4 (3.4)	5 (2.9)
Neck	1 (1.3)	3 (2.0)	4 (1.7)	0	2 (1.7)	2 (1.2)
Preauricular	1 (1.3)	2 (1.3)	3 (1.3)	0	1 (0.9)	1 (0.6)
Inner canthus	1 (1.3)	1 (0.7)	2 (0.9)	1 (1.8)	1 (0.9)	2 (1.2)
Chin	0	2 (1.3)	2 (0.9)	0	1 (0.9)	1 (0.6)
Other	12 (15.2)	25 (16.6)	37 (16.1)	8 (14.5)	22 (19.0)	30 (17.5)
Metastatic sites						
No	65 (82.3)	128 (84.8)	193 (83.9)	41 (74.5)	94 (81.0)	135 (78.9)
Yes	14 (17.7)	23 (15.2)	37 (16.1)	14 (25.5)	22 (19.0)	36 (21.1)
Current extent of disease (metastatic sites)[a]						
Lung	10 (71.4)	12 (52.2)	22 (59.5)	10 (71.4)	12 (54.5)	22 (61.1)
Bone	2 (14.3)	5 (21.7)	7 (18.9)	2 (14.3)	5 (22.7)	7 (19.4)
Axillary lymph nodes	1 (7.1)	3 (13.0)	4 (10.8)	1 (7.1)	3 (13.6)	4 (11.1)
Trunk	1 (7.1)	0	1 (2.7)	1 (7.1)	0	1 (2.8)
Other lymph nodes	0	3 (13.0)	3 (8.1)	0	2 (9.1)	2 (5.6)
Parotid lymph nodes	0	2 (8.7)	2 (5.4)	0	1 (4.5)	1 (2.8)
Submandibular lymph nodes	0	2 (8.7)	2 (5.4)	0	1 (4.5)	1 (2.8)
Supraclavicular lymph nodes	0	2 (8.7)	2 (5.4)	0	2 (9.1)	2 (5.6)
Brain	0	1 (4.3)	1 (2.7)	0	1 (4.5)	1 (2.8)
Head	0	1 (4.3)	1 (2.7)	0	1 (4.5)	1 (2.8)
Liver	0	1 (4.3)	1 (2.7)	0	1 (4.5)	1 (2.8)
Neck	0	1 (4.3)	1 (2.7)	0	1 (4.5)	1 (2.8)
Upper extremities	0	1 (4.3)	1 (2.7)	0	1 (4.5)	1 (2.8)
Other	3 (21.4)	2 (8.7)	5 (13.5)	3 (21.4)	2 (9.1)	5 (13.9)
Type of lesions						
Both target and non-target	41 (51.9)	73 (48.3)	114 (49.6)	27 (49.1)	50 (43.1)	77 (45.0)
Target only	38 (48.1)	75 (49.7)	113 (49.1)	28 (50.9)	63 (54.3)	91 (53.2)
Non-target only	0	2 (1.3)	2 (0.9)	0	2 (1.7)	2 (1.2)
Missing	0	1 (0.7)	1 (0.4)	0	1 (0.9)	1 (0.6)

	FAS			pEAS		
	Sonidegib 200 mg N=79	Sonidegib 800 mg N=151	All patients N=230	Sonidegib 200 mg N=55	Sonidegib 800 mg N=116	All patients N=171
Lesion characteristics	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
No. of lesions at baseline						
0 lesions	0	1 (0.7)	1 (0.4)	0	1 (0.9)	1 (0.6)
1 lesion	30 (38.0)	57 (37.7)	87 (37.8)	22 (40.0)	50 (43.1)	72 (42.1)
≥ 2 lesions	49 (62.0)	93 (61.6)	142 (61.7)	33 (60.0)	65 (56.0)	98 (57.3)
Measurable disease at baseline per investigator assessment						
Sum of longest diameters for patients with laBCC per RECIST 1.1 by clinical photography (mm)						
n	62	107	169	41	76	117
Median	50.0	42.0	45.0	55.0	35.5	42.0
Min-max	10-220	10-1155	10-1155	10-220	10-260	10-260
Sum of longest diameters for patients with mBCC per RECIST 1.1 by MRI or CT (mm)						
n	13	23	36	13	23	36
Median	50.0	51.0	50.5	50.0	51.0	50.5
Min-max	23-164	12-502	12-502	23-164	12-502	12-502
Measurable disease at baseline per central review						
Sum of longest diameters for patients with laBCC per RECIST 1.1 by clinical photography (mm)						
n	53	105	158	32	77	109
Median	47.8	48.0	47.9	43.8	47.2	46.4
Min-max	10.7-281.4	10.0-414.5	10.0-414.5	10.8-281.4	10.0-198.9	10.0-281.4
Sum of longest diameters for patients with mBCC per RECIST 1.1 by MRI or CT (mm)						
n	12	20	32	12	20	32
Median	38.0	53.0	49.0	38.0	53.0	49.0
Min-max	15.0-121.0	16.0-158.0	15.0-158.0	15.0-121.0	16.0-158.0	15.0-158.0

[a] Percentages calculated based on the numbers of patients with metastatic disease as the denominator

Table 29: Disease characteristics at baseline (FAS and pEAS)

	FAS			pEAS		
	Sonidegib 200 mg N=79	Sonidegib 800 mg N=151	All patients N=230	Sonidegib 200 mg N=55	Sonidegib 800 mg N=116	All patients N=171
Disease characteristics	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Time from initial diagnosis of primary site to first dose (mo)						
<6	16 (20.3)	26 (17.2)	42 (18.3)	13 (23.6)	19 (16.4)	32 (18.7)
6 to <12	2 (2.5)	7 (4.6)	9 (3.9)	1 (1.8)	5 (4.3)	6 (3.5)
12 to <24	4 (5.1)	7 (4.6)	11 (4.8)	2 (3.6)	5 (4.3)	7 (4.1)
≥ 24	54 (68.4)	101 (66.9)	155 (67.4)	36 (65.5)	80 (69.0)	116 (67.8)
Unknown	3 (3.8)	10 (6.6)	13 (5.7)	3 (5.5)	7 (6.0)	10 (5.8)
Time from initial diagnosis to first recurrence/relapse (mo)						
<1	7 (8.9)	5 (3.3)	12 (5.2)	6 (10.9)	3 (2.6)	9 (5.3)
1 to <2	2 (2.5)	4 (2.6)	6 (2.6)	2 (3.6)	4 (3.4)	6 (3.5)
2 to <3	2 (2.5)	2 (1.3)	4 (1.7)	1 (1.8)	1 (0.9)	2 (1.2)
≥ 3	44 (55.7)	88 (58.3)	132 (57.4)	31 (56.4)	74 (63.8)	105 (61.4)
Unknown	24 (30.4)	52 (34.4)	76 (33.0)	15 (27.3)	34 (29.3)	49 (28.7)
Time from most recent relapse to first dose (mo)						
<1	9 (11.4)	14 (9.3)	23 (10.0)	5 (9.1)	7 (6.0)	12 (7.0)
1 to <2	6 (7.6)	18 (11.9)	24 (10.4)	3 (5.5)	15 (12.9)	18 (10.5)
2 to <3	11 (13.9)	15 (9.9)	26 (11.3)	9 (16.4)	15 (12.9)	24 (14.0)
≥ 3	30 (38.0)	59 (39.1)	89 (38.7)	21 (38.2)	49 (42.2)	70 (40.9)
Unknown	23 (29.1)	45 (29.8)	68 (29.6)	17 (30.9)	30 (25.9)	47 (27.5)

Table 30: Prior antineoplastic therapy indicated for BCC-overall, by stratification (FAS and pEAS)

	FAS			pEAS		
	Sonidegib 200 mg	Sonidegib 800 mg	All patients	Sonidegib 200 mg	Sonidegib 800 mg	All patients
laBCC	**N=66**	**N=128**	**N=194**	**N=42**	**N=93**	**N=135**
Antineoplastic therapy						
Any therapy	**50 (75.8)**	**105 (82.0)**	**155 (79.9)**	**31 (73.8)**	**76 (81.7)**	**107 (79.3)**
Surgery[a]	49 (74.2)	104 (81.3)	153 (78.9)	30 (71.4)	76 (81.7)	106 (78.5)
Radiotherapy	5 (7.6)	10 (7.8)	15 (7.7)	4 (9.5)	7 (7.5)	11 (8.1)
Prior antineoplastic regimens	4 (6.1)	5 (3.9)	9 (4.6)	4 (9.5)	3 (3.2)	7 (5.2)
Number of regimens						
1	4 (6.1)	3 (2.3)	7 (3.6)	4 (9.5)	2 (2.2)	6 (4.4)
2	0	1 (0.8)	1 (0.5)	0	1 (1.1)	1 (0.7)
Unknown	0	1 (0.8)	1 (0.5)	0	0	0
mBCC	**N=13**	**N=23**	**N=36**	**N=13**	**N=23**	**N=36**
Antineoplastic therapy						
Any therapy	11 (84.6)	23 (100)	34 (94.4)	11 (84.6)	23 (100)	34 (94.4)
Surgery[a]	11 (84.6)	23 (100)	34 (94.4)	11 (84.6)	23 (100)	34 (94.4)
Radiotherapy	3 (23.1)	4 (17.4)	7 (19.4)	3 (23.1)	4 (17.4)	7 (19.4)
Prior antineoplastic regimens	0	1 (4.3)	1 (2.8)	0	1 (4.3)	1 (2.8)
Number of regimens						
1	0	1 (4.3)	1 (2.8)	0	1 (4.3)	1 (2.8)

[a] All surgeries are included as the indicator information of 'treatment for BCC' was not collected in the 'prior antineoplastic therapy—surgery' eCRF. Note: surgery also includes biopsies.

Numbers analysed

Analysis sets

Analysis presented were based on data collected up to 28-Jun 2013 (cut-off date).

The full analysis set (FAS) comprised all patients who were assigned study treatment irrespective of receiving it (all randomized patients).

The primary efficacy analysis set (pEAS) was a subset of the FAS including patients with laBCC with tumours that were adequately assessed by MRI or photography or both, and including all patients with mBCC included in the FAS. For patients with laBCC, adequate assessment by photography was defined as those with annotated photographs or those without annotated photographs and documentation of the absence of palpable sub-dermal components outside the margins of the photographed lesion(s). The pEAS was used to analyze all efficacy endpoints that were based on the assessment of tumour response per mRECIST for laBCC and RECIST 1.1 for mBCC patients, namely ORR, rate of CR, DoR, PFS, and TTR.

The safety analysis set included all patients who received at least one dose of study drug.

The per-protocol set (PPS) consisted of a subset of the patients in the pEAS who were compliant with the requirements of the protocol.

The following protocol deviations led to exclusion from the PPS:

• Type of indication differed from those required by the protocol (e.g. incorrect histology/cytology); • Prior therapy included systemic sonidegib or other hedgehog pathway inhibitors;• WHO performance status ≥ 3; • Another anti-neoplastic therapy was administered after start of study treatment and prior to first tumour assessment; • Measurable disease did not meet minimum requirements; • Patients who have taken part in an experimental drug study within 4 weeks of initiating treatment with LDE225; • Patients who are receiving other anti-neoplastic therapy (e.g. chemotherapy, targeted therapy or radiotherapy) concurrently or within 4 weeks of starting treatment with sonidegib; • Patients who did not receive any study treatment; •Treatment started more than 14 days after randomization.

All randomized patients were included in the FAS. Two-hundred-thirty patients with a diagnosis of laBCC (84.3%) or mBCC (15.7%) were randomized 1:2 to receive treatment with either sonidegib 200 mg daily (n=79) or sonidegib 800 mg daily (n=151) in the FAS. Fifty-nine patients were excluded from the FAS to form the pEAS essentially due to incomplete availability of documents for proper anti-tumour assessment (MRI and/or photography).

Table 31: Analysis sets

	Sonidegib 200 mg N=79 n (%)	Sonidegib 800 mg N=151 n (%)	All patients N=230 n (%)
Full analysis set	**79 (100.0)**	**151 (100.0)**	**230 (100.0)**
laBCC	66 (83.5)	128 (84.8)	194 (84.3)
Aggressive histology	37 (46.8)	75 (49.7)	112 (48.7)
Non-aggressive histology	29 (36.7)	53 (35.1)	82 (35.7)
mBCC	13 (16.5)	23 (15.2)	36 (15.7)
Primary efficacy analysis set (pEAS)	**55 (69.6)**	**116 (76.8)**	**171 (74.3)**
laBCC	42 (53.2)	93 (61.6)	135 (58.7)
Aggressive histology	24 (30.4)	56 (37.1)	80 (34.8)
Non-aggressive histology	18 (22.8)	37 (24.5)	55 (23.9)
mBCC	13 (16.5)	23 (15.2)	36 (15.7)
Per protocol set (PPS)	**54 (68.4)**	**112 (74.2)**	**166 (72.2)**
laBCC	41 (51.9)	89 (58.9)	130 (56.5)
Aggressive histology	23 (29.1)	55 (36.4)	78 (33.9)
Non-aggressive histology	18 (22.8)	34 (22.5)	52 (22.6)
mBCC	13 (16.5)	23 (15.2)	36 (15.7)
Safety set	**79 (100.0)**	**150 (99.3)**	**229 (99.6)**
Pharmacokinetic analysis set (PAS)	**79 (100.0)**	**150 (99.3)**	**229 (99.6)**
Pharmacokinetic/ECG analysis set	**27 (34.2)**	**35 (23.2)**	**62 (27.0)**

Outcomes and estimation

As of the 28-Jun-2013 data cut-off, the median study follow-up was 13.1 months for the pEAS and 13.9 months for the FAS. The Applicant also has provided 12-month (cut-off 31 December 2013) and 18-month (cut-off 11 July 2014) updated efficacy analyses.

Primary endpoint: Confirmed ORR per central review (pEAS population) - cut-off 28 June 2013

The ORR per central review for all patients combined was 36.4% (95% CI: 23.8, 50.4) and 33.6% (95% CI: 25.1, 43.0) for the 200-mg and 800-mg arms, respectively. Response rates met the predefined criteria for both treatment arms for point estimates to meet or exceed 30%. The lower bounds of the associated 95% CIs also exceeded 20%, the pre-specified threshold for clinical relevance as per the study design operating characteristics. Treatment at both dose levels resulted in minimal difference in ORR evident between the two treatment arms (Δ -2.7%; 95% CI: -18.73, 12.45).

• ORR of 42.9% (95% CI: 27.7, 59.0) and 15.4% (95% CI: 1.9, 45.4) was reported for the sonidegib 200-mg treatment arm for patients with laBCC and mBCC, respectively, in the pEAS.

• At the 800-mg dose, ORRs were 37.6% (95% CI: 27.8, 48.3) and 17.4% (95% CI: 5.0, 38.8), respectively, for patients with laBCC and mBCC; all were PRs.

Table 32: Best Overall response summary table according to IRC using mRECIST for laBCC and RECIST 1.1 for mBCC – pEAS and FAS (cut-off 28 June 2013)

	pEAS						FAS					
	laBCC		mBCC		Total		laBCC		mBCC		Total	
	200 mg N=42	800 mg N=93	200 mg N=13	800 mg N=23	200 mg N=55	800 mg N=116	200 mg N=42	800 mg N=93	200 mg N=13	800 mg N=23	200 mg N=55	800 mg N=116
ORR (CR+PR)												
n(%)	18 (42.9)	35 (37.6)	2 (15.4)	4 (17.4)	20 (36.4)	39 (33.6)	31 (47)	45 (35.2)	2 (15.4)	4 (17.4)	33 (41.8)	49 (32.5)
95%CI	28-59	28-48	2-45	5-39	24-50	25-43	35-60	27-44	2-45	5-39	31-53	25-40
Diff*	-5.2		2		-2.7		-8.6		11.7		-2.9	
BORR n(%)												
CR	2 (4.8)	0	0	0	2 (3.6)	0	2 (3.0)	0	0	0	2 (2.5)	0
PR	16 (38.1)	35 (37.6)	2 (15.4)	4 (17.4)	18 (32.7)	39 (33.6)	29 (43.9)	45 (35.2)	2 (15.4)	4 (17.4)	31 (39.2)	49 (32.5)
SD	21 (50)	39 (41.9)	10 (76.9)	15 (65.2)	31 (56.4)	54 (46.6)	29 (43.9)	55 (43)	10 (76.9)	15 (65.2)	39 (49.4)	70 (46.4)
PD	0	0	0	1 (4.3)	0	1 (0.9)	1 (1.5)	0	0	1 (4.3)	1 (1.3)	1 (0.7)
UNK	3 (7.1)	19 (20.4)	1 (7.7)	3 (13)	4 (7.3)	22 (19)	5 (7.6)	28 (21.9)	1 (7.7)	3 (13)	6 (7.6)	31 (20.5)

*IRC: Independent Review Committee assessment; pEAS: Primary efficacy analysis set; FAS: Full analysis set. *Diff: Difference between treatment groups (%). CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; UNK: Unknown. The 95% CI for the frequency distribution were computed using Clopper-Pearson method (Clopper and Pearson 1934)*

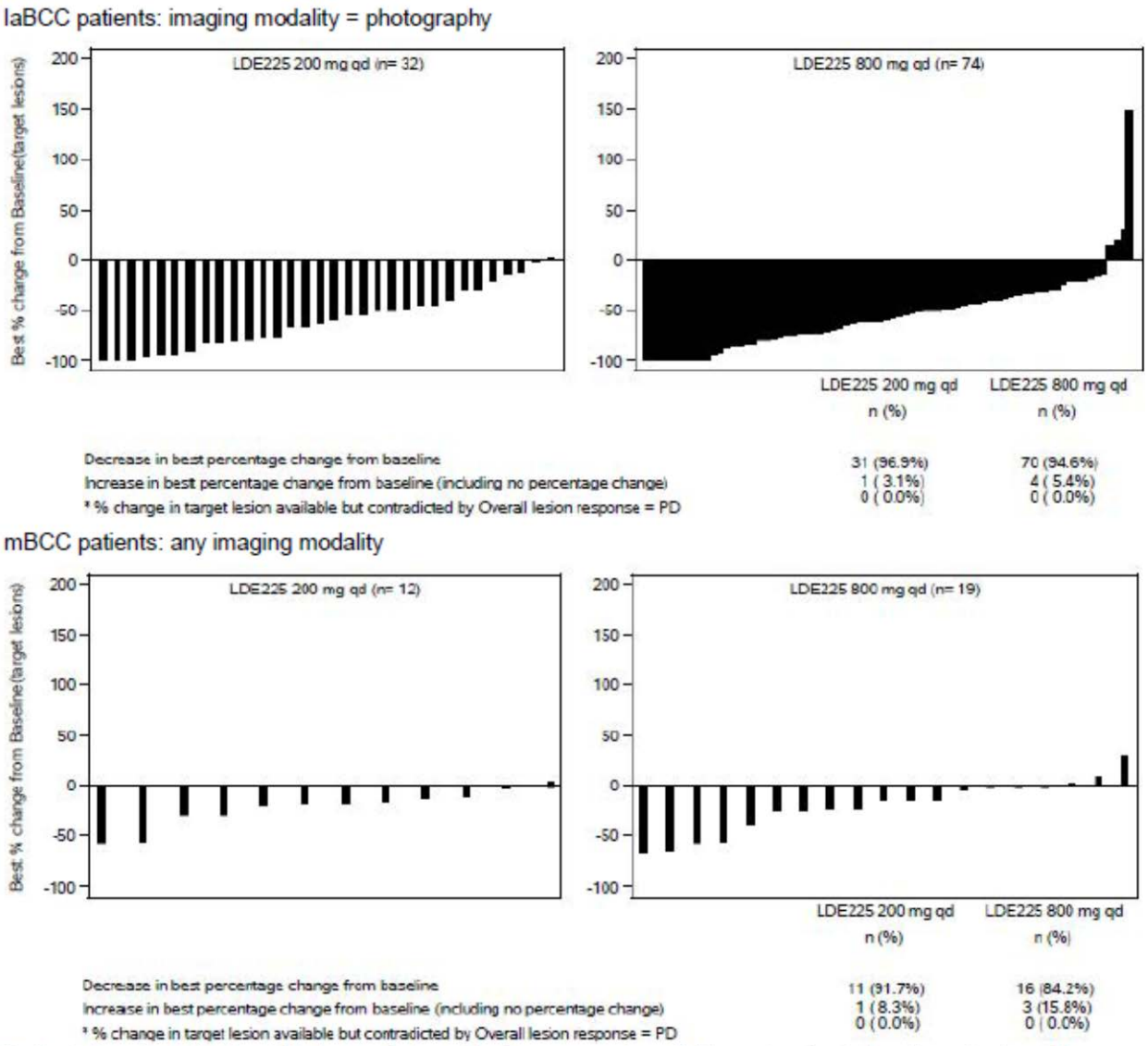
Results obtained in the pEAS population were similar to the results obtained in the FAS population according to IRC assessment (sensitivity analyses).

When looking at waterfall plots:

-laBCC: 96.9% and 94.6% of evaluable patients experienced a reduction in tumour size with sonidegib 200 mg and 800 mg, respectively, based on photographic evaluation of the target lesions;

-mBCC: 91.7% and 84.2% of evaluable patients experienced a reduction in tumour size with sonidegib 200 mg and 800 mg, respectively, based on any imaging modality.

Figure 15: Waterfall plot for best change from baseline in the target lesions per central review using mRECIST for laBCC and RECIST 1.1 for mBCC (pEAS cut-off 28 June 2013)



Patients for whom the best % change in target lesions was not available and patients for whom the best % change in target lesions was contradicted by best overall response = UNK were excluded from the analysis.

No patient with laBCC underwent surgical resection following confirmed PR per central review for the pEAS.

Secondary endpoints: ORR according to investigator's assessment – pEAS and FAS

ORRs were higher per investigator assessment than per central review for the pEAS. Overall ORRs per investigator assessment were 56.4% (95% CI: 42.3, 69.7) and 53.4% (95% CI: 44.0, 62.8) for the 200-mg and 800-mg treatment arms, respectively.

-Confirmed ORRs of 66.7% (95% CI: 50.5, 80.4) and 23.1% (95% CI: 5.0, 53.8) were reported for patients receiving treatment with sonidegib 200 mg with laBCC and mBCC, respectively.

-Corresponding ORRs for patients in the 800-mg treatment arm were 58.1% (95% CI: 47.4, 68.2) and 34.8% (95% CI: 16.4, 57.3) for laBCC and mBCC, respectively

Table 33: Best Overall response summary table according to INVESTIGATORS (INV) using mRECIST for laBCC and RECIST 1.1 for mBCC – pEAS and FAS (cut-off 28 June 2013)

	pEAS						FAS					
	laBCC		mBCC		Total		laBCC		mBCC		Total	
	200 mg N=42	800 mg N=93	200 mg N=13	800 mg N=23	200 mg N=55	800 mg N=116	200 mg N=42	800 mg N=93	200 mg N=13	800 mg N=23	200 mg N=55	800 mg N=116
ORR (CR+PR)												
n(%)	28 (66.7)	54 (58.1)	3 (23.1)	8 (34.8)	31 (56.4)	62 (53.4)	43 (65.2)	73 (57)	3 (23.1)	8 (34.8)	46 (58.2)	81 (53.6)
95%CI	50-80	47-68	5-54	16-57	42-70	44-63	52-76	48-66	5-54	16-57	47-69	45-62
Diff*	-8.6		11.7		-2.9		-8.1		11.7		-4.6	
BORR n(%)												
CR	3 (7.1)	12 (12.9)	0	2 (8.7)	3 (5.5)	14 (12.1)	5 (7.6)	15 (11.7)	0	2 (8.7)	5 (6.3)	17 (11.3)
PR	25 (59.5)	42 (45.2)	3 (23.1)	6 (26.1)	28 (50.9)	48 (41.4)	38 (57.6)	58 (45.3)	3 (23.1)	6 (26.1)	41 (51.9)	64 (42.4)
SD	11 (26.2)	28 (30.1)	8 (61.5)	11 (47.8)	19 (34.5)	39 (33.6)	16 (24.2)	37 (28.9)	8 (61.5)	11 (47.8)	24 (30.4)	48 (31.8)
PD	1 (2.4)	1 (1.1)	2 (15.4)	1 (4.3)	3 (5.5)	2 (1.7)	1 (1.5)	1 (0.8)	2 (15.4)	1 (4.3)	3 (3.8)	2 (1.3)
UNK	2 (4.8)	10 (10.8)	0	3 (13)	2 (3.6)	13 (11.2)	6 (9.1)	17 (13.3)	0	3 (13)	6 (7.6)	20 (13.2)

*INV: Investigator's assessment; pEAS: Primary efficacy analysis set; FAS: Full analysis set. *Diff: Difference between treatment groups (%). CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; UNK: Unknown. The 95% CI for the frequency distribution were computed using Clopper-Pearson method (Clopper and Pearson 1934).*

Results obtained in the pEAS population were similar to the results obtained in the FAS population according to INV assessment.

According to the corresponding waterfall plots per INV assessment in laBCC, in patients enrolled in the sonidegib 200 mg or 800 mg arms, tumour shrinkage in the pEAS was reported in 100% and in 94.7% of patients, respectively, and in the FAS in 96.7% and 95.2% of patients, respectively.

Concordance rates between the central review and investigator assessment – pEAS

-Sonidegib 200 mg arm: concordance rates of ORR were 50% and 46% for patients with laBCC and mBCC, respectively.
-Sonidegib 800 mg arm: concordance rates of ORR were 49% and 61% for patients with laBCC and mBCC, respectively.

ORR applying similar methodology as to the vismodegib Erivance trial in laBCC

Table 34: Best Overall response summary table according to IRC using update mRECIST for laBCC – pEAS

	Primary analysis: 28-Jun-2013 data cut-off		12-month analysis: 31-Dec-2013 data cut-off		18-month analysis: 11-Jul-2014 data cut-off	
	laBCC		laBCC		laBCC	
	Sonidegib 200 mg N=42	Sonidegib 800 mg N=93	Sonidegib 200 mg N=42	Sonidegib 800 mg N=93	Sonidegib 200 mg N=42	Sonidegib 800 mg N=93
Objective Response Rate (ORR: CR+PR)						
n (%)	22 (52.4)	45 (48.4)	26 (61.9)	51 (54.8)	25 (59.5)	52 (55.9)
95% CI (%)	(36.4, 68.0)	(37.9, 59.0)	(45.6, 76.4)	(44.2, 65.2)	(43.3, 74.4)	(45.2, 66.2)
Best Overall Response, n (%)						
CR, n (%)	7 (16.7)	28 (30.1)	8 (19.0)	30 (32.3)	9 (21.4)	31 (33.3)
95% CI	(7.0, 31.4)	(21.0, 40.5)	(8.6, 34.1)	(22.9, 42.7)	(10.3, 36.8)	(23.9, 43.9)
PR	15 (35.7)	17 (18.3)	18 (42.9)	21 (22.6)	16 (38.1)	21 (22.6)
SD	17 (40.5)	30 (32.3)	13 (31.0)	27 (29.0)	14 (33.3)	26 (28.0)
PD	0	0	0	1 (1.1)	0	1 (1.1)
UNK	3 (7.1)	18 (19.4)	3 (7.1)	14 (15.1)	3 (7.1)	14 (15.1)

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; UNK = unknown.
The 95% CI for the frequency distribution were computed using the Clopper-Pearson method (Clopper and Pearson 1934).
Composite overall response per preplanned sensitivity analysis applying Erivance-like methodology.

When applying the methodology used for vismodegib in the Erivance study, an improvement in Complete Response Rate is observed compared with the primary analysis in laBCC patients, where CRR according to IRC in the pEAS was 16.7 % and 30.1% in the sonidegib 200 mg and 800 mg arm, respectively. Consistent results were observed when assessment was made according to the FAS population.

A sensitivity analysis was conducted where only basic categories of responder vs non-responder yielded concordance rates between investigator and central review of 67 and 72%, respectively, for patients with laBCC and mBCC.

Secondary endpoint: Time to Tumour Response (TTR) - cut-off 28 June 2013

-TTR per IRC (pEAS and FAS): median TTRs in the pEAS in laBCC were 3.9 months (95% CI: 2.1, 4.0) and 3.7 months (95% CI: 2.0, 3.8) for the 200-mg and 800-mg treatment arms, respectively. Median TTRs for patients with mBCC were 4.6 months (95% CI: 1.8, 7.4) and 1.0 months (95% CI: 1.0, 2.1) for the 200-mg and 800-mg treatment arms, respectively. Similar results were observed in the FAS.
-TTR per INV (pEAS and FAS): Median TTRs in the pEAS laBCC were 1.9 months (95% CI: 1.2, 3.7) and 1.8 months (95% CI: 1.1, 2.0) for the sonidegib 200-mg and 800-mg treatment arms, respectively. Median TTR in mBCC were 1.0 months (95% CI: 0.9, 3.7) and 2.7 months (95% CI: 1.0, 5.6) for the 200-mg and 800-mg treatment arms, respectively. Similar results were observed in the FAS.

Secondary endpoints: Duration of response (DoR), Progression Free survival (PFS), Overall Survival (OS) - cut-off 28 June 2013

In general, data supporting durability of the primary endpoint (in terms of DoR, PFS, OS) were considered not conclusive due to the high rate of censoring. The results of the updated 18-month analysis have been provided by the Applicant within the Day 120 Response document and are presented at the end of the outcomes paragraph.

- Duration of response (DoR)

1*) Duration of response (DoR) according to IRC – pEAS and FAS*

a) pEAS:

-laBCC: only 4 of the 53 patients with laBCC per IRC who experienced an objective response reported PD at the cut-off date (28 June 2013), therefore median DoR was not estimable. Estimated progression-free rates at 9 months were 82.1% (95% CI: 44-95) and 92.3% (95%CI: 57-99) for the sonidegib 200 mg and 800 mg, respectively according to IRC er pEAS.

-mBCC: median DoR was 8.3 months in the sonidegib 800 mg arm, whereas it was not estimable in the 200 mg arm due to high rate of censoring.

b) FAS: DoR results in the FAS were very similar to the pEAS.

2)For the DoR results according to INV in the pEAS and FAS reference is made to summary table reported at the end of efficacy paragraph.

- Progression Free Survival (PFS)

1) PFS – IRC assessment (pEAS):

- *laBCC:* median PFS was non-estimable in both treatment arms, with 88.1% and 91.4% of patients censored in the respective analyses for the 200-mg and 800-mg treatment arms. Estimated 12-month PFS rates were 83.6% (95% CI: 58.9, 94.1) and 82.8% (95% CI: 67.3, 91.4) for sonidegib 200 mg and 800 mg, respectively. Similar results were observed in the FAS.
- *mBCC:* median PFS was 13.1 months (95% CI: 5.6, 13.1) and 7.6 months (95% CI: 6.2, 11.1) in the 200-mg and 800-mg treatment arms, respectively. Estimated 12-month PFS rates were 64.9% (95% CI: 24.9, 87.4) and 15.7% (95% CI: 1.0, 47.7) for the 200-mg and 800-mg treatment arms, respectively. Similar results were observed in the FAS.

2) PFS – INV assessment (pEAS):

- *laBCC:* median PFS was 22 months (95% CI: 13.7, 22.0) in the 200 mg treatment arm and non-estimable in the 800 mg arm. Similar results were observed in the FAS.
- *mBCC:* median PFS was 13.1 months (95% CI: 9.2, 16.6) and 13.3 months (95% CI: NE) in the 200-mg and 800-mg treatment arms, respectively. Similar results were observed in the FAS.

- Overall Survival (OS)

Median OS was non-estimable in both sonidegib 200-mg and 800-mg treatment arms, with 97.5% and 94.0% of patients censored in the respective arms.

As of the 28-Jun-2013 data cut-off date for the 200-mg arm, 1 death (1.5%) was reported among the 66 patients with laBCC and 1 death (7.7%) was reported among the 13 patients with mBCC. Estimated 12-month survival rates were 100% and 87.5% for patients with laBCC and mBCC, respectively.

In the 800-mg treatment arm, 7 deaths (5.5%) were reported among patients with laBCC and 2 deaths (8.7%) in patients with mBCC. Estimated 12-month survival rates were 92.4% and 91.3%, respectively.

Ancillary analyses

Secondary endpoint: Time to Tumour Response (TTR)

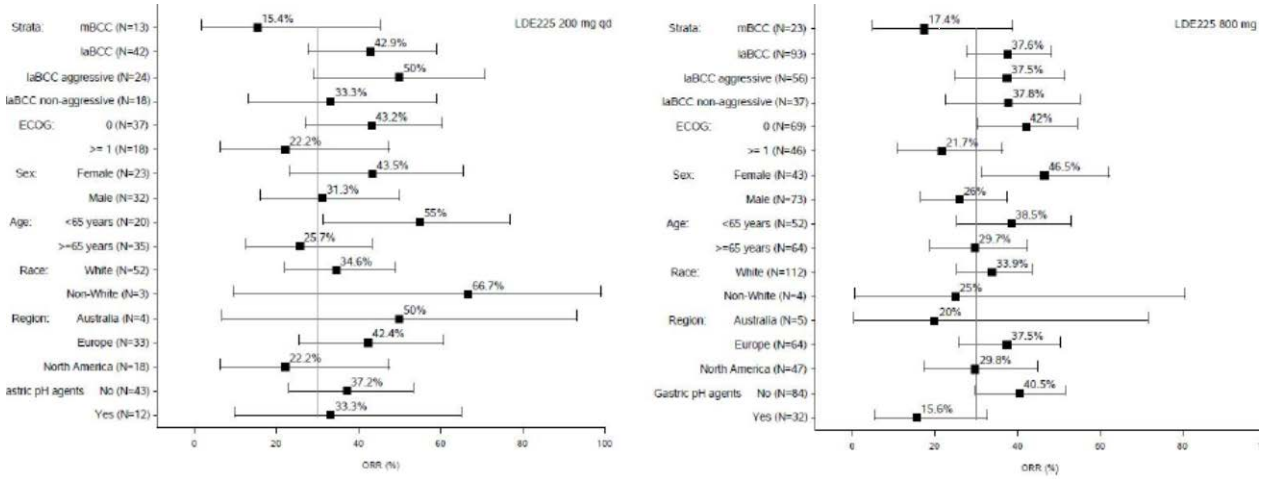
-TTR per IRC (pEAS and FAS): median TTR in the pEAS in laBCC was 3.9 months (95% CI: 2.1, 4.0)

and 3.7 months (95% CI: 2.0, 3.8) for the 200-mg and 800-mg treatment arms, respectively. Median TTR for patients with mBCC was 4.6 months (95% CI: 1.8, 7.4) and 1.0 months (95% CI: 1.0, 2.1) for the 200-mg and 800-mg treatment arms, respectively. Similar results were observed in the FAS.
-TTR per INV (pEAS and FAS): Median TTRs in the pEAS laBCC were 1.9 months (95% CI: 1.2, 3.7) and 1.8 months (95% CI: 1.1, 2.0) for the sonidegib 200-mg and 800-mg treatment arms, respectively. Median TTR in mBCC were 1.0 months (95% CI: 0.9, 3.7) and 2.7 months (95% CI: 1.0, 5.6) for the 200-mg and 800-mg treatment arms, respectively. Similar results were observed in the FAS.

Secondary endpoint: ORR, CRR, DoR, PFS and TTR per IRC and INV using RECIST 1.1
Analyses of primary and secondary endpoints according to RECIST 1.1. were provided for completeness as they were used as primary analysis before implementation of amendment 2. Results show significantly lower ORR compared with results analyzed with mRECIST, essentially because RECIST 1.1 does not allow appropriate assessment for locally advanced skin lesions.

Exploratory endpoint: subgroup analyses were provided evaluating treatment effect in terms of ORR by age, stage of disease, ECOG Performance Status, disease histology, sex, race, geographic region and use of gastric pH agents.

Figure 16: ORR per IRC in pEAS by subgroups



Exploratory endpoint: PROs-EORTC QLQ-C30 and H&N35

Compliance rates of patients completing the EORTC QLQ-C30 and QLQ-H&N35 questionnaires were high in both treatment arms at baseline (93% and 94%) and at week 33 (44% and 45%). The proportion of patients who completed the questionnaires at baseline and at least one post-baseline assessment was 88.7% and 90.0% for the QLQ-C30 and QLQ-H&N35, respectively. Pre-specified subscale scores for the C30 included: physical functioning, social functioning, pain, and fatigue. Pre-specified scales from the H&N35 included: trouble with social contact, head and neck pain, and weight loss.

Biomarker analysis

Evaluation of Gli-1 inhibition on archival and fresh tumour tissues shows, in the 200-mg arm, median percent inhibition that ranged from 81.9% to 92.3% overtime for patients with laBCC and 77.1% to 99.1% overtime for patients with mBCC. In the 800-mg arm, the median percent inhibition was >95% across visits for patients with laBCC and mBCC.

Evidence about the rate of inhibition of Gli1 under treatment with sonidegib was submitted but no clear correlation between the evolution of Gli1 levels and response to treatment was observed . In 11 patients that remained progression-free for a long time after drug discontinuation, data from modelling seem to suggest that following an initial sustained inhibition, Gli1 levels progressively increase, approaching baseline values, at the time of radiological or clinical confirmation of progressive disease.

Updated 18-months Efficacy analysis (cut-off July 2014)

According to the updated 18-months analysis (with cut-off 11 July 2014), provided by the Applicant in the Day 120 response document, in the **laBCC population**, ORRs, per central review were:
- in patients treated with sonidegib 200 mg: 54.8% (95% CI: 38.7, 70.2) in the pEAS and 56.1% (95% CI: 43.3, 68.3) in the FAS;
- in patients treated with sonidegib 800 mg: 47.3% (95% CI: 36.9, 57.9) in the pEAS and 45.3% (95% CI: 36.5, 54.3) in the FAS.
Consistent results were observed when assessment was made by investigators.

A total of 3 patients in sonidegib 200 mg with laBCC underwent *surgical resection* following confirmed PR per central review for the pEAS.

Duration of response (DoR), pEAS: per central review, median DoR was non-estimable for sonidegib 200 mg (due to 60.9% of patients censored) and 24.8 months (95% CI: 10.8, 26.4) for sonidegib 800 mg. According to investigator assessment, median DoR was 15.7 months (95% CI 12.9-23.0) for sonidegib 200 mg and 21.2 months (95% CI: NE) for sonidegib 800 mg. Consistent results were observed in the FAS.

Complete response rate (CRR), pEAS: per central review, CRR was 4.8% (95%CI: 0.6, 16.2) for sonidegib 200 mg and 1.1% (95%CI: 0.0, 5.8) for sonidegib 800 mg. According to investigator assessment, CRR was 9.5% (95%CI: 2.7, 22.6) for sonidegib 200 mg and 14% (95%CI: 7.7, 22.7) for sonidegib 800 mg. Consistent results were observed in the FAS.

Time to Tumour Response (TTR), pEAS: per central review, median TTR was 4.0 months (95% CI: 3.7, 5.6) for sonidegib 200 mg and 3.7 months (95% CI: 2.0, 5.5) for sonidegib 800 mg. According to investigator assessment, median TTR was 1.9 months (95% CI 1.8, 3.9) for sonidegib 200 mg and 1.8 months (95% CI: 1.1, 2.0) for sonidegib 800 mg. Consistent results were observed in the FAS.

Progression Free Survival (PFS), pEAS: per central review, median PFS was 22.1 months (95% CI: NE) for sonidegib 200 mg and 19.4 months (95% CI: 13.8, 30.5) for sonidegib 800 mg. Estimated 12-month PFS rates for patients with laBCC were 80.1% (95% CI: 60.4, 90.6) and 74.6% (95% CI: 59.1, 84.9) for the 200-mg and 800-mg arms, respectively. According to investigator assessment, median PFS was 20.1 months (95% CI: 14.8, 24.9) with a censoring rate of 57.1% in the 200-mg arm and 22.1 months (95% CI: NE) with a censoring rate of 78.5% in the 800-mg arm. Consistent results were observed in the FAS.

Overall Survival (OS): in total 3 deaths (4.5%) and 9 deaths (7%) were reported in the 200 mg and the 800 mg arm, respectively. Median OS was non-estimable for patients with laBCC in both the 200-mg and 800-mg treatment arms, with 95.5% and 93.0% of patients censored in the respective arms. The estimated 12-month survival rates were 100% and 92.1% for sonidegib 200 mg and 800 mg, respectively.

In the **mBCC population**, ORRs, per central review, were:
- in patients treated with sonidegib 200 mg: 7.7% (95% CI: 0.2, 36.0) in the pEAS and in the FAS;
- in patients treated with sonidegib 800 mg: 17.4% (95% CI: 5.0, 38.8) in the pEAS and in the FAS.

According to investigator's assessment, ORRs were:
- in patients treated with sonidegib 200 mg: 23.1% (95% CI: 5.0, 53.8) in the pEAS and in the FAS;
- in patients treated with sonidegib 800 mg: 34.8% (95% CI: 16.4, 57.3) in the pEAS and in the FAS.

No patients with mBCC underwent *surgical resection* during treatment with sonidegib.

Duration of response (DoR)(FAS and pEAS): per central review, median DoR for was non-estimable for sonidegib 200 mg and 800 mg (due to 100% and 75% of patients censored). According to investigator assessment, median DoR was 17.7 months (95% CI NE) for sonidegib 200 mg and 10.2 months (95% CI: NE) for sonidegib 800 mg.

Complete response rate (CRR)(FAS and pEAS): no patients with mBCC reported CR per central review, whereas according to investigator assessment no CR were reported for sonidegib 200 mg and CRR of 8.7% (95%CI: 1.1-28.0) for sonidegib 800 mg. .

Time to Tumour Response (TTR) (FAS and pEAS): per central review, median TTR was 1.8 months (95% CI: NE) for sonidegib 200 mg and 1.0 months (95% CI: 1.0, 2.1) for sonidegib 800 mg. According to investigator assessment, median TTR was 1.0 months (95% CI 0.9, 3.7) for sonidegib 200 mg and 2.7 months (95% CI: 1.0, 5.6) for sonidegib 800 mg.

Progression Free Survival (PFS) (FAS and pEAS): per central review, median PFS was 13.1 months (95% CI: NE) for sonidegib 200 mg and 11.1 months (95%CI: NE) for sonidegib 800 mg. Estimated 12-month PFS rates for patients with laBCC were 58.9% (95%CI: 23.4, 82.5) and 42.0% (95%CI: 17.6, 64.9) for the 200-mg and 800-mg arms, respectively. Per investigator assessment, median PFS for patients with mBCC was 13.1 months (95% CI: NE) and 14.3 months (95% CI: 11.1, 17.0) in the 200-mg and 800-mg treatment arms, respectively.

Overall Survival (OS): in total 3 deaths (23.1%) and 7 deaths (30.4%) were reported for the 200 mg and the 800 mg arm, respectively. Median OS was non-estimable for patients with mBCC in both the 200-mg and 800-mg treatment arms, with 76.9% and 69.6% of patients censored in the respective arms. The estimated 12-month survival rates were 90.9% and 91.3% for sonidegib 200 mg and 800 mg, respectively.

Table 35: Efficacy overview: laBCC and mBCC cohorts (pEAS and FAS, 18- month analysis)

	18-month analysis: 11-Jul-2014 data cut-off			
	laBCC		mBCC	
	Sonidegib 200 mg	Sonidegib 800 mg	Sonidegib 200 mg	Sonidegib 800 mg
Objective response rate, % (95% CI) per central review				
Primary efficacy analysis set (pEAS)	54.8 (38.7, 70.2)	47.3 (36.9, 57.9)	7.7 (0.2, 36.0)	17.4 (5.0, 38.8)
Full analysis set (FAS)	56.1 (43.3, 68.3)	45.3 (36.5, 54.3)	7.7 (0.2, 36.0)	17.4 (5.0, 38.8)
Objective response rate, % (95% CI) per investigator review				
Primary efficacy analysis set (pEAS)	71.4 (55.4, 84.3)	61.3 (50.6, 71.2)	23.1 (5.0, 53.8)	34.8 (16.4, 57.3)
Full analysis set (FAS)	71.2 (58.7, 81.7)	57.8 (48.8, 66.5)	23.1 (5.0, 53.8)	34.8 (16.4, 57.3)
Complete response per central review (pEAS)				
Complete response (CR), % (95% CI)	4.8 (0.6, 16.2)	1.1 (0.0, 5.8)	0 (0.0, 24.7)	0 (0.0, 14.8)
Disease control rate per central review (pEAS)				
Disease control rate (CR+PR+SD), %	92.9	82.8	92.3	91.3
Time to tumor response (mo) per central review (pEAS)				
Median (95% CI)	4.0 (3.7, 5.6)	3.7 (2.0, 5.5)	1.8 (NE)	1.0 (1.0, 2.1)
Duration of objective response (mo) per central review (pEAS)				
Median (95% CI)	NE	24.8 (10.8, 26.4)	NE	NE
Progression-free survival (PFS) (mo) per central review (pEAS)				
Median (95% CI)	22.1 (NE)	19.4 (13.8, 30.5)	13.1 (NE)	11.1 (NE)
12-month PFS rate (95% CI)	80.1 (60.4, 90.6)	74.6 (59.1, 84.9)	58.9 (23.4, 82.5)	42.0 (17.6, 64.9)
Overall survival (mo) (FAS)				
Median (95% CI)	NE	NE	NE	NE
12-month survival rate (95% CI)	100 (NE)	92.1 (84.8, 96.0)	90.9 (50.8, 98.7)	91.3 (69.5, 97.8)

CI=Confidence interval; CR=Complete response; NE=Not estimable; PR=Partial response; SD=Stable disease.

Table 36: Summary of Efficacy Results in the A2201 Study – pEAS – (primary analysis - cut off 28 June 2013

	IRC						INV					
	laBCC		**mBCC**		**Total**		**laBCC**		**mBCC**		**Total**	
	200 mg N=42	800 mg N=93	200 mg N=13	800 mg N=23	200 mg N=55	800 mg N=116	200 mg N=42	800 mg N=93	200 mg N=13	800 mg N=23	200 mg N=55	800 mg N=116
ORR (CR+PR)												
n(%)	18 (42.9)	35 (37.6)	2 (15.4)	4 (17.4)	20 (36.4)	39 (33.6)	28 (66.7)	54 (58.1)	3 (23.1)	8 (34.8)	31 (56.4)	62 (53.4)
95%CI	28-59	28-48	2-45	5-39	24-50	25-43	50-80	47-68	5-54	16-57	42-70	44-63
Diff*	-5.2		2		-2.7		-8.6		11.7		-2.9	
BORR n(%)												
CR	2 (4.8)	0	0	0	2 (3.6)	0	3 (7.1)	12 (12.9)	0	2 (8.7)	3 (5.5)	14 (12.1)
PR	16 (38.1)	35 (37.6)	2 (15.4)	4 (17.4)	18 (32.7)	39 (33.6)	25 (59.5)	42 (45.2)	3 (23.1)	6 (26.1)	28 (50.9)	48 (41.4)
SD	21 (50)	39 (41.9)	10 (76.9)	15 (65.2)	31 (56.4)	54 (46.6)	11 (26.2)	28 (30.1)	8 (61.5)	11 (47.8)	19 (34.5)	39 (33.6)
PD	0	0	0	1 (4.3)	0	1 (0.9)	1 (2.4)	1 (1.1)	2 (15.4)	1 (4.3)	3 (5.5)	2 (1.7)
UNK	3 (7.1)	19 (20.4)	1 (7.7)	3 (13)	4 (7.3)	22 (19)	2 (4.8)	10 (10.8)	0	3 (13)	2 (3.6)	13 (11.2)
Median **TTR,** months (95% CI)	3.9 (2.1-4.0)	3.7 (2.0-3.8)	4.6 (1.8-7.4)	1.0 (1.0-2.1)	3.9 (1.9-5.6)	3.7 (1.9-3.8)	1.9 (1.2-3.7)	1.8 (1.1-2.0)	1.0 (0.9-3.7)	2.7 (1.0-5.6)	1.9 (1.2, 3.7)	1.8 (1.1, 1.2)
Median **DoR,** months (95% CI)	NE	NE	NE	8.3 (NE)	NE	NE	20.2 (10-20)	NE	NE	10.2 (NE)	20.2 (10.1, 20.2)	NE
Median **PFS,** months (95% CI)	NE	NE	13.1 (5.6-13.1)	7.6 (6.2-11.1)	NE	NE	22 (13.7-22.0)	NE	13.1 (9.2-16.6)	13.3 (NE)	16.6 (9.9, 20.0)	NE

Table 37: Summary of Efficacy Results in the A2201 Study – FAS – (primary analysis - cut off 28 June 2013

Median **OS,** months (95% CI)	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

	IRC						**INV**					
	laBCC		**mBCC**		**Total**		**laBCC**		**mBCC**		**Total**	
	200 mg N=66	800 mg N=128	200 mg N=13	800 mg N=23	200 mg N=79	800 mg N=151	200 mg N=66	800 mg N=128	200 mg N=13	800 mg N=23	200 mg N=79	800 mg N=151
ORR (CR+PR)												
n(%)	31 (47)	45 (35.2)	2 (15.4)	4 (17.4)	33 (41.8)	49 (32.5)	43 (65.2)	73 (57)	3 (23.1)	8 (34.8)	46 (58.2)	81 (53.6)
95%CI	35-60	27-44	2-45	5-39	31-53	25-40	52-76	48-66	5-54	16-57	47-69	45-62
Diff*	-11.8		2		-9.3		-8.1		11.7		-4.6	
BORR n(%)												
CR	2 (3.0)	0	0	0	2 (2.5)	0	5 (7.6)	15 (11.7)	0	2 (8.7)	5 (6.3)	17 (11.3)
PR	29 (43.9)	45 (35.2)	2 (15.4)	4 (17.4)	31 (39.2)	49 (32.5)	38 (57.6)	58 (45.3)	3 (23.1)	6 (26.1)	41 (51.9)	64 (42.4)
SD	29 (43.9)	55 (43)	10 (76.9)	15 (65.2)	39 (49.4)	70 (46.4)	16 (24.2)	37 (28.9)	8 (61.5)	11 (47.8)	24 (30.4)	48 (31.8)
PD	1 (1.5)	0	0	1 (4.3)	1 (1.3)	1 (0.7)	1 (1.5)	1 (0.8)	2 (15.4)	1 (4.3)	3 (3.8)	2 (1.3)
UNK	5 (7.6)	28 (21.9)	1 (7.7)	3 (13)	6 (7.6)	31 (20.5)	6 (9.1)	17 (13.3)	0	3 (13)	6 (7.6)	20 (13.2)
Median **TTR,** months (95% CI)	3.9 (3.6-4.2)	3.7 (2.6-3.8)	4.6 (1.8-7.4)	1.0 (1.0-2.1)	3.9 (3.6-4.2)	3.7 (2.1-3.8)	1.9 (1.8-3.7)	1.9 (1.2-2.0)	1.0 (0.9-3.7)	2.7 (1.0-5.6)	1.9 (1.8, 3.7)	1.9 (1.4, 2.0)
Median **DoR,** months (95% CI)	NE	NE	NE	8.3 (NE)	NE	NE	20.2 (10-20)	NE	NE	10.2 (NE)	20.2 (10.1, 20.2)	NE
Median **PFS,** months (95% CI)	NE	NE	13.1 (5.6-13.1)	7.6 (6.2-11.1)	NE	NE	16.6 (13.7-22.0)	NE	13.1 (9.2-16.6)	13.3 (NE)	16.6 (10.4, 22.0)	NE
Median **OS,** months (95% CI)	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Table 38: ORR, CRR, DoR, PFS, and TTR per central review and investigator assessment using mRECIST for laBCC and RECIST 1.1 for mBCC (pEAS) (updated 18-month analysis- cut-off 11 July 2014)

	18-month analysis: 11-Jul-2014 data cut-off							
	Sonidegib 200 mg				Sonidegib 800 mg			
	Central		Investigator		Central		Investigator	
	laBCC N=42	mBCC N=13	laBCC N=42	mBCC N=13	laBCC N=93	mBCC N=23	laBCC N=93	mBCC N=23
Objective response rate (ORR), n (%)	23 (54.8)	1 (7.7)	30 (71.4)	3 (23.1)	44 (47.3)	4 (17.4)	57 (61.3)	8 (34.8)
95% CI	(38.7, 70.2)	(0.2, 36.0)	(55.4, 84.3)	(5.0, 53.8)	(36.9, 57.9)	(5.0, 38.8)	(50.6, 71.2)	(16.4, 57.3)
Best overall response, n (%)								
Complete response (CRR)	2 (4.8)	0	4 (9.5)	0	1 (1.1)	0	13 (14.0)	2 (8.7)
Partial response	21 (50.0)	1 (7.7)	26 (61.9)	3 (23.1)	43 (46.2)	4 (17.4)	44 (47.3)	6 (26.1)
Disease stabilization	16 (38.1)	11 (84.6)	9 (21.4)	8 (61.5)	33 (35.5)	17 (73.9)	25 (26.9)	11 (47.8)
Disease progression	0	0	1 (2.4)	2 (15.4)	1 (1.1)	1 (4.3)	1 (1.1)	1 (4.3)
Unknown	3 (7.1)	1 (7.7)	2 (4.8)	0	15 (16.1)	1 (4.3)	10 (10.8)	3 (13.0)
Time to tumor response (TTR), (mo)								
Median	4.0	1.8	1.9	1.0	3.7	1.0	1.8	2.7
95% CI	(3.7, 5.6)	(NE)	(1.8, 3.9)	(0.9, 3.7)	(2.0, 5.5)	(1.0, 2.1)	(1.1, 2.0)	(1.0, 5.6)
Duration of response (DoR), (mo)								
No. of progression events/deaths	9	0	14	1	14	1	13	4
No. censored	14	1	16	2	30	3	44	4
Median	NE	NE	15.7	17.7	24.8	NE	21.2	10.2
95% CI			(12.9, 23.0)	(NE)	(10.8, 26.4)		(NE)	(NE)
Event-free probability (%), (95% CI)								
6 months	86.4 (63.4, 95.4)	100.0 (NE)	92.9 (74.3, 98.2)	100.0 (NE)	90.9 (74.3, 97.0)	100.0 (NE)	92.7 (79.0, 97.6)	66.7 (19.5, 90.4)
9 months	70.8 (45.9, 85.8)	100.0 (NE)	88.6 (68.6, 96.2)	100.0 (NE)	76.3 (56.2, 88.0)	50 (0.6, 91.0)	80.6 (63.3, 90.3)	66.7 (19.5, 90.4)
12 months	58.8 (33.6, 77.2)	100.0 (NE)	79.3 (56.8, 90.9)	100.0 (NE)	68.2 (47.4, 82.2)	NE	73.4 (54.6, 85.4)	44.4 (6.6, 78.5)
Progression-free survival (PFS) (mo)								
No. of progression events/deaths	12	6	18	8	23	11	20	12
No. censored	30	7	24	5	70	12	73	11
Median	22.1	13.1	20.1	13.1	19.4	11.1	22.1	14.3
95% CI	(NE)	(NE)	(14.8, 24.9)	(NE)	(13.8, 30.5)	(NE)	(NE)	(11.1, 17.0)
Progression-free survival probability (%)								
6 months	94.4 (79.4, 98.6)	80.8 (42.3, 94.9)	94.8 (80.7, 98.7)	84.6 (51.2, 95.9)	91.5 (82.0, 96.1)	81.4 (57.6, 92.6)	91.8 (82.3, 96.3)	85.9 (62.2, 95.2)
9 months	91.4 (75.5, 97.1)	80.8 (42.3, 94.9)	83.3 (66.4, 92.1)	84.6 (51.2, 95.9)	83.2 (70.4, 90.8)	58.8 (33.7, 77.1)	85.8 (74.0, 92.5)	85.9 (62.2, 95.2)
12 months	80.1 (60.4, 90.6)	58.9 (23.4, 82.5)	79.8 (62.0, 89.9)	57.1 (25.1, 79.7)	74.6 (59.1, 84.9)	42.0 (17.6, 64.9)	71.4 (56.2, 82.1)	62.4 (33.2, 81.8)

NE = not estimable.

Table 39: ORR, CRR, DoR, PFS, and TTR per central review and investigator assessment using mRECIST for laBCC and RECIST 1.1 for mBCC (FAS) (updated 18-month analysis- cut-off 11 July 2014)

	18-month analysis: 11-Jul-2014 data cut-off							
	Sonidegib 200 mg				Sonidegib 800 mg			
	Central		Investigator		Central		Investigator	
	laBCC N=66	mBCC N=13	laBCC N=66	mBCC N=13	laBCC N=128	mBCC N=23	laBCC N=128	mBCC N=23
Objective response rate (ORR), n (%)	**37 (56.1)**	**1 (7.7)**	**47 (71.2)**	**3 (23.1)**	**58 (45.3)**	**4 (17.4)**	**74 (57.8)**	**8 (34.8)**
95% CI	(43.3, 68.3)	(0.2, 36.0)	(58.7,81.7)	(5.0, 53.8)	(36.5, 54.3)	(5.0, 38.8)	(48.8,66.5)	(16.4, 57.3)
Best overall response, n (%)								
Complete response (CRR)	3 (4.5)	0	6 (9.1)	0	1 (0.8)	0	16 (12.5)	2 (8.7)
Partial response	34 (51.5)	1 (7.7)	41 (62.1)	3 (23.1)	57 (44.5)	4 (17.4)	58 (45.3)	6 (26.1)
Disease stabilization	23 (34.8)	11 (84.6)	14 (21.2)	8 (61.5)	47 (36.7)	17 (73.9)	35 (27.3)	11 (47.8)
Disease progression	1 (1.5)	0	1 (1.5)	2 (15.4)	1 (0.8)	1 (4.3)	1 (0.8)	1 (4.3)
Unknown	5 (7.6)	1 (7.7)	4 (6.1)	0	22 (17.2)	1 (4.3)	18 (14.1)	3 (13.0)
Time to tumor response (TTR), (mo)								
Median	4.0	1.8	2.5	1.0	3.8	1.0	1.9	2.7
95% CI	(3.8, 5.6)	(NE)	(1.9, 3.7)	(0.9, 3.7)	(3.7, 5.5)	(1.0, 2.1)	(1.5, 2.0)	(1.0, 5.6)
Duration of response (DoR), (mo)								
No. of progression events/deaths	10	0	21	1	17	1	18	4
No. censored	27	1	26	2	41	3	56	4
Median	NE	NE	14.3	17.7	24.8	NE	21.2	10.2
95% CI	--	--	(12.0, 20.2)	(NE)	(12.2, 26.4)	--	(NE)	(NE)
Event-free probability (%), (95% CI)								
6 months	86.9 (68.6, 94.9)	100.0 (NE)	89.8 (74.8, 96.1)	100.0 (NE)	90.6 (76.9, 96.4)	100.0 (NE)	90.8 (79.4, 96.1)	66.7 (19.5, 90.4)
9 months	75.8 (55.7, 87.7)	100.0 (NE)	80.7 (63.5, 90.4)	100.0 (NE)	76.6 (59.6, 87.2)	50.0 (0.6, 91.0)	79.7 (65.4, 88.6)	66.7 (19.5, 90.4)
12 months	65.6 (43.2, 81.0)	100.0 (NE)	70.9 (52.2, 83.3)	100.0 (NE)	70.1 (52.1, 82.4)	NE	74.8 (59.6, 85.0)	44.4 (6.6, 78.5)
Progression-free survival (PFS) (mo)								
No. of progression events/deaths	15	6	26	8	28	11	27	12
No. censored	51	7	40	5	100	12	101	11
Median	22.1	13.1	19.4	13.1	22.0	11.1	22.1	14.3
95% CI	(NE)	(NE)	(16.6, 22.6)	(NE)	(16.7, 30.5)	(NE)	(NE)	(11.1, 17.0)
Progression-free survival probability (%)								
6 months	94.8 (84.6, 98.3)	80.8 (42.3, 94.9)	94.8 (84.7, 98.3)	84.6 (51.2, 95.9)	93.8 (86.6, 97.2)	81.4 (57.6, 92.6)	92.6 (85.0, 96.5)	85.9 (62.2, 95.2)
9 months	92.7 (81.5, 97.2)	80.8 (42.3, 94.9)	82.7 (69.3, 90.7)	84.6 (51.2, 95.9)	87.7 (78.0, 93.3)	58.8 (33.7, 77.1)	88.2 (78.9, 93.6)	85.9 (62.2, 95.2)
12 months	82.2 (67.0, 90.8)	58.9 (23.4, 82.5)	76.0 (61.4, 85.7)	57.1 (25.1, 79.7)	80.0 (67.8, 87.9)	42.0 (17.6, 64.9)	72.9 (60.3, 82.1)	62.4 (33.2, 81.8)

NE = not estimable (median not yet reached)
Sources:
ORR [SCE Addendum 2-Appendix 1-Table 14.2-1.2] [SCE Addendum 2-Appendix 1-Table 14.2-1.6]
TTR [SCE Addendum 2-Appendix 1-Table 14.2-3.2] [SCE Addendum 2-Appendix 1-Table 14.2-3.4];
DoR [SCE Addendum 2-Appendix 1-Table 14.2-2.2] [SCE Addendum 2-Appendix 1-Table 14.2-2.7]
PFS [SCE Addendum 2-Appendix 1-Table 14.2-4.2] [SCE Addendum 2-Appendix 1-Table 14.2-4.6]

Summary of main study

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

Table 40: Summary of efficacy for trial No. CLDE225A2201

Title: A phase II, randomized, double-blind study of efficacy and safety of two dose levels of LDE225 in patients with locally advanced or metastatic basal cell carcinoma (BOLT)	
Study identifier	Clinical Study Report **No. CLDE225A2201** EudraCT No. **2010-022629-14**
Design	Multi-center, adaptive, randomized, double-blind Phase II study

	Duration of main phase:		**20-Jul-2011** (first patient first visit) Early termination date: Not applicable; (study ongoing, this report is the interim analysis) Data cut-off date: **28-Jun-2013** (after all patients had reached the 24-Week visit or had discontinued from the study)
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis	Exploratory: two dose-levels evaluation of sonidegib in patients with locally advanced or metastatic basal cell carcinoma		
	Sonidegib		200 mg, 800 mg, once daily for 24-Weeks, 230 patients randomized, 79 with sonidegib 200 mg and 151 with sonidegib 800 mg.
	Placebo		Not considered
Endpoints and definitions	Primary endpoint	**ORR:** objective response rate	ORR assessed by central review according to: mRECIST in patients with laBCC RECIST 1.1 in patients with mBCC
	Secondary endpoint	duration of response **(DoR)**	• DoR determined by central review according to mRECIST in laBCC patients and RECIST 1.1 in mBCC patients
		rate of complete response **(CRR)**	• Rate of CR determined by central review according to mRECIST in laBCC patients and RECIST 1.1 in mBCC patients
	Other secondary efficacy endpoint	Evaluation of time to tumor response **(TTR)**	• TTR determined by central review according to mRECIST in laBCC patients and RECIST 1.1 in mBCC patients • PFS determined by central review according to mRECIST in laBCC patients and RECIST 1.1 in mBCC patients • Overall survival (OS) • ORR, DoR, PFS and TTR determined by site investigator according to mRECIST in laBCC patients and RECIST 1.1 in mBCC patients • ORR, DoR, PFS and TTR determined by central review according to RECIST 1.1 • ORR, DoR, PFS and TTR determined by site investigator according to RECIST 1.1
		progression-free survival **(PFS)**	
		overall survival **(OS)**	
Data cut-off	**28-Jun-2013**		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	**FAS** (ITT population), **pEAS**		
Descriptive statistics and estimate variability	Treatment group	Sonidegib **Arm 200 mg**	Sonidegib **Arm 800 mg**
	Number of subject	**FAS:** 79 **pEAS**: 55	**FAS:** 151 **pEAS**: 116
	0RR	**Central review** **Investigator** **FAS:**	**Central review** **Investigator** **FAS:**
	n(%) (95% CI)	33 (41.8) 46 (58.2) (30.8, 53.4) (46.6, 69.2)	49 (32.5) 81 (53.6) (25.1, 40.5) (45.4, 61.8)
	n(%) (95% CI)	**pEAS:** 20 (36.4) 31 (56.4) (23.8, 50.4) (42.3, 69.7)	**pEAS:** 39 (33.6) 62 (53.4) (25.1, 43.0) (44.0, 62.8)

	Diff. between tmt groups (%) (95% CI)	**Central review** **pEAS:** -2.7 (-18.73, 12.45) **FAS:** -9.3 (-22.7, 3.93)	**Investigator** -2.9 (-18.80, 13.42) -4.6 (-17.90, 9.25)
Effect estimate per comparison	Secondary endpoint **DoR** No. of progression events/death (%) Median (95% CI) (mo)	Sonidegib Arm 200 mg	Sonidegib Arm 800 mg
		Central review **pEAS**: 3 NE **FAS:** 4 NE	**Investigator** 5 20.2 (10.1, 20.2) 10 20.2 (10.1, 20.2)	**Central review** **pEAS**: 2 NE **FAS:** 4 NE	**Investigator** 7 NE 11 NE
	CRR (n%) 95% CI	**pEAS:** 2 (3.6) (0.4, 12.5) **FAS:** 2 (2.5) (0.3, 8.8)	3 (5.5) (1.1, 15.1) 5 (6.3) (2.1, 14.2)	**pEAS:** 0 (0.0, 3.1) **FAS:** 0 (0.0, 2.4)	14 (12.1) (6.8, 19.4) 17 (11.3) (6.7, 17.4)
	TRR Median (95% CI) (mo)	**pEAS**: 3.9 (1.9, 5.6) **FAS:** 3.9 (3.6, 4.2)	1.9 (1.2, 3.7) 1.9 (1.8, 3.7)	**pEAS**: 3.7 (1.9, 3.8) **FAS:** 3.7 (2.1, 3.8)	1.8 (1.1, 2.0) 1.9 (1.4, 2.0)
	PFS No. of progression events/death Median (95% CI) (mo)	**pEAS:** 9 NE **FAS:** 11 NE	16 16.6 (9.9, 22.0) 22 16.6 (10.4, 22.0)	**pEAS:** 18 NE **FAS:** 20 NE	19 NE 23 NE
	OS n patients who died (%) Median OS (mo)	**FAS:** 2 NE		**FAS:** 9 NE	
Notes					
Analysis description	**Secondary analysis**				
ORR	PPS analysis Sensitivity analysis				
DoR	PPS analysis Sensitivity analysis				
CRR	PPS analysis Sensitivity analysis				
PFS	Sensitivity analysis				

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

The applicant did not submit efficacy analyses performed across clinical trials.

Clinical studies in special populations

The applicant did not submit specific clinical studies conducted in special population.

The European Medicines Agency has waived the obligation to submit the results of studies with Odomzo in all subsets of the paediatric population in basal cell carcinoma (see section 4.2 for information on paediatric use).

Supportive study

Study X2101

Responses were observed in 8 patients in this phase 1 study, including 1 CR and 7 PR. All responses occurred in patients with BCC and medulloblastoma, consistent with the knowledge that Hedgehog pathway activation is an important driver for both of these diseases. Among patients with BCC the response rate was 6/16 (38%), including 1 CR, and among patients with medulloblastoma the response rate was 2/9 (22%).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The application is based on the results of one pivotal phase II A2201 (BOLT) study. Study A2201 was a non-comparative, randomized, double-blind study where BCC patients were randomized (1:2) to sonidegib 200 mg QD or 800 mg QD. The 800 mg QD dose regimen corresponds to the MTD observed in the phase I dose escalation X2101 study performed with sonidegib in advanced solid tumours and the 200 mg QD dose regimen was the lowest dose where anti-tumour activity was observed corresponding to exposures where Gli-1 inhibition was down regulated in preclinical models and also in early clinical studies. Thus, the dose selection and the regimens employed in the pivotal study are considered acceptable.

The CHMP expressed concern over the design of the BOLT study, where there was no control arm. The use of placebo or best investigator's choice as control arm would have been preferred. Nevertheless, the CHMP accepted that robust efficacy and safety data could still be derived from this study to support the applied indication as there were no critical issues raised with the conduct of study as such.

From a clinical point of view, ORR should be considered an appropriate endpoint only when supported by other clinical parameters (e.g. duration of response, PFS, improvement in disease resectability, etc) able to reassure over durability of the treatment effect and supporting translation into clinical benefit for patients. Moreover, ORR results should be convincing, in terms of magnitude and robustness of the effect.

The primary Efficacy Analysis Set (pEAS) was chosen by the Applicant as the target population to demonstrate the activity of sonidegib. There is a numerical difference of 59 pts (24 pts treated at the dose of 200 mg and 35 at 800 mg) between the FAS (ITT) and pEAS populations and this is the result

of the selection of patients based on completeness of their imaging and photography material, as specified in the amended study protocol. The implementation of modified RECIST for evaluation of response in patients with laBCC is also acceptable given that routine RECIST are not considered adequate to evaluate response in this kind of disease.

The study population enrolled in the pivotal A2201 study appears to be comparable to the typical population of patients with BCC and no obvious imbalances between study arms were observed in the demographic and baseline characteristics evaluated. Progressive disease (clinical or radiological) was not requested at study entry and thus, there was uncertainty concerning the status of disease (progressive or stable) at study entry for a high number of patients (23%) enrolled in the pivotal study. However, sensitivity analyses showed similar effect of sonidegib in patients with unknown disease status at baseline and patients with progressive disease, suggesting that the effect observed in the overall population was not driven by the effect observed in patients not yet progressing at time of study start.

Efficacy data and additional analyses

According to the primary analysis submitted (cut-off date 28 June 2013) in the pivotal A2201 study ORR per central review for all patients (enrolled in the pEAS) was 36.4% (95% CI: 23.8, 50.4) and 33.6% (95% CI: 25.1, 43.0) for the 200-mg and 800-mg arms, respectively. Response rates met the predefined criteria for both treatment arms for point estimates to meet or exceed 30%. Updated efficacy results (18-month analysis, cut-off 11 July 2014) were subsequently submitted.

In the laBCC population, ORRs of 54.8% (95% CI: 38.7, 70.2) and 47.3% (95% CI: 36.9, 57.9) were reported for the sonidegib 200-mg and 800-mg treatment arms, respectively, per central review in the pEAS, with consistent results observed in the FAS. ORRs appears higher in the analysis performed according to investigator assessment, with ORRs of 71.4% (95% CI: 55.4, 84.3) and 61.3% (95% CI: 50.6, 71.2) reported for the sonidegib 200-mg and 800-mg treatment arms, respectively.

In the mBCC population, ORRs of 7.7% (95%CI: 0.2, 36.0) and 17.4% (95%CI: 5.0, 38.8) were reported for the sonidegib 200-mg and 800-mg treatment arms, respectively, per central review. ORRs appear higher in the analysis performed according to investigator assessment, with ORRs of 23.1% (95%CI: 5.0, 53.8) and 34.8% (95%CI: 16.4, 57.3) reported for the sonidegib 200-mg and 800-mg treatment arms, respectively. Of note, a lower ORR was reported at the updated 18-month analysis (7.7%) in comparison with the original 6-month analysis (15.4%). There were concerns raised in relation to the low number of patients treated, the low rate of response observed (with no reported cases of CR) at the proposed 200 mg dose and the unlikely clinical relevance of an effect on asymptomatic lesions. Subsequently, based on the updated results submitted and the lower ORR observed at 18 months, the applicant withdrew the indication for the mBCC population.

ORR according to investigator assessment was higher in both laBCC and mBCC populations. Low concordance rates between IRC and INV assessment were observed (for the 200 mg arm 50% and 46% in the laBCC and mBCC population, respectively; for the 800 mg arm 49% and 61% in the laBCC and mBCC population, respectively). The reason for the low concordance could be attributed to the complexity of the response assessment implemented in the pivotal trial. The Applicant has provided a sensitivity analysis where only basic categories of responder vs non-responder yield concordance rates between investigator and central review of 67 and 72%, respectively, for patients with laBCC and mBCC providing further evidence on the robustness and reliability of the method used for the assessment.

Although median duration of response per central review and median OS could not be accurately estimated in both laBCC and mBCC populations due to high rate of censoring, PFS results reassure

overall durability of response. Indeed, in the laBCC population median PFS was 22.1 months with sonidegib 200 mg and 19.4 months with sonidegib 800 mg. In the mBCC population median PFS was 13.1 months with sonidegib 200 mg and 11.1 months with sonidegib 800mg. These data suggest also no significant difference in durability of response between patients treated with 200 mg and 800 mg sonidegib dose.

In the assessment of the narrative of several patients enrolled in the pivotal study an extremely long interval is observed between the discontinuation of the drug and observation of progression. Pharmacokinetic (PK) data indicate that patients continued to derive benefit from treatment long after discontinuation as a result of the long half-life of the drug. Moreover, modeling in 11 of such patients suggests that sustained Gli1 inhibition is associated with the systemic presence of the drug and, therefore, the 'long-term' beneficial effects observed could be attributed to treatment with sonidegib. It is possible that after an initial sustained inhibition by sonidegib, Gli1 levels progressively increase, approaching baseline values, at the time of radiological or clinical confirmation of progressive disease. The CHMP has requested the applicant to evaluate whether there is a correlation between Gli1 levels and disease progression as Gli1 levels could potentially act as a marker of sonidegib efficacy and that progressive disease could be identified by the return of Gli1 to baseline levels. Correlation between Gli1 levels and disease progression would allow the exploration of optimal drug schedule and explore discontinuation schedules to allow for better tolerability of sonidegib. This is a condition in the Annex II.

Evaluation of PROs showed that, with the limitations related to the large standard error, the majority of patients appear to experience a maintenance in their quality of life during treatment with sonidegib, with relatively more fatigue, pain and weight loss reported in patients treated with sonidegib 800 mg compared with the 200 mg arm.

Finally, an indirect comparison of efficacy between sonidegib and vismodegib was provided (data not shown). With the limitations related to inter study comparison, sonidegib appears comparable with vismodegib in terms of anti-tumour activity in laBCC patients.

Off-label use in patients with medulloblastoma, BCC appropriate for surgery or radiotherapy, and other cancers has been identified as missing information in the RMP.

2.5.4. Conclusions on the clinical efficacy

In patients with laBCC, treatment with sonidegib met the pre-specified 30% criteria in terms of ORR, suggesting a clinically relevant benefit in this patient population. The updated 18-month analysis and several sensitivity analyses appear to support the robustness of such finding. The updated PFS analysis supports durability of response.

Following the concerns raised by the CHMP on the relevance of the clinical benefit in patients with mBCC, the applicant withdrew the indication for the mBCC population.

Tumour shrinkage in oncology has been used as a tool to define the efficacy of medicinal products in exploratory or confirmatory clinical studies. To substantiate the assessment based on this endpoint, it is necessary to generate further efficacy data in the post-authorisation phase to verify the impact of the intervention on clinical outcome or disease progression. It is also necessary to verify whether the overall survival data in the post-authorisation phase is discordant with or confirmative of the outcome of the surrogate endpoint.

The CHMP considers the following measures necessary to be addressed issues related to of the efficacy

of the medicinal product were identified and can be resolved only after the medicinal product has been marketed:

1. Post-authorisation efficacy study (PAES): The MAH should submit by 30/10/2016 an analysis of Study CLDE225A2201 with:
    - an updated efficacy and safety analyses,
    - a correlative analysis of response to treatment and Gli1 levels for the entire study population of the pivotal study at different time points (e.g. baseline, time of response, time of progression, etc..)
    - an updated analysis of outcomes by aggressive vs non-aggressive histological subtypes. (30 months data)

    The clinical study report should be submitted by October 2016

- Post-authorisation efficacy study (PAES): The MAH should submit the final CSR for Study CLDE225A2201, including an updated analysis of outcomes by aggressive vs non-aggressive histological subtypes. (42 month data)

  The clinical study report should be submitted by October 2017.

- Post-authorisation efficacy study (PAES): The MAH should submit a molecular analysis in tumour material still available from patients treated in Study CLDE225A2201 experiencing disease progression in order to investigate the resistance mechanisms related to point mutations in SMO that may lead to reactivation of the Hh signaling pathway and tumour re-growth.

  The clinical study report should be submitted by October 2016.

2.6. Clinical safety

Patient exposure

Evaluation of safety of Odomzo is based on data from 293 patients that were treated with sonidegib monotherapy. This safety population consists of patients included in studies A2201 (full designation study CLDE225A2201) with mBCC and laBCC, in the dose escalation trial X2101 in patients with solid tumour (full designation study CLDE225X2101) and in Japanese patients with solid tumours in study X1101 (CLDE225X1101).

Additional sources of data consisted of a worldwide literature search, to capture any investigator reports on safety aspects not included in the study reports (01-Dec-2012 to 31-Dec-2013) and a review of SAE reports from ongoing studies (including clinical pharmacology studies.

Table 41: Safety population on sonidegib (N=293)

Study No.	Study design, objectives, and population	No. of patients				
		100 mg	200 mg	400 mg	600 mg	800 mg
Pooled dataset						
[A2201]	Randomized, double-blind, multicenter, Phase-II study Efficacy and safety in patients with laBCC or mBCC		79			150
[X2101]	Open-label, multicenter, Phase-I study Dose-escalation in patients with advanced solid tumors	6	6	5		26
Supportive data						
[X1101]	Open-label, multicenter, Phase-I study Dose-escalation in east Asian patients (Group 1: Japanese) with advanced solid tumors			12	9	
	Total	**6**	**85**	**17**	**9**	**176**

laBCC Locally advanced basal cell carcinoma; mBCC Metastatic basal cell carcinoma

Overall exposure

In Study A2201, the median duration of treatment with sonidegib 200 mg was 8.9 months compared to 6.5 months for the sonidegib 800-mg group (Table 42). The shorter exposure in the 800-mg treatment group was attributed to early discontinuation of patients as the result of AEs (and not to disease progression). As of the 28-Jun-2013 data cut-off, the median study follow-up was 13.1 months for the pEAS and 13.9 months for the FAS.

Table 42: Duration of exposure to sonidegib by dose – Study A2201 (safety set)

Duration of exposure (months)	Sonidegib 200 mg N=79	Sonidegib 800 mg N=150
Exposure categories-n (%)		
<1	0	7 (4.7)
1 - <4	7 (8.9)	38 (25.3)
4 - <8	29 (36.7)	50 (33.3)
8 - <12	22 (27.8)	27 (18.0)
12 - <16	14 (17.7)	13 (8.7)
16 - <20	6 (7.6)	15 (10.0)
≥ 20	1 (1.3)	0
Duration of exposure		
n	79	150
Mean (standard deviation)	9.5 (4.33)	7.4 (5.02)
Median	8.9	6.5
Minimum, maximum	1.3, 21.4	0.3, 19.1
Total patient-year exposure	**62.4**	**92.9**

In the SCS pool the median duration of exposure to sonidegib 200 mg and 800 mg was 8.4 months compared to 6.1 months for the sonidegib 800-mg group (Table 43).

Table 43: Duration of exposure to sonidegib by dose – SCS pool (safety set)

	Sonidegib			
Duration of exposure (months)	100 mg N=6	200 mg N=85	400 mg N=5	800 mg N=176
Exposure categories-n (%)				
<1	4 (66.7)	2 (2.4)	0	9 (5.1)
1 - <4	0	9 (10.6)	5 (100)	52 (29.5)
4 - <8	0	30 (35.3)	0	53 (30.1)
8 - <12	0	22 (25.9)	0	29 (16.5)
12 - <16	0	14 (16.5)	0	13 (7.4)
16 - <20	0	6 (7.1)	0	16 (9.1)
≥ 20	2 (33.3)	2 (2.4)	0	0
Duration of study treatment exposure				
n	6	85	5	172
Mean (standard deviation)	9.9 (14.37)	9.3 (5.00)	2.1 (1.12)	7.0 (5.04)
Median	1.0	8.4	1.8	6.1
Minimum, Maximum	0.79, 33.38	0.95, 28.98	1.15, 3.88	0.26, 19.12

Adverse events

Adverse events (AEs) were classified using v16.1 of the Medical Dictionary for Regulatory Activities (MedDRA) and arranged by system organ class (SOC). Laboratory parameters were classified into grades using the NCI common toxicity criteria of AE Version 4.03.

Safety and tolerability of sonidegib 200 mg and 800 mg QD are summarized in the table below. The contents of this table show that, regarding AEs, the 200 mg dose appeared more favourable than for the 800-mg dose.

Table 44: Overview of adverse event categories (Safety set study A2201)

	Sonidegib 200 mg N=79		Sonidegib 800 mg N=150	
Adverse event category	n	(%)	n	(%)
Any AE	75	(94.9)	150	(100.0)
Grade 3/4 AE	24	(30.4)	84	(56.0)
Grade 3/4 AE with suspected causality	18	(22.8)	63	(42.0)
Death on-treatment	0		4	(2.7)
SAE	11	(13.9)	45	(30.0)
SAE with suspected causality	3	(3.8)	18	(12.0)
AE leading to discontinuation	17	(21.5)	54	(36.0)
AE requiring dose interruption and/or reduction	25	(31.6)	90	(60.0)

In A2201 AEs were experienced by 94.9% of patients receiving sonidegib 200 mg and by 100.0% of patients in the sonidegib 800-mg group. More important, a substantial number of patients treated with the proposed 200 mg daily dose encountered grade 3 or 4 AE (CTCAE v4).

System organ class (SOC) defined AEs as reported ≥10% in the 200 mg sonidegib-arm encompassed primarily musculoskeletal and connective tissue disorders (e.g., muscle spasms 49.4%), skin and subcutaneous tissue disorders (alopecia 43.0%), nervous system disorders (e.g., dysgeusia 38%), blood abnormalities (e.g., elevated CPK 29.1%), fatigue (29.1%) and metabolism and nutrition disorders (loss of appetite in 19%).

The updated 18-month analysis of data from A2201 confirms observations from the initial analysis, i.e. that the rate of discontinuation due to AEs is relatively high, with 27.8% of patients treated at the 200 mg and 37.3% treated at 800 mg that decided to stop the ongoing therapy.

A refinement of the schedule in function of the molecular inhibition of Gli1 could be of help in warranting a higher adherence to treatment, with stop-and-go periods of treatment.

Adverse events in study X2101

Of the 103 patients studied in the dose escalation study X2101, 102 patients (99%) experienced an adverse event (AE) during the study, and the majority of patients (78 patients, 75.7%) had AEs suspected to be related to study drug. Approximately 60% of the patients experienced grade 3 - 4 AEs, and approximately one-half of patients experienced a SAE. The most common SAE was increased creatinine phosphokinase (CPK).

Table 45: Adverse events (greater than or equal to 5 percent), suspected to be drug-related, by preferred term, by treatment - Study X2101 Safety set

Preferred Term	100 mg q.d. N=6 n (%)	200 mg q.d. N=6 n (%)	400 mg q.d. N=5 n (%)	800 mg q.d. N=26 n (%)	1000 mg q.d. N=11 n (%)	1500 mg q.d. N=9 n (%)	3000 mg q.d. N=10 n (%)	250 mg b.i.d. N=14 n (%)	400 mg b.i.d. N=8 n (%)	750 mg b.i.d. N=8 n (%)	All N=103 n (%)
Any primary system class	5 (83.3)	5 (83.3)	2 (40.0)	20 (76.9)	9 (81.8)	6 (66.7)	6 (60.0)	11 (78.6)	6 (75.0)	8 (100.0)	78 (75.7)
Blood creatine phosphokinase increased	1 (16.7)	1 (16.7)	0	7 (26.9)	4 (36.4)	3 (33.3)	4 (40.0)	3 (21.4)	4 (50.0)	6 (75.0)	33 (32.0)
Muscle spasm	2 (33.3)	2 (33.3)	0	9 (34.6)	3 (27.3)	4 (44.4)	0	5 (35.7)	4 (50.0)	4 (50.0)	33 (32.0)
Dysgeusia	1 (16.7)	1 (16.7)	0	5 (19.2)	3 (27.3)	3 (33.3)	5 (50.0)	6 (42.9)	3 (37.5)	3 (37.5)	30 (29.1)
Nausea	3 (50.0)	1 (16.7)	0	4 (15.4)	3 (27.3)	4 (44.4)	2 (20.0)	3 (21.4)	1 (12.5)	5 (62.5)	26 (25.2)
Decreased appetite	2 (33.3)	1 (16.7)	1 (20.0)	4 (15.4)	3 (27.3)	0	2 (20.0)	3 (21.4)	2 (25.0)	1 (12.5)	19 (18.4)
Myalgia	0	1 (16.7)	0	4 (15.4)	3 (27.3)	2 (22.2)	2 (20.0)	3 (21.4)	0	2 (25.0)	17 (16.5)
Fatigue	4 ((66.7)	1 (16.7)	0	1 (3.8)	3 (27.3)	2 (22.2)	0	1 (7.1)	2 (25.0)	1 (12.5)	15 (14.6)
Vomiting	1 (16.7)	1 (16.7)	0	3 (11.5)	1 (9.1)	1 (11.1)	1 (10.0)	2 (14.3)	1 (12.5)	2 (25.0)	13 (12.6)
Alopecia	1 (16.7)	1 (16.7)	0	4 (15.4)	1 (9.1)	2 (22.2)	1 (10.0)	1 (7.1)	2 (25.0)	0	13 (12.6)
Asthenia	1 (16.7)	1 (16.7)	0	5 (19.2)	1 (9.1)	1 (11.1)	0	3 (21.4)	1 (12.5)	0	13 (12.6)
Weight decreased	0	0	0	4 (15.4)	1 (9.1)	0	2 (20.0)	2 (14.3)	1 (12.5)	1 (12.5)	11 (10.7)
Aspartate aminotransferase increased	0	0	0	1 (3.8)	0	1 (11.1)	1 (10.0)	3 (21.4)	1 (12.5)	1 (12.5)	8 (7.8)
Diarrhoea	0	0	0	2 (7.7)	0	0	1 (10.0)	1 (7.1)	1 (12.5)	2 (25.0)	7 (6.8)
Alanine aminotransferase increased	0	0	0	1 (3.8)	0	1 (11.1)	1 (10.0)	3 (21.4)	1 (12.5)	0	7 (6.8)
Lethargy	0	0	0	3 (11.5)	1 (9.1)0	0	1 (10.0)	1 (7.1)	0	1 (12.5)	7 (6.8)
Constipation	0	1 (16.7)	0	1 (3.8)	1 (9.1)	0	1 (10.0)	0	0	2 (25.0)	6 (5.8)

Preferred Term	100 mg q.d. N=6 n (%)	200 mg q.d. N=6 n (%)	400 mg q.d. N=5 n (%)	800 mg q.d. N=26 n (%)	1000 mg q.d. N=11 n (%)	1500 mg q.d. N=9 n (%)	3000 mg q.d. N=10 n (%)	250 mg b.i.d. N=14 n (%)	400 mg b.i.d. N=8 n (%)	750 mg b.i.d. N=8 n (%)	All N=103 n (%)

Source: Post-text Table 14.3.1-1.5

5% is based on 'All' Column.

Preferred terms are sorted in descending frequency, as reported in the 'All' column.

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

Only AEs occurring during treatment or within 28 days of the last study medication are reported.

A total of 24 patients (23.3%) had grade 3 - 4 AEs suspected to be study drug related. The most common grade 3 - 4 related AEs were increased blood creatine phosphokinase (18 patients, 17.5%), increased AST (4 patients, 3.9%), asthenia, increased alanine aminotransferase, and increased myoglobin blood (3 patients each, 2.9%). All other grade 3 - 4 AEs suspected to be study drug related occurred in 2 patients or less.

Table 46: Adverse events (greater than 1 percent) with maximal severity grade 3 - 4 by treatment, regardless of study drug relationship, by preferred term and treatment - Study X2101 Safety set

Preferred Term	100 mg q.d. N=6 n (%)	200 mg q.d. N=6 n (%)	400 mg q.d. N=5 n (%)	800 mg q.d. N=26 n (%)	1000 mg q.d. N=11 n (%)	1500 mg q.d. N=9 n (%)	3000 mg q.d. N=10 n (%)	250 mg b.i.d. N=14 n (%)	400 mg b.i.d. N=8 n (%)	750 mg b.i.d. N=8 n (%)	All N=103 n (%)
Total	2 (33.3)	2 (33.3)	3 (60.0)	12 (46.2)	8 (72.7)	6 (66.7)	8 (80.0)	7 (50.0)	6 (75.0)	7 (87.5)	61 (59.2)

Albeit that numbers of patients tested were small the lowest rate of grade 3-4 AEs was reported in the 100 and 200 mg QD groups.

14 patients included in this phase I trial died during the study. This course was mainly attributed to the patient's highly advanced disease and grave prognosis *ad vitam*: twelve of the patient deaths were related to disease progression. The other 2 deaths on study were cardiac arrest and sudden death, both AE were considered to be unrelated to sonidegib by the investigators. Other than DLTs, in this study there were no clinically significant changes in laboratory values, vital signs, or ECG parameters.

Adverse events for main trial A2201

Patients that were included in the A2201 study had an overall exposure of 155.3 patient-years, and are considered representative of the intended target population.

Mean duration of treatment with sonidegib 200 mg was 9.5 months, and 7.4 months with the 800-mg group. The median duration of treatment was 8.9 months and 6.5 months, respectively. The shorter exposure in the 800-mg group was attributed to the early discontinuation of patients as a result of AEs and not to disease progression. Overall, 43 (54.4%) and 21 patients (26.6%), respectively, were exposed to sonidegib 200 mg for periods ≥ 8 and ≥ 12 months. In the sonidegib 800-mg group, 55 patients (36.7%) and 28 patients (18.7%) respectively, were exposed to treatment for periods of ≥8 and ≥ 12 months. The median relative dose intensities were 97.2% and 91.8% for the sonidegib 200-mg and 800-mg treatment groups, respectively.

Dose reductions in A2201 were >2-fold more frequent in the sonidegib 800-mg treatment group than the 200-mg group. These dose modifications were primarily attributable to AEs. Dose interruptions were observed in similar proportions in the two treatment groups.

Table 47: Adverse events irrespective of causality occurring in at least 10% of patients treated with 200 mg or 800 mg sonidegib - Safety set A2201

	Sonidegib 200 mg N=79		Sonidegib 800 mg N=150	
System organ class MedDRA preferred term	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Any AE	**75 (94.9)**	**24 (30.4)**	**150 (100.0)**	**84 (56.0)**
Musculoskeletal and connective tissue disorders				
Muscle spasms	39 (49.4)	2 (2.5)	100 (66.7)	8 (5.3)
Myalgia	15 (19.0)	0	39 (26.0)	3 (2.0)
Arthralgia	10 (12.7)	1 (1.3)	12 (8.0)	1 (0.7)
Back pain	5 (6.3)	0	15 (10.0)	0
Skin and subcutaneous tissue disorders				
Alopecia	34 (43.0)	1 (1.3)	83 (55.3)	0
Nervous system disorders				
Dysgeusia	30 (38.0)	0	89 (59.3)	1 (0.7)
Headache	12 (15.2)	0	20 (13.3)	1 (0.7)
Gastrointestinal disorders				
Nausea	26 (32.9)	1 (1.3)	68 (45.3)	4 (2.7)
Diarrhoea	19 (24.1)	0	33 (22.0)	0
Constipation	6 (7.6)	1 (1.3)	20 (13.3)	0
Vomiting	5 (6.3)	1 (1.3)	39 (26.0)	2 (1.3)
Investigations				
Blood creatine phosphokinase increased	23 (29.1)	5 (6.3)	56 (37.3)	19 (12.7)
Weight decreased	21 (26.6)	1 (1.3)	57 (38.0)	8 (5.3)
General disorders and administration site conditions				
Fatigue	23 (29.1)	0	54 (36.0)	3 (2.0)
Metabolism and nutrition disorders				
Decreased appetite	15 (19.0)	0	46 (30.7)	6 (4.0)

Muscle spasms, alopecia, dysgeusia, and nausea were common AEs reported with sonidegib 200 mg QD: in fact each of these AE was reported in ≥30% of patients in A2201.

Overall, muscle spasms, alopecia, dysgeusia, fatigue, nausea, blood CK increased, musculoskeletal pain, weight decreased, diarrhoea, decreased appetite, myalgia, abdominal pain, headache, and pain were frequently reported (≥10%) in the 200 mg-arm. These events primarily regarded CTC grade 1/2 (mild/moderate) events.

At the initial MAA Grade 3 - 4 events were reported in 24 patients (30.4%) treated with 200 mg OD. and regarded mostly blood CPK elevation (6.3%) and at lowering frequencies: muscle spasms (2,5%), arthralgia, nausea, constipation vomiting and/or weight loss. (In comparison: 56% of patients in the 800 mg arm encountered CTC grade 3 /4 toxicity) (also refer to the section on laboratory findings).

Not surprisingly AEs were more prominent and more frequent in the 800 mg QD-arm when compared with the 200 mg QD-arm.

At the initial application dysgeusia was reported at lower frequency in the 200 mg sonidegib-arm than in the 800 mg-arm of A2201 (38% and 59.3% respectively). Also vomiting (6.3% and 26%), muscle spasms (49.4% and 66.7%), nausea (32.9% and 45.3%), alopecia (43% and 55.3%), decreased appetite (19% and 30.7%), and weight decrease (26.6% and 38%) were observed in higher frequencies in the 800 mg QD group op pivotal trial A2201. Nevertheless the frequencies as reported from the 200 mg arm-patients by itself must be considered substantial and the dose reduction/interruption or treatment discontinuation deemed necessary (more than 50% of cases) illustrate the severity of AEs.

Manageability of AEs

Most AEs were generally manageable with dose adjustments, concomitant medications, non-drug therapies, or dietary intervention.

The documented AEs CTC grade 3 and 4 are enumerated in detail in the following table:

Table 48: Adverse drug reactions by grade 3 or 4 - Study A2201 - Safety set

	Sonidegib 200 mg N=79			Sonidegib 800 mg N=150		
System organ class Grouped/preferred term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Metabolism and nutrition disorders						
Decreased appetite	15 (19.0)	0	0	46 (30.7)	6 (4.0)	0
Dehydration	0	0	0	8 (5.3)	3 (2.0)	0
Nervous system disorders						
Dysgeusia	30 (38.0)	0	0	89 (59.3)	1 (0.7)	0
Headache	12 (15.2)	0	0	20 (13.3)	1 (0.7)	0
Ageusia	0	0	0	13 (8.7)	0	0
Hypogeusia	0	0	0	8 (5.3)	2 (1.3)	0
Gastrointestinal disorders						
Nausea	26 (32.9)	1 (1.3)	0	68 (45.3)	4 (2.7)	0
Diarrhoea	19 (24.1)	0	0	33 (22.0)	0	0
Abdominal pain[a]	12 (15.2)	0	0	21 (14.0)	0	0
Constipation	6 (7.6)	1 (1.3)	0	20 (13.3)	0	0
Vomiting	5 (6.3)	1 (1.3)	0	39 (26.0)	2 (1.3)	0
Dyspepsia	4 (5.1)	0	0	8 (5.3)	0	0
Gastrooesophageal reflux disease	2 (2.5)	0	0	3 (2.0)	0	0
Skin and subcutaneous tissue disorders						
Alopecia[b]	37 (46.8)	1 (1.3)	0	84 (56.0)	0	0
Pruritus[c]	6 (7.6)	0	0	8 (5.3)	0	0
Rash[d]	4 (5.1)	0	0	13 (8.7)	0	0
Hair growth abnormal[e]	3 (3.8)	0	0	3 (2.0)	0	0
Musculoskeletal and connective tissue disorders						
Muscle spasms[f]	39 (49.4)	2 (2.5)	0	102 (68.0)	8 (5.3)	0
Musculoskeletal pain[g]	23 (29.1)	1 (1.3)	0	38 (25.3)	1 (0.7)	0
Myalgia	15 (19.0)	0	0	39 (26.0)	3 (2.0)	0
Myopathy[h]	3 (3.8)	0	0	9 (6.0)	1 (0.7)	0
Myositis	0	0	0	2 (1.3)	1 (0.7)	0
General disorders and administration site conditions						
Fatigue[i]	29 (36.7)	2 (2.5)	0	63 (42.0)	3 (2.0)	0
Pain[j]	10 (12.7)	1 (1.3)	0	21 (14.0)	0	0
Investigations						
Blood creatine phosphokinase increased	23 (29.1)	3 (3.8)	2 (2.5)	56 (37.3)	11 (7.3)	8 (5.3)
Weight decreased	21 (26.6)	1 (1.3)	0	57 (38.0)	8 (5.3)	0
Lipase increased	6 (7.6)	4 (5.1)	0	12 (8.0)	7 (4.7)	1 (0.7)
Hepatic enzyme increased[k]	1 (1.3)	1 (1.3)	0	10 (6.7)	7 (4.7)	0
Amylase increased	1 (1.3)	1 (1.3)	0	6 (4.0)	0	1 (0.7)

[a] Rash included dermatitis, drug eruption, dry skin, rash, rash erythematous, rash papular, and rash pruritic
[e] Hair growth abnormal included hair disorder, hair growth abnormal, and hair texture abnormal
[f] Muscle spasms included muscle contractions involuntary, muscle spasms, muscle spasticity, and muscle tightness
[g] Musculoskeletal pain included arthralgia, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, neck pain, pain in extremity, and pain in jaw
[h] Myopathy included muscle fatigue and muscular weakness
[i] Fatigue included asthenia, fatigue, lethargy, and malaise
[j] Pain included ear pain, eye pain, facial pain, gingival pain, oral pain, oropharyngeal pain, pain, and pain of skin
[k] Hepatic enzyme increased included alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, and hepatotoxicity

The AEs as encountered in study A2201 show a similar pattern to vismodegib (Erivedge). When vismodegib is used as indicated the most common adverse drug reactions (ADR) that occurred in ≥ 30% of patients were muscle spasms (74.6 %), alopecia (65.2 %), dysgeusia (57.2 %), weight decreased (48.6 %), fatigue (44.9 %) and nausea (34.8 %).

Serious adverse event/deaths/other significant events

CTC grade 4 AE from the A2201 study was only reported as elevation of blood CPK (2.5%). As stated grade 3 AEs were noted as raised serum lipase (5.1%), CPK (3.8%) and elevation of other laboratory parameters (liver enzymes, amylase, 1.3%), as well as fatigue, and muscle spasms (2.5%), and weight loss, gastro intestinal disorders and alopecia (each encountered at 1.3%).

The most common SAEs overall in this registration study were rhabdomyolysis (1.3% of patients in the 200-mg treatment group vs 3.3% in those that received 800 mg), blood CPK increased (1.3% vs 2.0%), and vomiting (0% vs 2.7%).

In the phase II pivotal study, 2 (14.3%) out of 14 women of either child-bearing potential or of child-bearing age sterilised by tubal ligation developed amenorrhoea while on treatment with Odomzo 200 mg or 800 mg once daily.

Secondary primary malignancies

Seven patients in study A2201 (N=229) developed cutaneous squamous cell carcinoma (SCC). This regarded 3 (3.8%) from the 200-mg treatment group and 4 (2.7%) from the 800-mg group. Other secondary malignancies reported with the use of sonidegib included malignant melanoma, prostate cancer and cases of B-cell lymphoma and vulva cancer.

A higher incidence of SPM is associated with higher sonidegib dose, with 12.7% (10 patients) and 15.3% (23 patients) in the 200 and 800 mg arm, respectively. No conclusive data about timing and type of second cancer types can be drawn at this stage.

Electrocardiography

No AEs with the preferred terms of ‘electrocardiogram QT prolonged’ or ‘Torsade de pointes’ were reported in patients included in study A2201, either in the sonidegib 200-mg group or in the sonidegib 800-mg group. In the 200 mg sonidegib arm of study A2201 increases of the QTcF- interval from baseline of >30 msec were reported for 7.6% of patients.

Fractures

In Study A2201, the current data indicate that there are 10 patients with 11 events of ‘fracture’ through 11-Jul-2014 for a rate of 530.9 fractures per 10000 patient-years (95% CI: 265.0-949.9) (for a cumulative exposure of 207.2 patient-years, 95% CI based on Poisson distribution).

Deaths

In the pivotal trial, at the 28-Jun-2013 cut-off date, 11 deaths (11/229, 4.8%) were reported, 2 (2.5%) in the sonidegib 200-mg group and 9 (6.0%) in the sonidegib 800-mg group. Of these fatalities four deaths occurred ‘on-treatment’ (defined as up to 30 days after the end of treatment) with all 4 deaths in the sonidegib 800-mg group. 2/11 of these deaths were attributed to the underlying malignancy. Of the remaining two, 1 was secondary to congestive cardiac failure and 1 was secondary to cardiac death.

Laboratory findings

Haematological abnormalities of any grade occurred in a higher proportion of patients with sonidegib 800 mg relative to the 200-mg group. In both the sonidegib 200-mg and 800-mg groups, the most frequently reported haematological abnormalities in >20% of patients were decreased haemoglobin (25.3% and 34.7%, respectively) and decreased lymphocytes (24.1% and 34.0%, respectively).

Table 49: Selected haematology abnormalities (Safety set study A2201)

	Sonidegib 200 mg N=79		Sonidegib 800 mg N=150	
Laboratory parameter	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Hematology				
Hemoglobin (hypo)	20 (25.3)	0	52 (34.7)	1 (0.7)
Lymphocytes (hypo)	19 (24.1)	1 (1.3)	51 (34.0)	5 (3.3)
Neutrophils (hypo)	6 (7.6)	0	12 (8.0)	1 (0.7)
Leukocytes (hypo)	5 (6.3)	0	22 (14.7)	1 (0.7)
Platelets (hypo)	5 (6.3)	0	18 (12.0)	1 (0.7)

The table displays the worst post-baseline values based on CTC grade for hemoglobin and lymphocytes, regardless of their baseline grade.

Results on abnormalities in chemistry laboratory parameters in study A2201 showed that in study A2201 increases in creatinine, cholesterol, CPK, glucose, lipase, and magnesium levels occurred in ≥ 30% of patients. The most frequently reported grade 3 - 4 clinical chemistry abnormalities were increased lipase (11.4%), increased CPK (6.3%), increased glucose and increased potassium (each 3.8%), and increased ALT and AST (each 2.5%). Incidence and severity of CK elevations appear to be related to the sonidegib dose administered.

Table 50: Selected clinical chemistry abnormalities (Safety set study A2201)

	Sonidegib 200 mg N=79		Sonidegib 800 mg N=150	
Laboratory parameter	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Clinical chemistry				
Creatinine (hyper)	73 (92.4)	0	139 (92.7)	2 (1.3)
Cholesterol (hyper)	56 (70.9)	0	105 (70.0)	0
Creatine kinase (hyper)	45 (57.0)	5 (6.3)	100 (66.7)	24 (16.0)
Glucose (hyper)	37 (46.8)	3 (3.8)	83 (55.3)	4 (2.7)
Lipase (hyper)	31 (39.2)	9 (11.4)	76 (50.7)	19 (12.7)
Magnesium (hypo)	25 (31.6)	1 (1.3)	43 (28.7)	1 (0.7)
Calcium (hyper)	16 (20.3)	0	36 (24.0)	0
Glucose (hypo)	16 (20.3)	0	34 (22.7)	0
Phosphate (hypo)	15 (19.0)	1 (1.3)	14 (9.3)	0
Potassium (hyper)	14 (17.7)	3 (3.8)	17 (11.3)	4 (2.7)
Alanine aminotransferase (hyper)	14 (17.7)	2 (2.5)	44 (29.3)	6 (4.0)
Alkaline phosphatase (hyper)	14 (17.7)	0	19 (12.7)	1 (0.7)
Calcium (hypo)	12 (15.2)	1 (1.3)	12 (8.0)	0
Aspartate aminotransferase (hyper)	12 (15.2)	2 (2.5)	46 (30.7)	8 (5.3)
Amylase (hyper)	11 (13.9)	1 (1.3)	26 (17.3)	3 (2.0)
Sodium (hyper)	10 (12.7)	0	18 (12.0)	1 (0.7)

ECG abnormalities

No AEs with the preferred terms of 'electrocardiogram QT prolonged' or 'Torsade des pointes' were reported in patients included in study A2201, either in the sonidegib 200-mg group or in the sonidegib 800-mg group. Nevertheless, increases from baseline of QTcF >30 msec were reported in 7.6% of patients in the sonidegib 200-mg group and 14.4% of patients in the 800-mg group. No increases from baseline in QTcF of >60 msec were observed in either treatment group. In the Day 120 Response document the Applicant has provided 18-month (cut-off 11 July 2014) updated safety analyses. Also here in overall no *clinically relevant* prolongation of QTc in patients' electrocardiography was observed.

Eye disorders

The table below shows the AEs for eye disorders in 800 mg arm. Of note, cases of corneal perforation, keratitis and keratinopathy were reported in study A2201 in 800 mg only.

Table 51: Adverse Events reported for eye disorders – study A2201

Treatment: LDE225 800 mg qd (N=150)

Primary system organ class Preferred Term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3/4 n (%)	All grades n (%)
Eye disorders -Total	16 (10.7)	2 (1.3)	1 (0.7)	0	1 (0.7)	19 (12.7)
Cataract	2 (1.3)	0	1 (0.7)	0	1 (0.7)	3 (2.0)
Blepharospasm	1 (0.7)	0	0	0	0	1 (0.7)
Conjunctivitis	3 (2.0)	0	0	0	0	3 (2.0)
Corneal perforation	0	1 (0.7)	0	0	0	1 (0.7)
Diplopia	1 (0.7)	0	0	0	0	1 (0.7)
Dry eye	3 (2.0)	0	0	0	0	3 (2.0)
Eye pain	1 (0.7)	0	0	0	0	1 (0.7)
Eye pruritus	1 (0.7)	0	0	0	0	1 (0.7)
Eyelid disorder	1 (0.7)	0	0	0	0	1 (0.7)
Keratitis	1 (0.7)	0	0	0	0	1 (0.7)
Keratopathy	1 (0.7)	0	0	0	0	1 (0.7)
Lagophthalmos	2 (1.3)	0	0	0	0	2 (1.3)
Ocular fistula	0	1 (0.7)	0	0	0	1 (0.7)
Vision blurred	3 (2.0)	0	0	0	0	3 (2.0)
Visual impairment	2 (1.3)	0	0	0	0	2 (1.3)

Safety in special populations

The median age of patients recruited to the registration phase II study A2201 was 66 years. There were no signs of an increased incidence of AEs reported in the elderly other than those that might be expected with increasing age.

The safety of sonidegib in paediatric patients has not been evaluated in this program. Too few non-Caucasians were included in the clinical development program to draw conclusions on safety in different racial groups.

Specific studies in patients with hepatic or renal impairment were not conducted, although a PK study is ongoing in patients with hepatic impairment. As sonidegib is eliminated primarily via the hepatic route, wording is included in the proposed label to indicate that impaired hepatic function may affect the PK of sonidegib.

The applicant did not submit data in pregnant women.

Table 52: Integrated summary of adverse events by treatment and age (Safety set)

	18-month analysis: data cutoff date: 11-Jul-2014							
	Sonidegib 200 mg				Sonidegib 800 mg			
MedDRA terms	Age <65 N=32 n (%)	Age 65 to <75 N=21 n (%)	Age 75 to <85 N=17 n (%)	Age ≥85 N=9 n (%)	Age <65 N=73 n (%)	Age 65 to <75 N=40 n (%)	Age 75 to <85 N=26 n (%)	Age ≥85 N=11 n (%)
Number of patients with at least one adverse event (AEs) by system organ class	**30 (93.8)**	**21 (100)**	**17 (100)**	**9 (100)**	**73 (100)**	**40 (100)**	**26 (100)**	**11 (100)**
Psychiatric disorders	6 (18.8)	5 (23.8)	1 (5.9)	0	17 (23.3)	7 (17.5)	2 (7.7)	2 (18.2)
Nervous system disorders	21 (65.6)	19 (90.5)	9 (52.9)	6 (66.7)	64 (87.7)	31 (77.5)	21 (80.8)	8 (72.7)
Accidents and injuries	1 (3.1)	2 (9.5)	4 (23.5)	3 (33.3)	6 (8.2)	6 (15.0)	2 (7.7)	1 (9.1)
Cardiac disorders	0	2 (9.5)	3 (17.6)	1 (11.1)	7 (9.6)	7 (17.5)	5 (19.2)	2 (18.2)
Vascular disorders	4 (12.5)	7 (33.3)	5 (29.4)	1 (11.1)	15 (20.5)	12 (30.0)	3 (11.5)	2 (18.2)
Cerebrovascular disorders	0	1 (4.8)	0	1 (11.1)	0	0	0	0
Infections and infestations	14 (43.8)	13 (61.9)	9 (52.9)	2 (22.2)	43 (58.9)	16 (40.0)	13 (50.0)	5 (45.5)
Anticholinergic syndrome[1]	0	0	0	0	0	0	0	0
Quality of life decreased[1]	0	0	0	0	0	0	0	0
Serious AEs	**3 (9.4)**	**3 (14.3)**	**5 (29.4)**	**3 (33.3)**	**26 (35.6)**	**14 (35.0)**	**9 (34.6)**	**7 (63.6)**
AEs leading to discontinuation	**4 (12.5)**	**10 (47.6)**	**7 (41.2)**	**3 (33.3)**	**20 (27.4)**	**19 (47.5)**	**14 (53.8)**	**6 (54.5)**
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	**4 (12.5)**	**4 (19.0)**	**5 (29.4)**	**3 (33.3)**	12 (16.4)	**8 (20.0)**	5 (19.2)	4 (36.4)
Dizziness	2 (6.3)	2 (9.5)	3 (17.6)	0	5 (6.8)	4 (10.0)	2 (7.7)	4 (36.4)
Fall	0	1 (4.8)	2 (11.8)	2 (22.2)	1 (1.4)	2 (5.0)	1 (3.8)	0
Hypotension	0	0	2 (11.8)	1 (11.1)	1 (1.4)	3 (7.5)	1 (3.8)	0
Syncope	2 (6.3)	0	0	0	4 (5.5)	0	1 (3.8)	0
Hand fracture	0	0	0	0	2 (2.7)	0	0	0

	18-month analysis: data cutoff date: 11-Jul-2014							
	Sonidegib 200 mg				Sonidegib 800 mg			
MedDRA terms	Age <65 N=32 n (%)	Age 65 to <75 N=21 n (%)	Age 75 to <85 N=17 n (%)	Age ≥85 N=9 n (%)	Age <65 N=73 n (%)	Age 65 to <75 N=40 n (%)	Age 75 to <85 N=26 n (%)	Age ≥85 N=11 n (%)
Upper limb fracture	0	0	1 (5.9)	0	0	0	0	1 (9.1)
Cervical vertebral fracture	0	0	0	0	0	0	0	1 (9.1)
Femoral neck fracture	0	0	0	1 (11.1)	0	0	0	0
Loss of consciousness	1 (3.1)	0	0	0	0	0	0	0
Lumbar vertebral fracture	0	1 (4.8)	0	0	0	0	0	0
Orthostatic hypotension	0	0	0	1 (11.1)	0	0	0	0
Presyncope	0	0	0	0	1 (1.4)	0	0	0
Spinal compression fracture	0	0	1 (5.9	0	0	0	0	0
Spinal fracture	0	0	0	0	1 (1.4)	0	0	0
Sternal fracture	0	0	0	0	0	0	1 (3.8)	0
Wrist fracture	0	0	0	0	0	1 (2.5)	0	0
Other AE appearing more frequently in older patients (≥ 10% of all patients)	**30 (93.8)**	**21 (100)**	**17 (100)**	**9 (100)**	**73 (100)**	**40 (100)**	**26 (100)**	**11 (100)**
Muscle spasms	20 (62.5)	11 (52.4)	7 (41.2)	5 (55.6)	54 (74.0)	28 (70.0)	18 (69.2)	4 (36.4)
Alopecia	14 (43.8)	11 (52.4)	9 (52.9)	5 (55.6)	48 (65.8)	26 (65.0)	11 (42.3)	2 (18.2)
Dysgeusia	14 (43.8)	11 (52.4)	7 (41.2)	4 (44.4)	50 (68.5)	25 (62.5)	10 (38.5)	5 (45.5)
Nausea	12 (37.5)	11 (52.4)	4 (23.5)	4 (44.4)	41 (56.2)	16 (40.0)	9 (34.6)	5 (45.5)
Weight decreased	8 (25.0)	6 (28.6)	5 (29.4)	5 (55.6)	30 (41.1)	18 (45.0)	11 (42.3)	5 (45.5)
Blood creatine phosphokinase increased	13 (40.6)	6 (28.6)	4 (23.5)	1 (11.1)	35 (47.9)	15 (37.5)	4 (15.4)	2 (18.2)
Fatigue	9 (28.1)	6 (28.6)	5 (29.4)	3 (33.3)	27 (37.0)	16 (40.0)	9 (34.6)	3 (27.3)
Decreased appetite	5 (15.6)	5 (23.8)	4 (23.5)	4 (44.4)	21 (28.8)	17 (42.5)	78 (30.8)	6 (54.5)
Diarrhoea	9 (28.1)	9 (42.9)	4 (23.5)	3 (33.3)	17 (23.3)	8 (20.0)	8 (30.8)	3 (27.3)

	18-month analysis: data cutoff date: 11-Jul-2014							
	Sonidegib 200 mg				Sonidegib 800 mg			
	Age <65	Age 65 to <75	Age 75 to <85	Age ≥85	Age <65	Age 65 to <75	Age 75 to <85	Age ≥85
	N=32	N=21	N=17	N=9	N=73	N=40	N=26	N=11
MedDRA terms	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Myalgia	8 (25.0)	4 (19.0)	3 (17.6)	0	29 (39.7)	8 (20.0)	2 (7.7)	3 (27.3)
Vomiting	4 (12.5)	2 (9.5)	2 (11.8)	1 (11.1)	27 (37.0)	10 (25.0)	2 (7.7)	3 (27.3)
Arthralgia	6 (18.8)	1 (4.8)	5 (29.4)	1 (11.1)	8 (11.0)	6 (15.0)	2 (7.7)	1 (9.1)
Constipation	3 (9.4)	2 (9.5)	1 (5.9)	0	10 (13.7)	8 (20.0)	4 (15.4)	1 (9.1)
Headache	8 (25.0)	3 (14.3)	1 (5.9)	0	13 (17.8)	4 (10.0)	2 (7.7)	1 (9.1)

[1] Novartis clinical database using the following search criteria (specific SOCs and HLTs; narrow SMQs; and preferred terms) in MedDRA version 17.1 yielded no results for the following: Anticholinergic syndrome: SMQ Anticholinergic syndrome (narrow search); Quality of life decreased: PT Quality of life decreased.
Source: [D120 Appendix 1-Table HAQ Q120-1]

Safety related to drug-drug interactions and other interactions

In vitro, sonidegib did not inhibit apical efflux transporters, PgP or MRP2, hepatic uptake transporters OATP1B1 or OATP1B3, renal organic anion uptake transporters OAT1 and OAT3, or the organic cation uptake transporters OCT1 and OCT2 at clinically relevant concentrations. Drug-drug interactions resulting from sonidegib-mediated inhibition of substrates for these transporters were considered unlikely to occur.

In study CLDE225A2108, a phase I, parallel group, open label, randomized, drug-drug interaction study the effect of rifampicin and ketoconazole on the pharmacokinetics of a single oral dose of sonidegib was assessed in healthy volunteers.

Discontinuation due to adverse events

The most frequently reported AEs as the reason for discontinuation of study drug for the 200 mg QD group in the first assessment period of Study A2201 were muscle spasms (3.8% of patients versus 8.7% in the 800 mg group), dysgeusia (2.5% vs 4.7%), weight loss (2.5% vs 4.7%) and nausea (2.5% vs 4.0%).

Overall discontinuation as the result of AEs was related to the same and known AEs that were reported in lower grading (CTC grade 1-2) in the 200 mg arm of A2201.

Table 53: Primary reason for treatment discontinuation (study A2201)

Disposition Reason	LDE225 200 mg qd N= 79 n (%)	LDE225 800 mg qd N=151 n (%)	All patients N=230 n (%)
Patients randomized			
Treated	79 (100.0)	150 (99.3)	229 (99.6)
Untreated	0	1 (0.7)	1 (0.4)
Patients treated			
Treatment ongoing	39 (49.4)	46 (30.5)	85 (37.0)
End of treatment	40 (50.6)	104 (68.9)	144 (62.6)
Primary reason for treatment discontinuation			
Adverse Event	16 (20.3)	48 (31.8)	64 (27.8)
Death	0	4 (2.6)	4 (1.7)
Lost To Follow-Up	1 (1.3)	4 (2.6)	5 (2.2)
Non-Compliance With Study Drug	0	3 (2.0)	3 (1.3)
Physician Decision	3 (3.8)	10 (6.6)	13 (5.7)
Progressive Disease	15 (19.0)	6 (4.0)	21 (9.1)
Protocol Violation	0	1 (0.7)	1 (0.4)
Withdrawal By Subject	5 (6.3)	28 (18.5)	33 (14.3)
Treatment unblinded by the site			
No	77 (97.5)	147 (97.4)	224 (97.4)
Yes	2 (2.5)	3 (2.0)	5 (2.2)
Study evaluation after the end of Treatment phase			
Patients continued to next Phase of the trial:	27 (34.2)	57 (37.7)	84 (36.5)
Post-Treatment Follow-Up	11 (13.9)	30 (19.9)	41 (17.8)
Survival Follow-Up	16 (20.3)	27 (17.9)	43 (18.7)

Table 54: Adverse events leading to discontinuation irrespective of causality (Study A2201 Safety set)

System organ class Preferred term	Sonidegib 200 mg N=79 n (%)	Sonidegib 800 mg N=150 n (%)
AE leading to discontinuation	**17 (21.5)**	**54 (36.0)**
Investigations	**5 (6.3)**	**11 (7.3)**
Weight decreased	2 (2.5)	7 (4.7)
Blood creatine phosphokinase increased	1 (1.3)	3 (2.0)
Amylase increased	1 (1.3)	0
Blood creatine phosphokinase mb increased	1 (1.3)	0
Lipase increased	1 (1.3)	0
Musculoskeletal and connective tissue disorders	**4 (5.1)**	**17 (11.3)**
Muscle spasms	3 (3.8)	13 (8.7)
Arthralgia	1 (1.3)	1 (0.7)
General disorders and administration site conditions	**3 (3.8)**	**7 (4.7)**
Fatigue	1 (1.3)	3 (2.0)
Asthenia	1 (1.3)	1 (0.7)
General physical health deterioration	1 (1.3)	1 (0.7)
Nervous system disorders	**2 (2.5)**	**16 (10.7)**
Dysgeusia	2 (2.5)	7 (4.7)
Ageusia	0	3 (2.0)
Hypogeusia	0	2 (1.3)
Gastrointestinal disorders	**2 (2.5)**	**12 (8.0)**
Nausea	2 (2.5)	6 (4.0)
Dysphagia	1 (1.3)	1 (0.7)
Abdominal pain upper	1 (1.3)	0
Dry mouth	1 (1.3)	0
Constipation	0	2 (1.3)
Psychiatric disorders	**2 (2.5)**	**0**
Agitation	1 (1.3)	0
Depression	1 (1.3)	0
Metabolism and nutrition disorders	**1 (1.3)**	**11 (7.3)**
Decreased appetite	1 (1.3)	8 (5.3)
Dehydration	0	3 (2.0)
Skin and subcutaneous tissue disorders	**1 (1.3)**	**9 (6.0)**
Alopecia	1 (1.3)	9 (6.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (1.3)**	**1 (0.7)**
Prostate cancer	1 (1.3)	0
Injury, poisoning and procedural complications	**1 (1.3)**	**0**
Lumbar vertebral fracture	1 (1.3)	0
Vascular disorders	**0**	**3 (2.0)**
Hypertension	0	2 (1.3)
Cardiac disorders	**0**	**3 (2.0)**
Blood and lymphatic system disorders	**0**	**2 (1.3)**
Anaemia	0	2 (1.3)

Adverse events are presented in descending frequency in the sonidegib 200-mg column by system organ class (SOC) and then by preferred term in each SOC.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple adverse events is counted only once in the total row.

The majority of patients in whom treatment was discontinued as the result of AEs experienced grade 1 - 2 events.

Dose adjustments (interruption or reduction) as a result of AEs appeared required for 31.6% of patients in the sonidegib 200-mg group and for 60.0% of patients in the sonidegib 800-mg group.

Post marketing experience

The applicant did not submit post-marketing data as it is has not yet been marketed.

2.6.1. Discussion on clinical safety

The hedgehog inhibitor sonidegib at the proposed dosage is, in general, well tolerated. At a median duration of exposure to sonidegib 200 mg of 8.9 months most AEs reported were musculoskeletal and connective tissue disorders, nervous system disorders, skin and subcutaneous tissue disorders, gastrointestinal disorders, laboratory abnormalities as well as ECG aberrations. The recommended dosage for patients in need for systemic treatment, 200 mg QD, showed AEs in almost all patients (94.9%) albeit that adverse events were primarily grade 1 or grade 2.

The commonly reported ADRs for sonidegib 200 mg (reported in ≥ 30% of patients) consisted of muscle spasms (49.4%), alopecia (43.0%), dysgeusia (38.0%), and nausea (32.9%). At the recommended dosage sonidegib (200 mg QD) grade 3 - 4 events were observed in 30.4% of patients (mostly increased blood CPK).

The patient's knowledge about the fact that their disease is not life-threatening may have contributed to consider stopping the drug, even for relatively low grade AEs. As expected, few patients had received further therapies following the discontinuation of sonidegib (60/230) and few of them received vismodegib (17% of the population as a whole and 4.5% of patients who stopped treatment in absence of disease progression).

Incidence and severity of CK elevations appear to be related to the sonidegib dose administered. The incidence of rhabdomyolysis was rare and reported in 1 and 5 patients treated with 200 mg and 800 mg QD, respectively. Literature data suggest that the hedgehog pathway may be involved in myogenesis as well as in skeletal muscle and myocardial toxicity[8]. This provides a rationale for dose delay or dose reduction in cases of elevated CPK as recommended in SmPC section 4.2. Analysis of the safety database for patients that died with possible cardiac involvement did not show elevated levels of CK-MB. No relation between CPK elevation and/or QT prolongation could be detected in patients with cardiac dysfunction or cardiac fatalities and thus, death due to cardiac toxicity has been, so far, ruled out. Therefore, muscle-related events have been identified as important identified risks. Interaction with drugs with a known risk of myopathy has been identified as important potential risks (please refer to comment on cardiac paragraph below.

Not surprisingly, sonidegib 200 mg showed a more favourable safety and tolerability than that of sonidegib 800 mg. One of five patients stopped treatment due to CTC grade 1-2 AEs with reasons for stopping treatment altogether were muscle spasms (3.8% of patients for the 200 mg group vs 8.7% for the 800 mg group), dysgeusia (2.5% vs 4.7%), weight decreased (2.5% vs 4.7%), and nausea (2.5% vs 4.0%).

Most AEs appeared reversible and non-cumulative. Dose adjustments (interruption or reduction) as a result of AEs were required in 31.6% of patients.

Until the initial cut-off date 4.8% (11) of all patients in A2201 were reported to have died. Two (2.5%) in the sonidegib 200-mg group and 9 (6.0%) in the sonidegib 800-mg group. The patients that died in the 200 mg sonidegib arm initially had pre-existing confounding heart conditions at baseline. Cardiac events (myocardial ischemia, cardiac failure and cardiac death) as well as syncope have been identified as important potential risks. Patients with recent myocardial ischemia or cardiac failure have identified as missing information.

[8] Straface et al. J Cell Mol Med, 2009, Volume 13, pp. 2424-2435

Aberrant laboratory parameters due to sonidegib were noted. The most frequently reported haematological aberrations were decreased haemoglobin and decreased lymphocytes. The most frequently reported grade 3 - 4 clinical chemistry abnormalities (with incidences of ≥ 2.0%) were increased lipase (11.4% and 12.7% for the 200-mg and 800-mg treatment groups, respectively), increased blood CPK (6.3% and 16.0%), increased glucose (3.8% and 2.7%), increased potassium (3.8% and 2.7%), increased AST (2.5% and 5.3%), increased ALT (2.5% and 4.0%), and increased amylase (1.3% and 2.0%). All other biochemistry abnormalities were single occurrences. Patients with anemia (haemoglobin of <9 g/dL) have been identified as missing information.
Secondary primary skin tumours of different histology have been observed and could be another class-related effect that requires special awareness and monitoring (SmPC section 4.4). Other secondary malignancies reported with the use of sonidegib included malignant melanoma, prostate cancer and cases of B-cell lymphoma and vulva cancer. Moreover, secondary primary tumours (SPM) have been identified as an important potential risk and will be monitored in the Periodic Safety Update Report (PSUR)/Development Safety Update Report (DSUR). Patients with advanced BCC have an increased risk of developing cuSCC. Cases of cuSCC have been reported in advanced BCC patients treated with Odomzo. It has not been determined whether cuSCC is related to Odomzo treatment. Therefore, all patients should be monitored routinely while taking Odomzo, and cuSCC should be treated according to the standard of care (SmPC section 4.4).

Ten patients and eleven AEs coded as “fracture” have been identified. The incidence of bone fractures appears to be slightly higher when compared with literature data and in 6 out of ten patients no other potentially concurring comorbidities were found. No clear causality and patterns (preferred sites, time to onset, et cet) can be established at this time. Therefore, bone fractures will be followed in PSURs and has been identified as an important potential risk.

There were three cases related to corneal disorders (keratitis, keratopathy and corneal perforation) in study A2201, all in the 800 mg group. Cases of keratitis have also been observed with vismodegib, another Hh signalling pathway inhibitor. Furthermore, there is evidence in the literature that Hh signalling may play a role in maintaining the corneal epithelium. Hence, corneal disorder has been included in the RMP as potential important risks.

The long term safety of sonidegib treatment in laBCC patients has been identified as missing information.

Sonidegib has been shown to have teratogenic potential and foeto-development toxicity as presented in the reproductive toxicological non-clinical studies (see non-clinical discussion). The reproductive toxicity and teratogenicity has been identified as an important identified risk. Therefore, specific warnings have been introduced in the SmPC in section 4.4 and 4.6 on the risk of sonidegib treatment in pregnant women and to the foetus. A detailed pregnancy prevention progamme will be implemented, as well as the dissemination of educational material to the HCP and the patients to advise on the risks to the developing foetus. These additional risk minimization measures have been introduced in the RMP as well as conditions in the Annex II.

In dose escalation studies, Odomzo was administered at doses up to 3000 mg orally once daily. Patients should be monitored closely for adverse events and given appropriate supportive measures in all cases of overdose.

Although the safety database is small, the ADRs observed are consistent with those that have been observed with products that are the same class of products, i.e. inhibitors of the hedgehog pathway such as vismodeib.

2.6.2. Conclusions on the clinical safety

The safety of the sonidegib has been adequately investigated. In general, the ADRs observed are considered manageable and the management of ADRs has been appropriately addressed in the SmPC sections 4.4, 4.6 and 4.8 and appropriate dose modifications in section 4.2 for the management for symptomatic CK elevations and muscle-related adverse events.

Considering that products such as sonidegib, that target the hedgehog pathway, are known to cause foetal loss, severe developmental abnormalities and teratogenicity, a pregnancy prevention programme has been implemented that women of childbearing age must comply with in order to be eligible to receive the treatment. The content and the key elements of this program include awareness in the product information, HCP and patient educational material and reminder card.

The CHMP considers the following measures in the RMP necessary to address issues related to safety:

1. Analyses of adverse events of special interest in the ongoing studies without a final CSR, including the registration study A2201, C2301, X2114, X2116, X2203, and will be analysed in the final CSRs for these studies. In addition, longer term data using the 30-month and 42- month data will be analysed and reported in order to better characterize and understand the risks for cardiac events, second primary malignancies and fractures.
2. Analyses of adverse events of special interest in study CLDE225X2104 and CLDE225C2301 in order to better characterise and understand the risk post-natal developmental defects.
3. The Applicant is requested to submit within 3 months of EC decision, a full protocol for the proposed non-interventional PASS.
4. Measuring the effectiveness of the Odomzo Pregnancy Prevention Programs in agreement with National Competent Authority.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.1 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC advice.

The CHMP endorsed this advice with the following changes: three analyses from phase II study (LDE225A2201), which is currently ongoing, is a condition of the marketing authorization as a post-authorisation efficacy study (see Section 2.5.4 and 4).

The applicant implemented the changes in the RMP as requested by PRAC and CHMP.

The CHMP endorsed the Risk Management Plan version 2.3 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Muscle-related events Reproductive toxicity (teratogenicity) Food interactions Interactions with strong CYP3A4 inhibitors and CYP3A4 inducers
Important potential risks	Impaired fertility Second primary malignancies Post-natal development defects Fractures Interactions with sensitive CYP2B6, CYP2C9, and BCRP substrates with low therapeutic index Interaction with proton-pump inhibitors Interaction with drugs with a known risk of myopathy Cardiac events (myocardial ischemia, cardiac failure and cardiac death) Syncope Corneal disorders
Missing information	Carcinogenicity studies Patients with severe renal impairment Patients with severe hepatic impairment Races other than Caucasians Female patients of childbearing potential taking concomitant oral contraceptives Long term safety in laBCC patients Off-label use in patients with medulloblastoma, BCC appropriate for surgery or radiotherapy, and other cancers Patients with anemia (haemoglobin of <9 g/dL) Patients with recent myocardial ischemia or cardiac failure

Pharmacovigilance plan

Activity / Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status Planned, started,**	**Date for submission of interim or final reports (planned or actual)**
Measuring the effectiveness of the Odomzo Pregnancy Prevention Programs on a country-specific level, in agreement with National Competent Authorities (3)	To assess HCPs' knowledge on the risk of teratogenicity associated with sonidegib's exposure during pregnancy and impaired fertility after the delivery of the HCP educational materials including the DHCP letter.	Reproductive toxicity: (teratogenicity) and impaired fertility	Planned start after product local launch	Regularly as a part of PSUR
A relative bioavailability study to evaluate timing of meal relative to dose and fasting conditions and effect of light meal (low fat meal) (3)	To estimate the risks of overexposure and underexposure from different food conditions (in terms of timing and from a light meal (low fat meal)) and to potentially provide more guidance for the dosing recommendation.	Food interaction	Planned start after product launch (Q1-2016)	Q4-2016
Study LDE225A2113 A phase I, open label, multi-center, single dose study to evaluate the pharmacokinetics of sonidegib in healthy subjects with normal hepatic function and subjects with impaired hepatic function (3)	To evaluate the pharmacokinetics of a single oral dose of sonidegib in subjects with impaired hepatic function as compared to healthy subjects	Safety in patients with hepatic impairment	Protocol final (original)-19-Jul-2012; Protocol amendment 1-31-May-2013; Protocol amendment 2-25-Jul-2014; FPFV-20-Mar-2013 Planned LPLV-Q3-2015	Interim report 03-Nov-2014 Final report Q3-2016 (planned)
Study LDE225A2112 A Phase Ib, multicenter, two parallel group, open label, drug-drug interaction study to assess the effect of sonidegib on the PK of bupropion and warfarin in patients with advanced solid	To evaluate effect of sonidegib on the pharmacokinetics of warfarin and bupropion.	Interaction with CYP2B6 and CYP2C9 substrate	Protocol final (original)-10-Oct-2012 Protocol amendment 1-22-Aug-2014 FSFV: 29-Apr-2013 Planned LPLV: Q4-2018	CSR final: Q2-2017

Activity / Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
tumours (3)				
Analyses of AESI in the ongoing studies without a final CSR, including the registration study A2201, C2301, X2114, X2116, X2203, and will be analyzed in the final CSRs for these studies. In addition, longer term data using the 30-month and 42-month data will be analyzed and reported (3)	To analyze AESI in order to better characterize and understand these risks	Cardiac events, second primary malignancies, and fractures	LDE225A2201 Protocol final (original) 28-Feb-2011 FPFV 29-Jun-2011 LPLV 06-Dec-2012 LDE225C2301 Protocol final (original) 17-Aug-2012 FPFV:06-May-2013 LPLV:30-Jun-2015 LDE225X2114 Protocol final (original) 27-Feb-2015 Protocol ammendment-3 19-Aug-2014 FPFV: 04-Jul-2012 LPLV: 25-May-2015 LDE225X2116 Protocol original 05-Feb-2013 FPFV: 08-May-2013 LPLV: 21-Dec-2015 LDE225X2203 Protocol final (original) 04-Feb-2013 FPFV: 30-May-2013 LPLV: 27-Jun-2016	Final CSR: Oct-2017 Final CSR: Q4-2015 Final CSR: Q4-2015 Final CSR: Q1-2017 Final CSR: Q4-2016
Analyses of AESI in study CLDE225X2104 and CLDE225C2301 (3)	To analyze AESI in order to better characterize and understand the risk	Post-natal developmental defects	LDE225X2104: Protocol final (original) 15-Sep-2010 Protocol	Final CSR: Q2 2015

Activity / Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
			amendment 1 11-Jul-2011 FPFV 09-Feb-2011 LPLV 03-Oct-2014 LDE225C2301: Protocol final (original) 26-Jul-2012 Protocol amendment 1 13-Sep-2013 FPFV 06-May-2013 Planned LPLV 29-Apr-2015	Final CSR: Q4 2015
Analyses of long term safety data available from the registration Study A2201 (3)	To analyze long term safety data available from the registration Study A2201, and report in the final CSR	Long term safety in laBCC patients	Planned	Final CSR: Q2-2017
A non-interventional post-authorization safety study (PASS) is being planned to further characterize long-term safety (3)	Noninterventional (PASS) study: To assess the long-term safety and tolerability profile of sonidegib, when administered as per local label, in patients with laBCC, as determined by the occurrence of adverse events and serious adverse events.	Long term safety in laBCC patients	Protocol submission May-2015 Planned study start Q4-2016 Planned study finish Q4-2023	Q4-2024 (after the completion of 3-year follow-up for each enrolled patient)
A randomized study to investigate the effect of esomeprazole (proton-pump inhibitor) on the pharmacokinetics of sonidegib in healthy volunteers (3)	To determine the effect of esomeprazole on the pharmacokinetics of a single oral dose of sonidegib in healthy subjects	Interaction with proton-pump inhibitor	Protocol submission 26-Aug-2014 FSFV 13-Oct-2014 LSLV 05-Jan-2015	Dec-2015
A study to perform an evaluation of a subset of tissues from the 6-month rat study using KI-67	To address missing information relating to carcinogenicity	Carcinogenicity	Protocol submission -NA Planned study start/finish - NA	Dec-2016

Activity / Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
immunohistochemistry and to quantify cell proliferation (3)				
Provision of the Study CLDE225A2201 interim analysis (1)	To provide the following: -updated efficacy and safety analyses. -a correlative analysis of response to treatment and Gli1 levels for the entire study population of the pivotal study at different time points (e.g. baseline, time of response, time of progression, etc.) -an updated analysis of outcomes by aggressive vs non-aggressive histological subtypes.	NA	Interim analyses (30-month data)	30-Oct-2016
Provision of the Final CSR for Study CLDE225A2201 (1)	To provide an updated analysis of outcomes by aggressive vs non-aggressive histological subtypes.	NA	Final CSR	30-Oct-2017
Provision of the Study CLDE225A2201 interim analysis (1)	To provide a molecular analysis in tumor material still available from patients treated in study A2201 experiencing disease progression.	NA	Interim analyses (30-month data)	30-Oct-2016

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Muscle-related events	This item is appropriately communicated through current labeling: Dose modifications guidelines for creatine phosphokinase (CK) elevations and muscle related events in SmPC Section 4.2 Posology and method of administration. SmPC Section 4.4 Special Warnings and Precautions for use of sonidegib in case of muscle related symptoms, blood CK testing prior to treatment initiation and monitoring based on clinical signs/symptoms. Relevant PTs are included as ADRs in SmPC Section 4.8 Undesirable effects.	None
Reproductive Toxicity (teratogenicity)	This item is appropriately communicated through current labeling: SmPC Section 4.3 Contraindications for women who are pregnant or breast-feeding. SmPC Section 4.4 Special Warnings and Precautions for women taking sonidegib who must not be pregnant or become pregnant during treatment and for 20 months after ending treatment. Warning for male patients, even those who have had a vasectomy, must always use a condom when having sex with a female partner while taking sonidegib and for at least 6 months after ending treatment. SmPC Section 4.6 Fertility, pregnancy, and lactation provides an important information on reproductive toxicity.	Educational material consisting of DHCP letter as well as educational brochure for physicians and patients/caregivers.
Food interactions	This item is appropriately communicated through current labeling: SmPC Section 4.5, Interaction with other medicinal products and other forms of interaction, provides the guidance for sonidegib use with foods that affect serum concentration. SmPC Section 5.2 Pharmacokinetic properties, describes the bioavailability of sonidegib in conjunction with food.	None
Interactions with strong CYP3A4 inhibitors and CYP3A4 inducers	This item is appropriately communicated through current labeling: SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction details that concomitant use of sonidegib and strong CYP3A inhibitors and inducers should be avoided.	None
Impaired fertility	SmPC Section 4.6 Fertility, pregnancy and lactation states that based on findings from animal studies, male and female fertility may be compromised with sonidegib. The potential for sonidegib to cause infertility in male and female patients is unknown. Fertility preservation strategies should be discussed prior to starting treatment with sonidegib.	Educational material consisting of DHCP letter as well as educational brochure for physicians and patients/caregivers.
Second primary malignancies	SmPC Section 4.4 Special Warnings and Precautions for use state that patients with	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	advanced BCC have an increased risk of developing cuSCC. It has not been determined whether cuSCC is related to sonidegib treatment. Therefore, all patients should be monitored routinely while taking sonidegib, and cuSCC should be treated according to the standard of care.	
Post-natal developmental defects	SmPC Section 5.3 Preclinical safety data suggests that majority of adverse effects of sonidegib can be attributed to its pharmacological mechanism of action on developmental pathways and effects in rats and dogs were similar.	None
Fractures	Currently available data do not support the need for risk minimization.	None
Interaction with sensitive CYP2B6, CYP2C9, and BCRP substrates with low therapeutic index	This item is appropriately communicated through current labeling: SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction describes that concomitant use of substrates (with narrow therapeutic window) of CYP2B6 and CYP2C9 enzymes or BCRP transporter, should be avoided.	None
Interaction with proton-pump inhibitors	This item is appropriately communicated through current labeling: SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction describes that concomitant use of PPIs may alter the bioavailability of sonidegib	None
Interaction with drugs with a known risk of myopathy	This item is appropriately communicated through current labeling: SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction provides the details of overlapping toxicities in patients taking sonidegib, who are also taking medications known to increase the risk of muscle related toxicity, and patients should be closely monitored and dose adjustments should be considered if muscle symptoms develop.	None
Cardiac events (myocardial ischemia, cardiac failure and cardiac death)	Currently available data do not support the need for risk minimization.	None
Syncope	Currently available data do not support the need for risk minimization.	None
Corneal disorders	Currently available data do not support the need for risk minimization.	None
Carcinogenicity	Currently available data do not support the need for risk minimization.	None
Patients with severe renal impairment	This item is appropriately communicated through current labeling: SmPC Section 4.2 Posology and method of administration details that dose adjustment is not necessary in patients with renal impairment. No safety data are available in patients with severe renal impairment. SmPC Section 5.2 Pharmacokinetic	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	properties details that since sonidegib is not renally excreted, no change in systemic exposure is anticipated in patients with renal impairment.	
Patients with severe hepatic impairment	This item is appropriately communicated through current labeling: SmPC Section 4.2 Posology and method of administration suggests that sonidegib should be used with caution in these patients SmPC Section 5.2 Pharmacokinetic properties details that no dose adjustment is necessary in patients with mild or moderate hepatic impairment	None
Races other than Caucasians	This item is appropriately communicated through current labeling: PK information in SmPC Section 5.2 Pharmacokinetic properties.	None
Female patients of childbearing potential taking concomitant oral contraceptives	Currently available data do not support the need for risk minimization.	None
Long term safety in laBCC patients	Currently available data do not support the need for risk minimization.	None
Off label use in patients with medulloblastoma, BCC appropriate for surgery or radiotherapy, and other cancers	This item is appropriately communicated through current labeling: Sonidegib must be strictly used only in the approved indication detailed in SmPC Section 4.1 Therapeutic indications.	None
Patients with anemia (hemoglobin of < 9 g/dL)	Currently available data do not support the need for risk minimization.	None
Patients with recent myocardial ischemia or cardiac failure	Currently available data do not support the need for risk minimization.	None

2.9. Product information

2.9.1. 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

According to the primary 6-month analysis submitted (cut-off date 28 June 2013), in the pivotal A2201 study ORR per central review for all patients (enrolled in the pEAS) was 36.4% (95% CI: 23.8, 50.4) and 33.6% (95% CI: 25.1, 43.0) for the 200-mg and 800-mg arms, respectively. Response rates met the predefined criteria for both treatment arms for point estimates to meet or exceed 30%. In the updated efficacy results (18-month analysis, cut-off 11 July 2014), the efficacy in the laBCC population was ORRs of 54.8% (95% CI: 38.7, 70.2) and 47.3% (95% CI: 36.9, 57.9) were reported for the sonidegib 200-mg and 800-mg treatment arms, respectively, per central review in the pEAS, with consistent results observed in the FAS.

In the mBCC population, ORRs of 7.7% (95%CI: 0.2, 36.0) and 17.4% (95%CI: 5.0, 38.8) were reported for the sonidegib 200-mg and 800-mg treatment arms, respectively, per central review. Following concerns raised by the assessment of the CHMP on the low number of patients treated, the low rate of response observed (with no reported cases of CR) at the proposed 200 mg dose and the unlikely clinical relevance of an effect on asymptomatic lesions, the applicant withdrew the indication in mBCC patients.

Regarding PFS, in the laBCC population median PFS was 22.1 months with sonidegib 200 mg and 19.4 months with sonidegib 800 mg. No significant difference in durability of response between patients treated with 200 mg and 800 mg sonidegib dose was observed. Evaluation of PRO's shows that, with the limitations related to the large standard error, the majority of patients appear to experience maintenance of their QoL during treatment with sonidegib. The aggressive behaviour of LaBCC can lead to pain, fatigue and severe disfigurement, which in turn, could impact on the physical and social function of individuals. With the clinical benefit observed, it is highly likely that treatment with sonidegib in laBCC patients may lead to an improvement of chances to surgery with curative intent, long lasting tumour reduction with cosmetics and/or functional improvement, healing of tumour ulceration, improvement in survival, in symptoms and/or health related quality of life.

Uncertainty in the knowledge about the beneficial effects

The median DoR, and OS were not evaluable due to the high rate of censoring at the updated analysis (cut-off date11 July 2014), therefore, there is uncertainty on the effect of sonidegib in the long term on DoR and OS. The Applicant has committed to provide interim update (30 months) and final (42 months) analyses post-approval. The CHMP has imposed post-authorisation measures to address the uncertainty, requesting the submission of updated efficacy analyses, including analyses of outcomes by aggressive versus non-aggressive histological subtype at 30 months (to be submitted by 30th October 2016) and 42 months (to be submitted by 30th October 2017) post-treatment.

Preliminary data in 11 patients treated and achieving persistent response also after stopping of study treatment for reasons other than progression seem to suggest that following an initial sustained inhibition, Gli1 levels progressively increase, approaching baseline values at the time of radiological or clinical confirmation of progressive disease. Therefore, the CHMP has imposed the submission of an analysis of response to treatment and Gli1 levels for the entire study population at different time points (as already done for the selected sample of 11 patients).

Risks

Unfavourable effects

Overall, the sonidegib ADRs include muscle spasms, alopecia, dysgeusia, fatigue, nausea, elevated blood CPK, musculoskeletal pain, weight decreased, diarrhoea, decreased appetite, myalgia, abdominal pain, headache, pain, and constipation. The most comment ADRs of sonidegib treatment are muscle cramps (49.9%), muscle pain (19%), hair loss (43%), alteration or loss of taste (38.0%), nausea (32.9%) or diarrhoea (24.1%).

In all patients that were studied in the pivotal study A2201 with sonidegib at the recommended dosage (200 mg OD) 94.9% of all (79) patients encountered an adverse event and 30.4% a CTC AE grade 3 or 4. Treatment discontinuation was reported in 17 (21.5%) of patients treated with sonidegib 200 mg and in 54 (36%) patients treated with 800 mg. Reasons for study discontinuation were in line with the safety profile of sonidegib. Muscle spasms (3.8% of patients in the 200 mg group) formed the main reason. Dysgeusia was reported in 2.5%. Also loss of weight (2.5%) and nausea (2.5%) were reasons to study withdrawal.

The results of the 18-month update safety analysis were in line with the original 6-month analysis.

The pattern of ADRs observed appears to be similar to the recently approved vismodegib.

The risk of teratogenicity and embryotoxicity to the foetus is a known adverse drug reaction for Hh inhbitors such as sonidegib. Therefore, specific warnings have been implemented in the SmPC on the risk to the foetus and the recommendations on using effective contraception. A pregnancy prevention programme has been implemented and key elements of this program include awareness in the product information, HCP and patient educational material and a reminder card.

Uncertainty in the knowledge about the unfavourable effects

The relatively small safety database of short follow-up of 18 months still represents one of the limitations in the evaluation of the safety related to sonidegib since long term safety effects (e.g. second primary malignancy induction, cardiac events) may still be underreported. The CHMP has imposed a post-authorisation measure to submit updated safety data.

There is uncertainty on the effects of sonidegib on the heart and skeletal muscle. The increased myoglobin levels in patients were of concern although rhabdomyolysis did not seem to involve toxicity of the heart muscle. This risk has been included in the SmPC and in the RMP. The effect of sonidegib on cardiac function is uncertain. The occurrence of sonidegib induced QTcF prolongation still suggests a potential arrhythmogenic effect, but no clinically relevant abnormalities have been observed. This risk has been highlighted in the SmPC as well as in the RMP.

A class effect ADR known for Hh inhibitors is the risk for secondary malignancies. The risk will be monitored with the PSUR.

Benefit-risk balance

Importance of favourable and unfavourable effects

Sonidegib has shown long-lasting tumour shrinkage in a substantial subgroup of laBCC patients treated, a clinically relevant ORR that appears to have had cosmetic and functional improvement achieved in this patient population, as supported by the documented photographic evidence of lesions. Durability of response was also documented by the PFS results. The safety of sonidegib appears to be manageable (with SmPC recommendations and additional risk minimisation activities) and as expected

in this therapeutic class. There is uncertainty on the risk of carcinogenicity with long term use of sonidegib. Therefore, the CHMP has imposed a non-clinical post-authorisation study to evaluate the potential of carcinogenicity in rats.

Benefit-risk balance

Based on the totality of the data from the pivotal study, the benefits of sonidegib treatment in adult patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy outweighed the risks. Therefore, the CHMP considers that the benefit-risk balance for sonidegib in the proposed indication is positive.

Discussion on the benefit-risk balance

In patients with laBCC, treatment with sonidegib met the pre-specified 30% criteria in terms of ORR, supporting the proposed indication at the proposed dose regimen of 200 mg OD. The PFS results, as well as several sensitivity analyses provided in the updated 18-month analysis provide further reassurance on the durability of the responses and the robustness of the primary analyses. The ADRs for sonidegib treatment appear manageable at the 200 mg QD dose and have been adequately addressed in the SmPC and RMP with appropriate recommendations on the management of the important identified risks such as muscle related events. Women of childbearing age are advised to use effective contraception when being treated with sonidegib as there is a clear risk to the foetus given that Hh inhibitors have a teratogenic potential. Therefore, the implementation of a pregnancy prevention programme and dissemination of educational material for the HCP and patients is required in order to communicate the risks of sonidegib treatment to the foetus. These measures have been addressed in a satisfactory manner as part of the RMP (additional risk minimisation activities) and as Annex II conditions to the MA.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Odomzo in the treatment of adult patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted 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 agreed subsequent updates of the RMP.

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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Prior to launch in each Member State the Marketing Authorisation Holder (MAH) shall agree the following with the National Competent Authority:

- The national part of the DHPC
- Methodology to collect information on the use of Odomzo and the compliance with the pregnancy pharmacovigilance programme and its effectiveness
- The format and content of the Healthcare professional and patient material

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 Odomzo being prescribed and dispensed

The MAH shall continuously ensure that all physicians who are expected to prescribe Odomzo 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 Odomzo should contain the following key elements:

- Brief background on Odomzo, its licensed indication and posology
- A requirement to inform patients of the teratogenic risks associated with Odomzo 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 Odomzo
- Safety advice for women of childbearing potential
- Safety advice for men
- Requirements in the event of pregnancy
- Inform patients that they should not donate blood during treatment with Odomzo and for at least 20 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 Odomzo Verification of Counselling Form which is to be present in the healthcare professional educational material
- Adverse event reporting

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

- Information for patients on the teratogenic risks associated with Odomzo and the need to avoid foetal exposure
- The need for adequate contraception and definition of adequate contraception
- National or other applicable specific arrangements for a prescription for Odomzo to be dispensed
- Not to give Odomzo to any other person as well as information on the disposal of unwanted medication and the need to keep Odomzo capsules out of sight and reach of children
- That the patient should not donate blood during treatment and for at least 20 months after their final dose
- That the patient should not breastfeed during treatment and for 20 months after their final dose
- That the patient should tell the healthcare professional about any adverse event
- Information for women of childbearing potential
- Information for men

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

- Information for women of childbearing potential
- Information for men
- 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
- Remind patients to return unused capsules at the end of the treatment (disposal will depend on local requirements)
- Remind patients not to donate blood during treatment and for at least 20 months after final dose

The patient reminder card should contain the following key elements:

- Information for patients of the teratogenic risks associated with Odomzo and the need to avoid foetal exposure
- Not to donate blood during treatment and for at least 20 months after the final dose
- Information for women of childbearing potential
- Information for men
- To return unused capsules at the end of the treatment (disposal will depend on local requirements)
- Emergency contact phone numbers

- **Obligation to complete post-authorisation measures**

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

Description	**Due date**
1. Post-authorisation efficacy study (PAES): The MAH should submit an analysis of Study CLDE225A2201 with: • an updated efficacy and safety analyses, • a correlative analysis of response to treatment and Gli1 levels for the entire study population of the pivotal study at different time points (e.g. baseline, time of response, time of progression, etc..) • an updated analysis of outcomes by aggressive vs non-aggressive histological subtypes.	30/10/2016
2. Post-authorisation efficacy study (PAES): The MAH should submit the final CSR for Study CLDE225A2201, including an updated analysis of outcomes by aggressive vs	30/10/2017

Description	Due date
non-aggressive histological subtypes.	
3. Post-authorisation efficacy study (PAES): The MAH should submit a molecular analysis in tumour material still available from patients treated in study Study CLDE225A2201 experiencing disease progression in order to investigate the resistance mechanisms related to point mutations in SMO that may lead to reactivation of the Hh signaling pathway and tumour re-growth.	30/10/2016

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

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