



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Odomzo

Proprietary Product Name: Sonidegib

Sponsor: Novartis Pharmaceuticals Australia Pty
Ltd

November 2019

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Common abbreviations

Abbreviation	Meaning
AAN	Australian Approved Name
ACM	Advisory Committee on Medicines
ADME	Absorption, distribution, metabolism and excretion
AE	Adverse event
ALT	Alanine aminotransferase
ARTG	Australian Register of Therapeutic Goods
AST	Aspartate transaminase
AUC	Area under the plasma concentration-time curve
AUC _{0-24h}	Area under the plasma concentration-time curve from time zero to 24 hours
AUC _{0-∞}	Area under the plasma concentration-time curve from time zero to infinity
AUC _(last)	Area under the plasma concentration-time curve calculated to the time of the last quantifiable concentration
BCC	Basal cell carcinoma
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutics classification system
bd	Twice daily
BLRM	Bayesian logistic regression model
CER	Clinical evaluation report
CHMP	Committee on Medicinal Products for Human Use (EMA/EU)
CI	Confidence interval
CK (CPK)	Creatine kinase (creatinine phosphokinase)
CL/F	Apparent plasma clearance after oral administration
C _{max}	Maximum plasma concentration
C _{min}	Trough plasma concentration
CNS	Central nervous system

Abbreviation	Meaning
CPMP	Committee for Proprietary Medicinal Products (EMA/EU)
CR	Complete response
CRR	Complete response rate
CSR	Clinical study report
CT	Computerised tomography
CTCAE	Common Technical Criteria Adverse Event
CV	Coefficient of variation
CYP	Cytochrome P450
DDI	Drug-drug interaction
DLT	Dose limiting toxicity
DoR	Duration of objective tumour response
ECG	Electrocardiogram
EMA	European Medicines Agency
EU	European Union
F	Bioavailability
FAS	Full analysis set
FDA	Food and Drug Administration (US)
FMI	Final marketing image
GLP	Good Laboratory Practice
Hh	Hedgehog
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRC	Independent Review Committee
IV	Intravenous
laBCC	Locally advanced basal cell carcinoma
LDE225	Sonidegib

Abbreviation	Meaning
mBCC	Metastatic basal cell carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MRI	Magnetic resonance imaging
MRP2	Multi-resistance protein 2
MTD	Maximum tolerated dose
NBCCS	Nevoid basal cell carcinoma syndrome
NE	Not-estimable
NMSC	Non melanoma skin cancer
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
ORR	Objective response rate
OS	Overall survival
PD	Pharmacodynamic(s)
pEAS	Primary efficacy analysis set
PFS	Progression free survival
P-gp	P-glycoprotein
pH	Negative logarithm of hydrogen ion concentration
PK	Pharmacokinetic(s)
PK/PD	Pharmacokinetic(s)/pharmacodynamic(s)
PPI	Protein pump inhibitor
PR	Partial response
PRO	Patient reported outcome
PTCH1	Protein patched homolog 1
qd	Once daily

Abbreviation	Meaning
QT	QT interval in ECG
QTc	QT corrected for heart rate
QTcF	QT corrected for heart rate according to formula of Fridericia
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SCC	Squamous cell carcinoma
SCS	Summary of Clinical Safety
SD	Standard deviation or stable disease
SHh	Sonic Hedgehog
Smo	Smoothened
SMQ	Standardized MedDRA query
SOC	System Organ Class (MedDRA)
$t_{1/2}$	Half-life associated with the terminal slope
T_{max}	Time to reach maximum drug concentration
TTR	Time to tumour response
ULN	Upper limit of normal
V_{ss}/F	Apparent volume of distribution at steady state
WHO	World Health Organization
~	Approximately
Δ	Change in
∞	Infinity
§	Section

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New chemical entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	6 August 2015
<i>Date of entry onto ARTG</i>	10 August 2015
<i>ARTG number:</i>	226544
<i>Active ingredient:</i>	Sonidegib diphosphate
<i>Product name:</i>	Odomzo
<i>Sponsor's name and address:</i>	Novartis Pharmaceuticals Australia Pty Ltd 54 Waterloo Road North Ryde NSW 2113
<i>Dose form:</i>	Hard gelatin capsule
<i>Strength:</i>	200 mg
<i>Container:</i>	Blister foils
<i>Pack sizes:</i>	10 or 30
<i>Approved therapeutic use:</i>	<i>Odomzo is indicated for the treatment of adult patients with:</i> <ul style="list-style-type: none">– <i>Locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy.</i>– <i>Metastatic BCC.</i>
<i>Route of administration:</i>	Oral
<i>Dosage:</i>	General target population: 200 mg taken orally once daily on an empty stomach at the same time each day at least 1 hour before, or 2 hours after a meal. Odomzo capsules must be swallowed whole. Do not crush or chew. If a dose is missed, the recommended dose of Odomzo should be taken within 6 hours after the missed dose. If more than 6 hours have passed, the patient should be instructed not to take the missed dose. The patient should continue treatment with the next prescribed dose.

Product background

This AusPAR describes the application by Novartis Pharmaceuticals Australia Pty Ltd (the sponsor) to register a new chemical entity, sonidegib diphosphate (Odomzo) for the following indications:

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.*

Sonidegib is a potent, selective and orally bioavailable smoothened (Smo) antagonist. Smo is a G protein-coupled receptor-like molecule that positively regulates the Hedgehog (Hh) signal transduction pathway. Hh pathway activation of Smo leads to activation and nuclear localisation of glioma-associated oncogene (GLI) transcription factors, and is linked to the pathogenesis of several types of cancer including basal cell carcinoma (BCC). Sonidegib binds Smo with high affinity to inhibit GLI mediated target gene activation thereby inhibiting Hh signalling.

Sonidegib is a second in class inhibitor of Smo, which blocks the activation of the hedgehog pathway. This pathway is critical for mammalian limb development and is implicated in development of basal cell carcinoma (BCC) and fetal cerebral cleavage abnormalities.

Pharmacological agents targeting this pathway include itraconazole (indicated for systemic and superficial mycoses, but with evidence of efficacy in BCC), vismodegib (indicated for the treatment of metastatic or locally advanced BCC where surgery and/or radiation are not appropriate) and arsenic trioxide (indicated for induction of remission in adults with acute promyelocytic leukaemia).

BCCs are treated with surgery, photodynamic therapy and other topical treatments (for example, 5- FU; imiquimod). Locally advanced or metastatic BCC are very rare, and are seen in patients presenting late or in patients with recurrent, aggressive BCC.

Almost all sporadic BCCs are the result of enhancement of the hedgehog signalling pathway, with 90% having alterations in at least 1 allele of PTCH1;¹ and 10% having activating mutations in Smo. This results in constitutive activation of the pathway and leads to uncontrolled proliferation of basal cells.

Patients with the autosomal dominant Gorlin's syndrome (basal cell nevus syndrome; birth incidence of 1:19000) develop many BCCs. These patients have inherited a defective copy of PTCH1 (there are many detected variants), resulting in constitutive activity of the hedgehog pathway as is seen with sporadic BCCs.

Sonidegib was submitted to the European Medicines Agency (EMA) via the centralised assessment procedure. A positive opinion was given by the EMA's Committee on Medicinal Products for Human Use (CHMP) on 25th June 2015 for the indication:

'For the treatment of adults with locally advanced basal cell carcinoma (BCC)'

The submission proposes registration of 200 mg hard gelatin capsules. Four strengths were formulated (50 mg, 100 mg, 200 mg, 250 mg), but the sponsor is submitting only the 200 mg strength for registration.

¹ PTCH1; Protein patched homolog 1 is a member of the patched gene family and is the receptor for sonic hedgehog, a secreted molecule implicated in the formation of embryonic structures and in tumorigenesis

Regulatory status

Australian regulatory history

Related submissions

This is the first submission from the sponsor to register sonidegib in Australia. There has been a previous submission from Roche resulting in the registration of vismodegib (Erivedge), the 'first in class' Smo antagonist inhibiting the Hh signalling pathway approved by the TGA for the treatment of advanced BCC. Vismodegib is approved for 'the treatment of adult patients with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma where surgery and/or radiation therapy are not appropriate'. The drug was included in the Australian Register of Therapeutic Goods (ARTG) on 9 May 2013.

Apart from vismodegib, there are no other therapeutic goods approved in Australia specifically for the treatment of advanced BCC. Australian guidelines relating to the treatment of BCC published prior to the approval of vismodegib, state that 'systemic treatment chemotherapy is rarely used in metastatic BCC or for locally advanced disease'. The guidelines note that most chemotherapy regimens for the treatment of metastatic basal cell carcinoma (mBCC) or locally advanced basal cell carcinoma (laBCC) 'include cisplatin or carboplatin', and that 'chemotherapy achieves response in (mBCC) and can be used to control symptoms'. However, neither cisplatin nor carboplatin are approved in Australia for the treatment of mBCC or laBCC.

Overseas regulatory history

At the time of the Australian submission, sonidegib had not been registered in any overseas countries. A marketing authorisation submission had been made to the European Union (EU) at the time of the Australian submission, and further submissions were planned for the USA and Canada. The sponsor confirmed that the data package submitted in the EU was generally similar to that submitted in Australia. The dataset differences for the four regulatory jurisdictions are provided. Perusal of the listed differences indicates that the datasets are essentially similar with no significant differences being identified.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Registration time line

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 1: Registration timeline for Submission PM-2014-01865-1-4

Description	Date
Submission dossier accepted and first round evaluation commenced	1 September 2014
First round evaluation completed	23 February 2015

Description	Date
Sponsor provides responses on questions raised in first round evaluation	14 April 2015
Second round evaluation completed	18 June 2015
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	7 July 2015
Sponsor's pre-Advisory Committee response	N/A
Advisory Committee meeting	N/A
Registration decision (Outcome)	6 August 2015
Completion of administrative activities and registration on ARTG	10 August 2015
Number of working days from submission dossier acceptance to registration decision*	200

*Target timeframe for standard applications is 220 working days

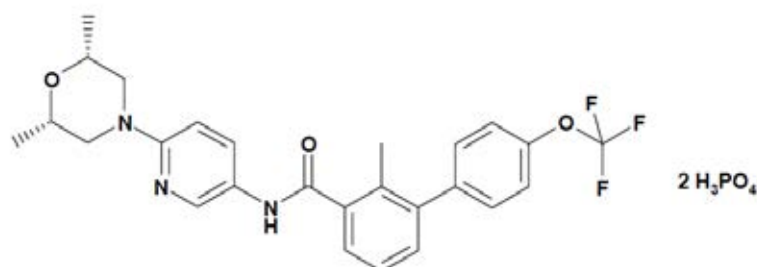
Evaluations included under Quality findings and Nonclinical findings incorporate both the first and second round evaluations.

III. Quality findings

Drug substance (active ingredient)

Sonidegib (structure shown below) is a white to slightly yellow powder that is a potent selective and orally bioavailable Smo antagonist. It is a weak base (pKa 4.3) that is poorly soluble in water (0.007 mg/mL) but displays moderate permeability (Biopharmaceutics classification system (BCS) class II). Three polymorphic forms have been identified (A, D and P); the form used in the proposed product is Form A.

Figure 1: Structure of sonidegib (active ingredient)



Sonidegib is synthetic. It has two asymmetric carbons, but also a mirror plane; so it is not optically active.

CAS Registry Number: 1218778-77-8 (diphosphate), CAS Registry Number: 956697-53-3 (base)

Drug product

Formulation development used bioavailability studies in dogs. To achieve high doses required manufacturing methods such as roller compaction or wet granulation, not dry blending, to attain usable density. Surfactants were initially chosen to improve wettability. During development, the amount of water used in granulation was increased to ensure consistent conversion of the drug substance to the monophosphate (controlled in the finished product specification).

Clinical trial formulations in Phase I studies used 50, 100, 200, and 250 mg strength capsules with directly scaled fills; the 200 mg fill formulation matches that proposed for registration. Film-coated tablet and oral suspension formulations are under investigation separately (tablets were used in one pharmacokinetic comparison study).

Only 200 mg capsules were used in the pivotal clinical study (Study CLDE225A2201), identical to the formulation proposed for registration.

A different capsule fill formulation was used with (¹⁴C) sonidegib in the human absorption, distribution, metabolism, and excretion Study A2110.

Quality summary and conclusions

Summary of quality data evaluation report

Registration is not recommended with respect to chemistry and quality control aspects. The following issues should be addressed:

- The sponsor is invited to comment on possible amendment of the Australian Approved Name (AAN) sonidegib diphosphate to sonidegib phosphate (United States Adopted Name (USAN)).
- The sponsor was invited to comment and proposes adoption of sonidegib phosphate as the AAN. This has been accepted by the AAN committee. The PI and labels have been correspondingly updated. This is acceptable.

There were outstanding issues at the time the summary was written as outlined below:

- The sponsor is invited to comment on whether 6-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-pyridin-3-amine ('C4', or 501-10) should be considered as a potentially genotoxic impurity. In response the sponsor states 'C4 was shown to be devoid of a mutagenic potential in the Ames test using 5 strains of *Salmonella* with and without metabolic activation. Following the recommendation of the ICH guideline M7;² it is therefore not required to regard C4 as a mutagenic impurity.' Comment from the nonclinical section has been sought.
- Please state whether poloxamer with an antioxidant is, or will be, used. The sponsor confirmed that the Poloxamer 188 excipient used (8.00 mg per capsule) contains the antioxidant butylated hydroxytoluene ('BHT'). The level is not stated.
- The sponsor specific Odomzo blister packaging specifications should be submitted.
- Please provide updated stability data, with clear information on which dissolution stages and tiers were used in sample testing. In the response provided Assay data show a somewhat perturbing correlation across batches with time of testing, casting doubt on the accuracy of the assay. This should be reconsidered in the context of future variation applications. Due to an increase in the moisture content during

² EMA/CHMP/ICH/83812/2013 ICH guideline M7(R1) on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk

storage at 30°C/75% room humidity and capsule brittleness after storage at high temperature, the proposed storage conditions are 'Do not store above 25°C and protect from moisture'

Overall the pharmaceutical chemistry evaluation was supportive of registration, notwithstanding minor amendments to the PI.

Biopharmaceutics

Assessment and conclusion of bioavailability aspects

Absorption of sonidegib from various formulations was rapid with median time to reach maximum drug concentration (T_{max}) of 2 to 5 hours across stages and treatments within each stage. Sonidegib maximum plasma concentration (C_{max}) and $AUC_{0-\infty}$ were increased to 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. Therefore, food intake should be avoided around the time of dose administration to avoid overexposure to sonidegib.

IV. Nonclinical findings

Introduction

In support of the efficacy and safety of sonidegib, a comprehensive dossier of high quality studies has been submitted. The pivotal toxicological studies were performed to Good Laboratory Practice (GLP) standards and were mostly conducted in the sponsor's laboratories. Aside from a few studies that were considered irrelevant to understanding the properties of sonidegib, all the sponsor's studies have been evaluated.

Pharmacology

Primary pharmacology

The Hedgehog family of proteins plays multiple important roles in vertebrate embryonic development. These proteins (such as Sonic Hedgehog (SHh)) also play roles in adult stem cell renewal, and responsive stem cell populations have been identified in mouse hair follicle and brain. Hedgehog proteins bind the protein patched homolog 1 (PTCH) membrane receptor patched (PTCH), resulting in its displacement from primary cilia. This allows the accumulation in cilia of the membrane receptor smoothed (Smo), along with repressor complexes of Suppressor of Fused (SuFu) and Gli transcription factors. Gli proteins then dissociate from SuFu and transfer to the nucleus where they activate genes associated with cell proliferation, cell survival, and adult stem cell renewal. Most sporadic basal cell carcinomas (BCCs) (as well as a significant fraction of sporadic medulloblastomas) show ligand-independent activation of Hedgehog signalling due to inactivating mutations of *PTCH* (tumour suppressor gene) or activating mutations of Smo. This makes the Hedgehog signalling pathway an attractive target for chemotherapy of BCC.

Like other Hedgehog signalling pathway inhibitors, such as vismodegib and the naturally occurring steroid cyclopamine, sonidegib was designed to target Smo. The sponsor's *in vitro* studies showed that sonidegib has a higher affinity for human Smo than does cyclopamine (half maximal inhibitory concentration (IC_{50}) values of 7 to 11 and 45 to

280 nM, respectively) and was about 10 fold more potent than cyclopamine as an antagonist of agonist-induced, Smo-dependent transcription of a reporter gene in a mouse cell line. Sonidegib was also shown to inhibit Hh protein induced expression of Gli1 mRNA in human HepM cells with an IC_{50} of 12.7 nM. Sonidegib showed similar effectiveness to vismodegib at inhibiting Hedgehog signalling in basaloid nests derived from embryo or newborn mouse skin. In a model using serum-starved human medulloblastoma cells treated with SHh in the presence of test compound for 24 hours and then measured for Gli1 mRNA content, sonidegib inhibited Gli1 mRNA production with an IC_{50} of 3 nM, whilst vismodegib was 2 fold less potent, and various sonidegib metabolites were inactive (M48, the major circulating metabolite) or 4 fold (M25) or more less potent than the parent compound.

In vivo studies examined effects of sonidegib on mouse hair follicle function and on mice bearing medulloblastomas with constitutive Hedgehog pathway signalling due to inactivating mutations of *PTCH*. Sonidegib produced dose-dependent inhibition of Gli1 production and regression of the medulloblastomas. Similarly, when applied to skin, sonidegib (at 1%) produced a delay of anagen and an inhibition of transcription of marker genes for Hedgehog pathway signalling (that is, Gli1 and cyclin D1).

The sponsor's primary pharmacology studies support the proposed mechanism of action and indication for sonidegib.

Secondary pharmacodynamics and safety pharmacology

Incubation of sonidegib (10 μ M) with a panel of receptors, ion channels, transporters, and enzymes indicated inhibition of cannabinoid receptor type 2 (human) (IC_{50} = 9.68 μ M), melatonin receptor MT1 (human) (IC_{50} = 1.06 μ M), monoamine receptor (rabbit) (IC_{50} approximately 10 μ M), and sodium channel site 2 (rat) (IC_{50} = 0.824 μ M). The C_{max} at steady state for cancer patients given the recommended dose of 200 mg once daily was 2.1 μ M, and the unbound drug fraction in human plasma at this concentration is approximately 2.0%, giving a free drug concentration of approximately 0.04 μ M. As the above assays are performed in the absence of extraneous protein, this suggests that off-target effects at the identified proteins are unlikely to occur in patients. Similar studies with the major sonidegib metabolite, M48, did not identify possible off-target effects.

Safety pharmacology studies examined possible effects of sonidegib on the cardiovascular and central nervous system (CNS)/respiratory systems. Rats dosed orally at 600 mg/kg showed no respiratory or CNS effects. Cardiovascular studies were performed using isolated rabbit hearts (Langendorff) perfused with increasing concentrations of sonidegib. Conduction velocity was slowed at 2 μ M sonidegib (-80% in one experiment and -14% in another experiment), suggesting drug interaction with the fast inward sodium current, the membrane ionic pumps (for example, the sodium/potassium ion (Na^+/K^+) pump), acidosis, or calcium overload. There was no arrhythmia or alterations in action potential duration.

In assays assessing the effect of sonidegib on the cardiac potassium ion current in human ether-à-go-go (hERG)-transfected HEK-293 cells;³ the corrected residual hERG tail current was inhibited by approximately 21% at the highest concentration of sonidegib tested, 0.5 μ M. The free fraction C_{max} for sonidegib in patients is about 10 fold lower than the highest tested concentration. This small margin suggests that sonidegib has some potential for QT⁴ interval prolongation. *In vivo* cardiovascular studies were performed with beagle dogs given oral doses of sonidegib up to 1000 mg/kg (produced a mean C_{max} of 6805 ng/mL (14 μ M), compared with clinical C_{max} of 2.1 μ M). Neither study indicated changes in

³ HEK-293 cells = Human embryonic kidney 293 cells, are a specific cell line originally derived from human embryonic kidney cells grown in tissue culture.

⁴ QT = QT interval in the ECG, the time interval from the start of the Q-wave to the end of the corresponding T-wave.

electrocardiogram (ECG) parameters that could be attributed to the test article. Cardiovascular parameters were also monitored during repeat-dose toxicity studies using dogs. Daily oral dosing for 2 or 13 weeks at up to 1000 (C_{max} of 56 μM) or 10 (C_{max} of approximately 9.6 μM) mg/kg/day, respectively, produced no changes in ECG parameters. However, in the 2 week study with high doses of sonidegib, ECG was determined before dosing when plasma drug levels were low. In the 13-week study, ECG was performed at 2 hours postdosing with highest C_{max} in dogs approximately 5 times the clinical C_{max} . In a 26 week repeat dose toxicity study, dogs that had been dosed at 50 mg/kg/day for 88 days showed mild increases (compared with controls) in QRS duration (approximately 12%) and in corrected QT interval (QTc) (approximately 7%). Based on toxicokinetic measurements made on day 23 of dosing, C_{max} and $AUC_{0-24\text{ h}}$ values for these dogs on Day 88 of dosing would have been > 15 times clinical exposure at steady state. This relatively large margin combined with the relatively small effects on canine ECG parameters suggests that cardiac effects are not expected to occur in patients receiving the recommended dose of sonidegib.

Pharmacokinetics

The passive permeability of sonidegib across Caco-2 cell;⁵ monolayers was approximately 20×10 to $5 \text{ cm} \cdot \text{min}^{-1}$, suggesting that it is a moderately permeable drug substance.

The plasma kinetics of sonidegib following single PO and/or intravenous (IV) dosing of rats, dogs, and pigs and after single PO dosing of humans are shown in the table below. Plasma kinetics were also determined in conjunction with repeat-dose toxicity studies using rats and dogs and with reproduction studies using rats and rabbits. Studies examining plasma kinetics after dermal application of sonidegib to pigs are not discussed here as they have little relevance to the intended method of clinical use.

Absorption

The level of absorption was high in rats (78%), only about half that value for dogs, and was even lower in humans (~6 to 7%). The rate of absorption (T_{max}) was moderate to slow in rats and dogs (4 and 48 hours, respectively), compared with 2 hours in humans. The rate of sonidegib elimination from plasma ($t_{1/2}$)⁶ after IV dosing also showed inter-species differences ranging from 3.2 hours for rats to 25.3 hours for dogs. The volume of distribution was relatively high for rats, dogs, and pigs (4.8, 10.8, and 7.1 L/kg, respectively) suggesting extensive tissue distribution of sonidegib.

Toxicokinetic data were obtained from toxicity studies in rats and dogs of both sexes. Rats receiving PO doses over the range 0.2 to 20 mg/kg/day showed an over-proportional increase in plasma exposure, which was attributed to markedly more rapid metabolism of sonidegib after lower doses. After 6-months dosing at these levels, sonidegib exposure had increased approximately 3 fold, whereas M48 (the major circulating metabolite) exposure increased approximately 40 fold. Over a higher dose range, there was a less-than-dose-proportional increase in plasma exposure, probably due to saturated absorption at high doses. Similar exposures were obtained for both rat sexes. Dogs receiving PO doses over the range 0.1 to 10 mg/kg/day showed approximately dose-proportional increases in exposure after the first dose, however, after multiple doses there was an over-proportional increase in exposure. After 11 weeks of dosing at 0.1 to 10 mg/kg/day, exposure to sonidegib had increased by approximately 2 fold at the low dose and by ~15 fold at the high dose, suggesting drug accumulation. Dogs of both sexes showed similar exposures.

⁵ Caco-2 cell line is a continuous line of heterogeneous human epithelial colorectal adenocarcinoma cells.

⁶ $t_{1/2}$ = half-life associated with the terminal slope.

Table 2: Species comparison of mean plasma pharmacokinetic parameters after a single dose of sonidegib

		Rat (Male, n = 3)	Dog (Male, n = 2/3)	Pig (Male, n = 3)	Man ^a (Male, n = 6)
Route	Study no.	R0700684-01	1100218	0900883	LDE225A2110
	Dose (mg/kg) ^b	PO = 25, IV = 2	PO = 10.2, IV = 0.927	IV = 1.04	PO = 800
PO	C _{max} (ng/mL)	6680	218	–	154
	t _{max} (h)	4	48	–	2
	AUC _{0-∞} (ng·h/mL)	118,000	10,490	–	8680
	t _{1/2} (h)	–	30	–	319
	Absorption (%)	78	34	–	–
IV (bolus)	AUC _{0-last} (ng·h/mL)	1740	2034	1228	–
	CLT (L/h/kg)	1.08	0.476	0.887	–
	t _{1/2} (h)	3.2	25.3	18.6	–
	Vd _{ss} (L/kg)	4.8	10.8	7.09	–

^aHealthy male subjects; ^bdose as mg/kg for animals and mg/subject for humans.

Distribution

Sonidegib showed a high level of binding to plasma proteins from all species examined and there was no effect of sonidegib concentration (over the range 0.001 to 2.5 µg/mL) on the level of binding (approximately 2 to 3% of sonidegib was unbound in the presence of human plasma and 1 to 3% in mouse, rat, dog and pig plasma). Sonidegib was bound strongly by albumin and α1-acid glycoprotein, but did not appear to distribute into red blood cells. In incubations with microsomes or hepatocytes, radiolabelled sonidegib and/or metabolites showed some capacity for covalent bonding to protein.

Consistent with a high volume of distribution value, radiolabelled sonidegib showed rapid and widespread tissue distribution in rats after IV administration. Tissue to plasma radioactivity concentration ratios greater than 3, at 1 hours after dosing, were found for various tissues (including adrenal medulla and cortex, heart, kidney cortex, liver, lymph nodes, pancreas, small intestine, and thyroid), whilst brain and testis showed ratios of ~1. The result for brain suggests that sonidegib and/or its metabolites can cross the blood/brain barrier. Sonidegib-derived radioactivity showed a long half-life in tissues (most values in the range 76.5 to 257 hours). Such long half-lives might, in part, be related to covalent bonding to protein (see above). The persistence and high levels of radioactivity in the eye choroid of pigmented compared with albino rats suggested uptake of sonidegib and/or its metabolites into melanin-containing structures.

Metabolism

Incubation of sonidegib with microsomal preparations from baculovirus-infected insect cells expressing a recombinant human cytochrome P450 (CYP) enzyme showed that only CYP3A4, and CYP3A5 to a minor extent, produced metabolites. No other tested CYPs or flavin monooxygenases showed activity towards sonidegib. The metabolites detected in *in vitro* reactions derived mainly from oxidation/reduction reactions at the morpholine moiety of sonidegib. Consistent with the involvement of CYP3A4 in sonidegib metabolism, clinical studies showed that inhibition of CYP3A4 with ketoconazole increased sonidegib exposure, whilst induction of CYP3A4 with rifampicin reduced exposure. Hence, administration of sonidegib with agents that modulate CYP3A4 levels should be avoided.

Although *in vitro* studies indicated the prominence of morpholine moiety oxidation/reduction reactions, *in vivo* studies, involving IV or PO dosing of rats, dogs, and

pigs, showed that the plasma metabolite giving highest exposure was M48 (amide hydrolysis product of sonidegib), which is pharmacologically inactive. In rats, dogs, and pigs exposure to M48 was generally higher than that for parental compound. After oral dosing of humans with sonidegib, M48 was also the most prominent metabolite in plasma along with M16 and M25 (morpholine moiety metabolism products), which were also formed in rats and dogs and were approximately 100 and 4 fold less potent, respectively, than sonidegib in the inhibition of Hedgehog pathway signalling. Parental drug was a prominent component of faeces from rats and dogs, likely reflecting poor absorption of sonidegib. Other prominent components in faeces included the morpholine moiety oxidation/reduction products M31 (rats and pigs) and M37 (dogs and pigs), as well as M48 (dogs). Human faeces contained a high level of parental drug (~89% of dose), as well as low levels of various morpholine moiety oxidation/reduction products. Although the metabolism of sonidegib was complex (For example 34 metabolites were detected in pig plasma), the metabolites found in humans were also generally detectable in one or more animal models.

Excretion

Faeces was the major route of excretion in rats, dogs, pigs, and humans. Following oral administration of radiolabelled sonidegib to male beagle dogs, within 168 hours post-dose, 75% of the radioactivity was recovered from faeces and ~1% was recovered in urine. Similar data were obtained from rats and humans, although pigs showed significant excretion via urine. Around 20% and 60% of radiolabel were recovered in bile after oral and IV dosing, respectively, of bile duct-cannulated male rats. Most of the remaining radiolabel was found in faeces, presumably representing direct secretion through the intestinal wall into the lumen.

Conclusion

The pharmacokinetics (PK) of sonidegib can differ significantly between species. Nevertheless, the various points of commonality between the human and animal pharmacokinetic data suggest that the animal models used provide a reasonable basis for extrapolation of toxicity findings to humans.

Pharmacokinetic drug interactions

Studies incubating sonidegib with pooled human liver microsomes indicated potent inhibition of CYP2B6 (inhibition constant (K_i) = 0.007 μ M) and weaker inhibition of CYP2C9 (K_i = 0.237 μ M). Concentrations of sonidegib up to 100 μ M showed no inhibition of other CYP activities (1A2, 2A6, 2C8, 2C19, 2D6, 2E1, and 3A4/5), and concentrations up to 50 μ M showed no time-dependent inhibition of CYPs 1A2, 2C9, 2D6, or 3A. Hence, sonidegib may increase exposure to drugs primarily cleared by CYP2B6 and/or CYP2C9. Sonidegib did not activate the pregnane X-receptor transcription factor (induces transcription of CYP3A4) in a human cell line, and measurement of CYP levels in human hepatocytes exposed to sonidegib under *in vitro* conditions suggested that sonidegib is unlikely to be an inducer of CYP1A2, CYP2B6, CYP2C9, or CYP3A under clinical dosing conditions.

In vitro studies using cell monolayers treated with efflux transporter inhibitors suggested that sonidegib is not a substrate of P-glycoprotein (P-gp), multidrug-resistance protein 2 (MRP2), or breast cancer resistance protein (BCRP). Similarly, sonidegib was not an inhibitor of P-gp or MRP2. Sonidegib did, however, show inhibition of BCRP activity (IC_{50} 1.54 μ M). Hence, *in vivo* there is the potential for sonidegib to increase uptake of BCRP substrates.

There was no effect of organic anion transporter (OAT), organic anion transporting polypeptide (OATP), or organic cation transporter (OCT) transporter family inhibitors on sonidegib uptake by normal human hepatocytes, suggesting that sonidegib is not a

substrate of these transporters. Furthermore, derivatives of the human embryonic kidney cell line HEK293 that overexpress OAT, OATP, or OCT transporter family members showed little or no effect of sonidegib concentrations up to 6.6 μ M on uptake of substrates of these transporters.

Toxicity

Acute toxicity

Single-dose toxicity was examined in female Wistar rats given an oral dose of 2000 mg/kg of sonidegib. This dose did not produce clinical signs or mortalities, indicating a maximum non-lethal dose of > 2000 mg/kg. One incidental death 7 days after dosing was not attributable to treatment. This suggests that sonidegib, when delivered via the clinical route, has low acute toxicity.

Repeat-dose toxicity

Pivotal studies were performed with rats and dogs and had durations of up to 6 months. All studies used once daily, oral dosing, which is consistent with the mode and frequency of clinical dosing. The design of the studies was consistent with the relevant EMA guideline.⁷ Bone toxicity and skeletal muscle effects were further investigated in additional studies.

Relative exposure

Relative exposures to sonidegib were calculated relative to the mean plasma AUC_{0-24h} value from population pharmacokinetic analysis based on clinical Studies CLDE225A2201, CLDE225X2101, and CLDE225X1101 in cancer patients. The relative exposure at the NOAEL dose, for both rats and dogs, was low: approximately 0.3 for rats dosed for 6 months and around a tenth of that value for dogs dosed for 6 months (see table below).

Table 3: Relative exposure in repeat-dose toxicity studies ^a

Species	Study number	Study duration (day of TK sampling)	Dose (mg/kg/day) ^b	Sex	AUC _{0-24h} (ng-h/mL)	Exposure ratio ^c
Rat (Wistar)	0770732	4 weeks (29)	20, 100, 600	M	54000, 125000, 223000	2.4, 5.6, 10
				M	115000, 367000, 579000	5.1, 16, 26
	0870704	13 weeks (74)	0.2, 2d, 20	M	65.1, 8090, 75800	0.003, 0.4, 3.4
				F	66.3, 6720, 156000	0.003, 0.3, 7.0
	1070056	26 weeks (149)	0.5, 3, 10	M	437, 6470, 19800	0.02, 0.3, 0.9
				F	429, 7140, 61500	0.02, 0.3, 2.8
Dog (beagle)	0770733	4 weeks (22)	3, 12.5, 50	M	1610, 7030,	0.07, 0.3, 2.1

⁷ CPMP/SWP/1042/99 Rev 1 Guideline on repeated dose toxicity

Species	Study number	Study duration (day of TK sampling)	Dose (mg/kg/day) ^b	Sex	AUC _{0-24h} (ng·h/mL)	Exposure ratio ^c
					47900	
				F	2730, 4790, 26500	0.1, 0.2, 1.2
	0870705	13 weeks (77)	0.1, 1, 10	M	125, 1600, 82500	0.006, 0.07, 3.7
				F	153, 1610, 95700	0.007, 0.07, 4.3
	1070055	≤26 weeks (149)	0.1, 0.5, 10	M	97.9, 349, 56900	0.004, 0.02, 2.5
M				68.3, 397, 34700	0.003, 0.02, 1.6	
Human (cancer patients)	Clinical study	steady state	(200 mg)	M + F	22348	-

a. All listed studies are GLP compliant; b. doses given PO (gavage); c. animal:human plasma AUC_{0-24 h}; d. values at no observed adverse effect level (NOAEL) dose are bolded and underlined (where no value is so indicated, NOAEL was < low dose).

Major toxicities

Findings were similar for rats and dogs and showed no prominent differences between the sexes. Major target organs for sonidegib were bone, teeth, reproductive tract, skin, and GI tract.

The most prominent effects were seen in bone and teeth. With continued dosing with sonidegib, at less than or around an exposure ratio of 1, young adult rats and dogs showed progressive reductions in growth plate volume to zero. This effect was associated with decreases in trabeculae and proliferating chondrocytes, as well as decreases in serum levels of bone-specific alkaline phosphatase (B-ALP) (found on cell surface of osteoblasts) and of bone biomarkers such as cartilage oligomeric matrix protein (COMP) (cartilage turnover) and procollagen type 1 N-propeptide (P1NP) (bone formation). Concomitant administration to rats of parathyroid hormone (PTH) with sonidegib was shown protect against thinning of the growth plate, reduction in chondrocyte proliferation, and decreases in bone biomarkers. However, PTH did not fully protect against these sonidegib-induced effects. Continuous dosing with PTH (for example, via osmotic minipump) was shown to be moderately more effective than once daily bolus injection of sonidegib-treated rats. Given the age of epiphyseal closure in humans and that sonidegib is not proposed for paediatric use, it is unlikely that these bone effects would be of relevance to clinical use.

Repeat dosing of rats with sonidegib produced loose or missing incisors that correlated with histological findings of atrophy of the tissues of the tooth root, degeneration of ameloblasts, ectopic dentin in the pulp, irregular dentin, altered shape of the tooth, and periodontal inflammation. These findings occurred in rat incisors but not molars, and are likely related to the continuous growth of rat incisors. Hence, these findings are unlikely to be relevant to adult humans.

The bone and teeth effects of sonidegib in rats were generally not reversed during a drug-free recovery period.

Alopecia, which was correlated with hair follicle atrophy, was noted in both rats and dogs receiving daily sonidegib doses at exposure ratios ≥ 1 for periods of a month or more. In rats, this change was reversed during a drug-free recovery period. Alopecia was also

identified as a very common adverse reaction to sonidegib dosing in clinical trials (sponsor's PI).

GI tract inflammation was noted in both rats and dogs and appeared to be a primary effect of the test article. Rats dosed for 26 weeks at 10 mg/kg/day (exposure ratio approximately 1 to 3) showed minimal to moderate inflammation of glands/crypts at various locations in the GI tract that was characterised by enlarged glandular or crypt lumens containing mucus, necrotic debris, fragmented polymorphonuclear cells, and macrophages. In addition, the epithelial lining was irregularly thick/thin with sites of rupture showing accumulation of mucus, necrotic debris, polymorphonuclear cells, and macrophages in the lamina propria near the rupture. Dogs dosed for 13 weeks at 10 mg/kg/day (exposure ratio approximately 4) showed dispersed single cell necrosis of epithelial cells of the ileum. The 26 week study at 10 mg/kg/day (exposure ratio approximately 2) showed stomach attenuation related to degeneration/necrosis of the gastric epithelium. Consistent with such non-clinical findings, GI tract disorders were a very common adverse reaction to sonidegib dosing in clinical trials (sponsor's PI).

Lymphoid depletion in various lymphoid tissues including thymus, spleen, and lymph nodes was noted in both rat and dog studies, however, it was generally unclear whether this was a direct effect of the test article or a response to stress.

Renal toxicity was noted in rats of both sexes dosed for 4 weeks at 600 mg/kg/day (exposure ratio approximately 10 for males and approximately 26 for females) and presented as tubular necrosis and mineralisation of tubular epithelium.

Reproductive tract changes were seen in rats and dogs of both sexes. Rats dosed for 4 weeks at ≥ 20 mg/kg/day (exposure ratio \geq approximately 5) showed uterine atrophy (wall of the uterus was small and thin) or dilation. Uterine atrophy, plus ovarian atrophy, was also seen in rats dosed with 10 mg/kg/day for 26 weeks (exposure ratio 1 to 3) and in dogs (reported as immaturity of uterus and atresia or degeneration of ovarian follicles) at ≥ 12.5 mg/kg/day (exposure ratio approximately 0.2) for 4 weeks. Acute inflammation of the prostate (characterised by isolated focal or multifocal small ducts or glands dilated with infiltrates of neutrophils, macrophages, and necrotic debris in ductile lumens) was observed in the 26 week rat study at 10 mg/kg/day. Dogs dosed for 4 weeks at 50 mg/kg/day (exposure ratio approximately 2) showed testis changes including reduced spermatogenesis, the presence of numerous spermatic giant cells in the testes, aspermia, and cellular debris in the epididymides.

These changes showed some reversal during the recovery period.

The major target organs for sonidegib-induced toxicity in rats and dogs are consistent with locations where the Hedgehog signalling pathway is known to have a critical role in cellular survival, growth, and/or differentiation. Indicative findings include:

- Indian hedgehog stimulates expression of parathyroid hormone-related peptide, which delays hypertrophy of chondrocytes that occur near the articular surface of developing rodent growth plates and increases their proliferation.
- SHh is required for the generation of enamel-secreting ameloblasts from stem cells in rodent incisors and for the proliferation and differentiation of dentin-secreting odontoblasts.
- The maintenance of hair follicle stem cells and the induction of anagen in the hair follicle cycle are dependent on Hedgehog signalling.
- The Hedgehog signalling pathway has demonstrated roles in the maintenance/proliferation of stem cell populations in the gut.
- SHh is anti-apoptotic and promotes the proliferation and differentiation of early T cells and B cells.

- Hedgehog signalling promotes the survival of germ cells in the rat testis and has roles in intercellular communication in the mouse ovary.

To explain clinical findings of muscle toxicity in sonidegib-treated patients, possible synergy between simvastatin (a known inducer of muscle toxicity) and sonidegib was tested under *in vitro* and *in vivo* conditions. Cultures of human myotubes exposed to both drugs (sonidegib to a maximum concentration of 25 μM) showed evidence of toxicity due to simvastatin, but there was no evidence of synergy between the drugs. However, daily dosing of rats for 12 days with sonidegib (20 mg/kg/day, producing a C_{max} on Day 1 of approximately 7 μM) plus simvastatin (80 mg/kg/day) produced a synergistic increase in skeletal (but not cardiac) muscle injury as evidenced by increases in muscle damage serum markers (alanine aminotransferase (ALT), aspartate transaminase (AST), and creatine kinase (CK)), increases in serum levels of skeletal muscle biomarkers (cardiac troponin I (cTnI), myosin light chain 3 (Myl3) and fatty acid binding protein 3 (FABP3)), and increases in histological myofibre degeneration. Sonidegib dosing alone did not produce muscle toxicity (no changes in serum markers or histopathology). Repeat dosing of rats or dogs with sonidegib alone, for periods longer than 12 days, also did not produce direct evidence for muscle toxicity. One of ten female rats dosed for 26 weeks at 10 mg/kg/day (exposure ratio approximately 2.8) showed significant elevations of serum levels of both AST and CK during the dosing period. However, terminal necropsy microscopic examination of muscle from this animal showed no muscle damage.

In vitro studies with human and mouse myotube cultures showed that high concentrations of sonidegib could induce various changes in gene expression including induction of a muscle cell death gene (FOXO1) and decreased expression of muscle differentiation-associated and energy metabolism genes. However, these off-target effects were found after prolonged exposure at 50 μM sonidegib (at least 10 times clinical C_{max}) but were not found at 10 μM sonidegib.

Genotoxicity

Sonidegib was not mutagenic at up to 5 mg/plate, in both the presence and absence of metabolic activation, in standard *Salmonella typhimurium* strains. Tests of *in vitro* (normal human lymphocytes and transformed human lymphoblastoid cells) and *in vivo* (rat bone marrow micronucleus test) clastogenicity were also negative. The assays used and the conditions employed were consistent with the relevant EMA guideline.⁸

Carcinogenicity

No studies were submitted. According to ICH guideline S1A;⁹ and S9;¹⁰ pharmaceuticals intended for the treatment of advanced cancers do not require testing for carcinogenicity. The lack of genotoxicity and hyperplasia in repeat dose studies suggests that this drug is unlikely to induce tumours.

Reproductive toxicity

The scope and design of the studies were appropriate and consistent with the relevant EMA guideline.¹¹ Critical studies were performed to Good Laboratory Practice (GLP) standards.

Results from the dosing of pregnant rabbits with sonidegib showed distribution into fetuses (fetal concentration was around double circulating level in doe at 24 hours after

⁸ CPMP/ICH/141/95 ICH Guideline S2A: Specific aspects of regulatory genotoxicity tests for pharmaceuticals.

⁹ CPMP/ICH/140/95 ICH Guideline S1A: The need for carcinogenicity studies of pharmaceuticals.

¹⁰ ICH S9 nonclinical evaluation for anticancer pharmaceuticals

¹¹ CPMP/ICH/386/95 Note for guidance on the detection of toxicity to reproduction for medicinal products & toxicity to male fertility.

oral dosing at 5 mg/kg/day). Excretion of sonidegib by lactating animals was not examined.

Sonidegib was assessed for effects on fertility (both sexes) using Wistar rats. Male mating, fertility, and sperm counts were unaffected at up to 20 mg/kg/day for 50 days before mating (exposure ratio approximately 3.4). Although female mating and oestrous cycling were unaffected by dosing, female fertility was very sensitive to sonidegib. Pregnancy rate was significantly decreased at 2 mg/kg/day (exposure ratio approximately 0.3), with no pregnant animals at 20 mg/kg/day (exposure ratio approximately 7). Early resorptions were also increased at 2 mg/kg/day.

Embryofetal development in rabbits was also highly sensitive to sonidegib. External and skeletal malformations were found at 17.8 mg/kg/day from gestation Day 7 to 9 and followed by 5 mg/kg/day until gestation day 20 with (exposure ratio at 5 mg/kg/day: 0.05), whilst the incidence of skeletal variations was elevated after doses (0.01 mg/kg/day) that did not produce detectable levels of sonidegib in the maternal circulation (exposure ratio < 0.0001). The results suggest induction of both teratogenicity and fetotoxicity.

The teratogenicity of sonidegib is not surprising given the multiple important roles that the Hedgehog signalling pathway performs during vertebrate embryonic development and the induction of birth defects in lambs exposed *in utero* to the Smo inhibitor cyclopamine. Effects on embryofetal development were not studied in a second animal species. This is acceptable because of the teratogenicity seen in rabbits and the known mechanisms of action discussed above.

Juvenile rats dosed orally with sonidegib for five weeks showed high sensitivity to toxic effects of sonidegib (exposure ratio at no observed adverse effect level (NOAEL) of approximately 0.02 to 0.03 compared with exposure ratio at NOAEL in adult rats of 0.3 to 0.4). The spectrum of tissues showing test article-related changes was similar to that for adults (bone, teeth, oral cavity, and GI tract). In addition, minimal to slight degeneration of nerve fibres was noted in the sciatic and spinal nerve. This might be a secondary effect resulting from early bone growth plate closure causing compression of the growing nerve; however, direct effects of sonidegib cannot be ruled out since it has been shown that structural and functional integrity of peripheral nerves depends on DHH.

Table 4: Relative exposure in reproductive toxicity studies ^a

Species	Study type (number)	Treatment period (day of sampling)	Dose (mg/kg/day) ^b	Sex	AUC _{0-24h} (ng·h/mL)	Exposure ratio ^c
Rat (Wistar)	Fertility (0970632)	M = ≥ 50 days pre-mating + 2-week mating period; F = 5 weeks pre-mating, during mating, and through GD6	0.2d, 2, 20 ^d	M	65.1 ^e , 8090 ^e , 75800 ^e	0.003, 0.4, 3.4
				F	66.3 ^e , 6720 ^e , 156000 ^e	0.003, 0.3, 7.0
	Juvenile (0770903)	PND14–PND49 (Week 5);	1, 3, 10, 30	M	443, 4120, 15400, 61300	0.02, 0.2, 0.7, 2.7
				F	635, 4510, 38400, 90900	0.03, 0.2, 1.7, 4.1
Rabbit (NZW)	Embryofetal (0970631)	GD7–GD20 (GD20)	0.01, 0.1, 5		–, 2.28, 1080	–, 0.0001, 0.05

^a All listed studies are GLP compliant; ^b doses given PO (gavage); ^c animal:human plasma AUC_{0-24 h} based on human AUC of 22348 ng·h/mL; ^d values at NOAEL dose are bolded and underlined (maternal or juvenile value) or bolded and boxed (paternal value) (where no value is so indicated, NOAEL was < low dose (for example embryofetal effects)); ^e values are taken from day 74 of the repeat-dose toxicity Study No. 0870704. F = female. M = male

Pregnancy classification

The sponsor has proposed Pregnancy Category X;¹² (that is 'should not be used in pregnancy or when there is a possibility of pregnancy'). This category is appropriate given the aforementioned reproductive toxicity results and the classification for another Smo inhibitor, vismodegib.

Local tolerance

Sonidegib showed no phototoxicity in the 3T3 cell *in vitro* assay.¹³

Sonidegib produced slight-to-moderate, transient eye irritation, and little-to-no dermal irritation in rabbits. Following application of sonidegib to mouse ear (either with or without ultraviolet-A light irradiation) in the mouse local lymph node assay, there was no evidence for an increase in weight or cell numbers in ear-draining lymph nodes, suggesting that sonidegib is neither a photo-allergen nor an inducer of contact sensitivity.

Impurities

No toxicology studies were provided to qualify any impurity.

Paediatric use

Sonidegib is not proposed for paediatric use.

Nonclinical summary and conclusions

- The nonclinical studies were comprehensive and of high quality, and the pivotal toxicological studies were performed to GLP standards.
- Most BCCs show ligand-independent activation of the Hedgehog signalling due to inactivating mutations of the tumour suppressor gene 'patched' (*PTCH*, Hedgehog receptor) or activating mutations of the proto-oncogene 'smoothed' (*Smo*). Such mutations lead to constitutive activation of genes associated with cell proliferation and survival. Accordingly, the Hedgehog signalling pathway is an attractive target for chemotherapy of BCC. Sonidegib was designed to target the membrane receptor Smo. The sponsor's primary pharmacology studies demonstrated that sonidegib has nanomolar range affinity for Smo and is effective at inhibiting the Hedgehog signalling pathway under both *in vitro* and *in vivo* conditions.
- Secondary pharmacodynamic testing of sonidegib and its major metabolite (M48) against a panel of receptors, ion channels, enzymes, and transporters suggested that off-target effects are unlikely at clinically relevant concentrations.
- *In vitro* studies with hERG-transfected cells showed that sonidegib at 0.5 µM inhibited the corrected residual hERG tail current by approximately 21%. That value is more than ten times the concentration of unbound sonidegib at the clinical C_{max} (2.1 µM x 0.02 = 0.04 µM). Hence, sonidegib may have some potential for pro-arrhythmic effects. However, dogs given daily, oral dosing for up to 13 weeks at an exposure ratio of

¹² Pregnancy Category X is defined as Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

¹³ 3T3 cell line = 3-day transfer, inoculum 3×10⁵ cells. This cell line was originally established from the primary mouse embryonic fibroblast cells that were cultured by the designated protocol, so-called '3T3 protocol'.

approximately 4 showed no changes in ECG parameters, although mild increases in QRS (~ 12%) and in QTc;¹⁴ (~ 7%) were observed in the 26-week repeat dose toxicity study at 50 mg/kg/day (exposure ratio based on C_{max} and $AUC_{0-24 h} \geq 15$).

- Pharmacokinetic parameters for sonidegib showed considerable variability between rats, dogs, pigs, and humans. Nevertheless, the various points of commonality between the human and animal data suggested that the animal models used provide a reasonable basis for extrapolation of toxicity findings to humans. Sonidegib showed a relatively high volume of distribution for rats, dogs, and pigs (4.8 to 10.8 L/kg) and, consistent with this finding, radiolabelled sonidegib showed an extensive distribution in rats with tissue to plasma ratios, at 1 hours after dosing, greater than 3 for various tissues. Sonidegib and/or its metabolites appeared to cross the blood-brain barrier in rats.
- Sonidegib showed a high level of binding to human (97 to 98%) and animal (97 to 99%) plasma proteins and there was no effect of sonidegib concentration (over the range 0.001 to 2.5 µg/mL) on the level of binding. Sonidegib was bound strongly by albumin and α1-acid glycoprotein, and did not appear to distribute into red blood cells.
- *In vitro* studies with human CYP enzymes showed that sonidegib primarily underwent oxidation/reduction reactions on its morpholine moiety that were catalysed by CYP3A4. This is consistent with the clinical finding that inhibition of CYP3A4 with ketoconazole increased sonidegib exposure. The major circulating and excreted metabolite in animals and humans was M48 (an amide hydrolysis product of sonidegib), which is not pharmacologically active. Faeces was the major route of excretion in animals and humans, with only trivial excretion via urine.
- Sonidegib showed no evidence for induction of various CYP isoforms but was an inhibitor of CYP2B6 and CYP2C9. Sonidegib was not a substrate of the efflux transporters P-gp, MRP2, and BCRP, but showed inhibition of BCRP. Hence, sonidegib could increase absorption and/or excretion of co-administered drugs that are BCRP substrates. Uptake of sonidegib by human hepatocytes appeared to be by passive diffusion and did not involve OAT, OATP, or OCT transporter proteins.
- Repeat-dose toxicity studies identified bone, teeth, reproductive tract, skin, and GI tract as the major targets for toxic action of sonidegib in rats and dogs. The effects seen generally occurred at around clinical exposure levels. Skin and GI tract effects were also commonly found in clinical studies. The effects on teeth are likely related to the continuous growth of rat incisors and are unlikely to be relevant to adult humans. Sonidegib induced growth plate closure in rats and dogs. However, given that sonidegib is indicated for adult use, this effect is unlikely to be of clinical relevance. The major sites for sonidegib-induced toxicity in rats and dogs are consistent with locations where the Hedgehog signalling pathway is known to have a critical role in cellular survival, growth, and/or differentiation.
- Repeat dosing of rats with sonidegib plus simvastatin produced a synergistic increase in skeletal muscle injury, as evidenced by histological and plasma marker findings. With the exception of one female rat in the 26-week study at 10 mg/kg/day (exposure ratio ~2.8), which showed significant elevations of serum levels of both AST and CK during the dosing period but no microscopic evidence of muscle damage at terminal necropsy, there was no evidence from repeat dosing studies in rats or dogs for the induction of muscle toxicity by sonidegib. *In vitro* studies with human and mouse myotube cultures suggested that sonidegib could induce various changes in gene expression, however, these off-target effects were only found after prolonged exposure at high concentrations (around 10 times clinical C_{max}).

¹⁴ QTc = QT corrected for heart rate

- Sonidegib showed no evidence for induction of mutations in standard bacterial reverse mutation assays. The drug also showed no evidence for clastogenicity in both *in vitro* (human peripheral blood lymphocytes) and *in vivo* (rat bone marrow micronucleus) assays. Sonidegib was not tested for carcinogenicity. According to ICH guideline S1A;⁹ pharmaceuticals intended for the treatment of advanced cancers do not require testing for carcinogenicity. The lack of activity shown by sonidegib in standard tests for genotoxicity and absence of hyperplasia in repeat dose toxicity studies suggests that this drug is unlikely to induce tumours.
- Female rat fertility was very sensitive to sonidegib (exposure ratio at NOAEL of ~0.003 for ≥ 6 weeks dosing), with evidence for induction of early resorptions. Embryofetal development in rabbits was also highly sensitive to sonidegib. External and skeletal malformations were found at the higher doses tested (exposure ratios > 0.05), whilst the incidence of skeletal variations was elevated after doses that did not produce detectable levels of sonidegib in the maternal circulation (exposure ratio << 0.0001). The results suggest induction of both teratogenicity and fetotoxicity. These results are not surprising given that the prototype Hedgehog small-molecule antagonist, cyclopamine, was discovered due to its teratogenicity in sheep. It is therefore appropriate that sonidegib be placed in Pregnancy Category X.¹²
- Juvenile rats dosed orally with sonidegib for five weeks showed high sensitivity to toxic effects (exposure ratio at NOAEL of approximately 0.02 to 0.03). The spectrum of tissues showing test article-related changes was similar to that for adults (bone, teeth, and alimentary tract), but with the addition of minimal to moderate sciatic nerve fibre degeneration.
- Sonidegib produced slight-to-moderate, transient eye irritation, and little-to-no dermal irritation in rabbits. Mouse local lymph node assays showed no potential for contact allergy or photo-allergy. Sonidegib was not phototoxic in an *in vitro* assay.

Nonclinical conclusions and recommendation

- The nonclinical studies presented were comprehensive and had no major deficiencies.
- The results of the primary pharmacology studies support the use of sonidegib for the treatment of basal cell carcinoma.
- Secondary pharmacodynamics and safety pharmacology studies did not identify any unexpected clinical hazards. *In vitro* assays of effects on the cardiac potassium ion current suggest potential for QT interval prolongation in patients, but there were no significant changes in ECG parameters in dogs.
- CYP3A4 is the major enzyme in the metabolism of sonidegib; thus plasma sonidegib levels can be affected by drugs that inhibit or induce CYP3A4. Sonidegib is an inhibitor of CYP2B6 and CYP2C9 enzymes and of the BCRP transporter and has the potential to interact with drugs that are substrates of these proteins.
- Repeat-dose studies in rats and dogs identified bone, teeth, reproductive tract, skin, and GI tract as the major target organs for sonidegib-induced toxicity.
- The evidence presented suggested that sonidegib does not pose a genotoxic risk.
- Based on its fetotoxic and teratogenic effects, sonidegib was appropriately categorised as Pregnancy Category X.¹²
- There are no nonclinical objections to the registration of sonidegib.
- The draft Product Information should be amended as directed.

V. Clinical findings

A summary of the clinical findings is presented in this section.

Introduction

Clinical rationale

The Application Letter and Clinical Overview included a clinical rationale for the submission. The following clinical rationale is based on the sponsor's submitted documents, supplemented by relevant published data reviewed by the clinical evaluator.

Basal cell carcinoma is the most common human malignancy. The two most common forms of non-melanoma skin cancer (NMSC) in Australia are basal cell carcinoma and squamous cell carcinoma. However, the exact incidence and prevalence of BCC (and squamous cell carcinoma (SCC)) in Australia are unknown. While data on all other cancers are reportable in Australia and collected by state and territory registries, the two most common types of NMSC (BCC and SCC) are not reportable and not generally recorded in Australian cancer registries. In 2008, it was estimated that in Australia there were 296,000 new cases of BCC (169,483, males; 126,530, females) and 137,600 new cases of SCC (253,384, males; 180,229, females). Overall, it was estimated that in 2008, around 434,000 patients (253,000, males; 180,000, females) were diagnosed with one or more NMSC in Australia. The 2008 Australian estimates for BCC, SCC, and all NMSC were based on the results of a 2002 medically verified self-reporting population survey.

While BCC is usually amenable to local therapy, recurrence rates vary from 5% to 14% after resection. Treatment of mBCC has primarily been palliative as regimens using radiation, surgery, and chemotherapy have typically been ineffective. Currently, vismodegib (Erivedge) is the only approved systemic treatment for advanced BCC. Consequently, the sponsor states that there is an unmet need for systemic treatments for patients with laBCC who are not amenable to curative surgery or radiation therapy and for patients with mBCC.

The sponsor's clinical rationale for the submission is considered to be satisfactory.

Guidance

Officers of the TGA and representatives of the sponsor held a pre-submission meeting on 15 April 2014.

Contents of the clinical dossier

Scope of the clinical dossier

The submission contained the following clinical information:

- 4 clinical pharmacology studies.
- 2 PK/pharmacodynamic (PD) studies in patients (1 x PK/CK; 1 x PK/EFF).
- 1 population pharmacokinetic analysis.
- 1 pivotal Phase II efficacy and safety study supporting the proposed indication.
- 1 Phase II dose-finding study in patients with nevoid basal cell carcinoma syndrome.
- 1 QT Analysis Report, 1 x Safety Adjudication Report, Summary of Clinical Safety (SCS), Appendices.

- 15 individual reports of bioanalytical methods use to assess sonidegib and metabolite concentrations in the human PK studies.
- 16 human biomaterial reports.
- An Application letter, application form draft Australian PI and CMI, documents relating to compliance with meetings at pre-submission processes, overseas regulator status, summary of biopharmaceutics studies, Risk Management Plan (RMP) for Australia.
- Clinical Overview, Summary of Biopharmaceutic Studies and Associated Analytical Methods, Summary of Clinical Pharmacology, Summary of Clinical Efficacy Advanced BCC, literature references, synopses of individual studies.

The clinical evaluation was undertaken using the comprehensive data provided., Studies are identified by the last letter and following four numerals (for example, Study CLDE225A2201 = Study A2201). The data package included only one, pivotal Phase II clinical efficacy and safety study in the proposed patient population.

Paediatric data

No paediatric data were submitted supporting the use of sonidegib in paediatric patients. The sponsor has a waiver from the European Medicines Agency (EMA) from having to submit a European Paediatric Investigation Plan (PIP). In addition, the sponsor has a full waiver from the Food and Drug Administration (FDA) from having to submit a Pediatric Assessment in the USA. In essence, the waivers have been granted on the basis that advanced BCC is limited to adult patients.

The sponsor's decision not to submit paediatric data is acceptable. It is considered that laBCC and mBCC are primarily diseases of adults, and that the occurrence of these conditions in a paediatric population would be very unusual.

Good clinical practice

The sponsor stated that all studies in the sonidegib BCC clinical development program have been conducted in full compliance with Good Clinical Practice (GCP).

Pharmacokinetics

Studies providing pharmacokinetic data

Healthy subjects

The oral pharmacokinetics (PK) of sonidegib were studied in four, Phase I studies in 238 healthy subjects detailed in the table below.

Table 5: Phase I oral PK studies in healthy volunteers

Study ID	Pharmacokinetic Objectives	N	Treatment
Phase I A2114	Food-effect Relative bioavailability	137 M 9 F	SC (USA), SD, PG study to estimate the relative bioavailability of three new FMI formulations versus capsule formulation, and the effects of food on sonidegib capsules - sonidegib 200, 600, 800, 1200, 1400 mg.

Study ID	Pharmacokinetic Objectives	N	Treatment
Phase I A2110	ADME Mass-balance	6 M	SC (Netherlands), SD, sonidegib 800 mg containing a tracer amount of radiolabelled (¹⁴ C)-sonidegib (~74kBq)
Phase I A2108	DDI - ketoconazole/sonidegib DDI - rifampicin/sonidegib	45 M 5 F	SC (USA) Arm 1 - sonidegib 800 mg, single-dose; Arm 2 - ketoconazole 200 mg bd for 2 weeks + sonidegib 800 mg, single-dose on Day 5; Arm 3 - rifampicin 600 mg qd for 2 weeks + sonidegib 800 mg, single-dose on Day 5
Phase I A1102	PK - Japanese subjects	36 M	SC (Japan), SD, DE - sonidegib 200, 400, 800 mg

Study Reports, PK = pharmacokinetics; ADME = absorption, distribution, metabolism, excretion; bd = twice daily; DDI = drug-drug interaction; SC = single-centre; SD = single-dose; FMI = final marketing image; DE = dose-escalation; M = male; F = female qd = once daily

Patients

The oral PK of sonidegib were studied in four Phase I/II studies in patients with advanced solid tumours, laBCC, mBCC, and nevoid basal cell carcinoma syndrome (NBCCS) (also known as Gorlin syndrome). The four studies are outlined below.

Table 6: Phase I/II studies in patients with cancer containing PK data

Study ID	Patients	Objectives	N	Treatment
A2201 Phase II	laBCC or mBCC	Efficacy, safety, PK-ECG data	143 M 86 F	Sonidegib 200 or 800 mg qd
X2101 Phase I	Advanced, solid tumours	MTD, safety, tolerability, PK, preliminary anti-tumour activity, PD.	63 M 40 F	Sonidegib 100, 200, 400, 800, 1000, 1500, or 3000 mg qd; or 250, 400, or 750 mg bd
X1101 Phase I	Advanced, solid tumours in Japanese patients.	MTD, safety, tolerability, PK, preliminary anti-tumour activity, PD.	8 M 13 F	Sonidegib 400 or 600 mg qd in 21 patients in Group 1 included in the submission; 800 mg qd in patients in Group 2 was on-going at the time of the submission
B2209 Phase II	NBCCS (Gorlin syndrome)	Efficacy, safety, PK.	4 M 4 F	Sonidegib 400 mg qd; 8 patients on active treatment (4 M, 4 F); placebo 2 patients (2 M). Study halted after a planned interim analysis failed to meet pre-specified efficacy endpoint.

PK = pharmacokinetics; PD = pharmacodynamics; MTD = maximum tolerated dose; laBCC = locally advanced basal cell carcinoma; mBCC = metastatic basal cell carcinoma; NBCCS = nevoid basal cell carcinoma syndrome; qd = once daily; bd = twice daily.

Pooled studies

In addition to the PK data from individual studies referred to above, the submission also included five pooled PK analyses from healthy subjects and/or patients. The pooled reports included the following analyses:

- Exposure versus Grade 3 or 4 creatine kinase (CK) elevations (exposure-CK);
- PK versus electrocardiogram (ECG) data (PK-QTc);
- potential ethnic differences between Japanese healthy subjects and healthy subjects in Western countries (PK ethnic sensitivity); and
- population PK (popPK) data.

In addition, an analysis of exposure versus confirmed best overall response, progression-free survival (PFS), and time to tumour response (TTR) was conducted using the pivotal Phase II data (exposure-efficacy) from Study A2201. The PK ethnic sensitivity and the popPK analyses was reviewed in the Pharmacokinetics section of the clinical evaluation report [not included with this AusPAR], while the PK-QTc, exposure-CK, and exposure-efficacy analyses was reviewed in the Pharmacodynamics section of the clinical evaluation report [not included with this AusPAR]. The five pooled analyses are outlined in the table below.

Table 7: Pooled analyses in healthy subjects/patients with cancer administered sonidegib

Analysis	Pooled studies	N *	Description of the analysis
PK-QTc	BCC patients (A2201, PK/ECG set); cancer patients (A2201, X2101, X1101, B2209); healthy subjects (A1102, A2108, A2110, A2114)	62 BCC 341 CA 204 HS	Effect of sonidegib on change from baseline in QTcF based on linear effects model.
Exposure-efficacy	BCC patients (A2201)	191	PK versus efficacy on best overall response, PFS, and TTR.
Exposure-CK	Cancer patients (A2201, X2101, X1101, B2209)	336	PK versus Grade 3 or 4 CK elevation
PopPK	Healthy subjects (A1102, A2114); cancer patients (A2201, X2101, X1101), including BCC patients	85 HS 351 CA	Structural PK model and error modes and covariate effects.
PK ethnic sensitivity	Healthy subjects (A1102, A2114)	61	Comparison of PK in healthy subjects - Japanese versus Western countries.

BCC = Basal cell carcinoma; CA = carcinoma; HS = healthy subjects; PK = pharmacokinetics; PopPK = population pharmacokinetics; CK = creatine kinase; PFS = progression free survival; TTR = time to tumour response; N * = number of subjects in the analysis set (could have been smaller than the total number of patients enrolled in individual studies); QTcF = QT corrected for heart rate according to formula of Fridericia

Human biomaterial studies

The submission included 16 human biomaterial reports relevant to the clinical pharmacokinetics of sonidegib. The evaluation of these reports is primarily a matter for the nonclinical evaluator.

Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated. The sponsor indicates that the clinical pharmacology studies were initiated before the decision was made to seek approval of sonidegib 200 mg qd for treatment of the proposed indication rather than sonidegib 800 mg qd. This decision was based on the results of the pivotal Phase II efficacy and safety Study A22010.

Evaluator's conclusions on pharmacokinetics

The submitted data have adequately characterised the pharmacokinetics of sonidegib in humans. However, the following deficiencies were identified in the submitted PK data: no absolute bioavailability study; no study investigating the effect of hepatic impairment on the pharmacokinetics of sonidegib; no study investigating the effect of renal impairment on the pharmacokinetics of sonidegib; no dedicated drug-drug interaction (DDI) study investigating the effect of protein pump inhibitors (PPIs) on the pharmacokinetics of sonidegib; no dedicated DDI studies investigating the effect of sonidegib on the pharmacokinetics of CYP2B6 or CYP2C9 substrates; and no dedicated DDI studies investigating the effect of sonidegib on substrates of BCRP-mediated efflux.

The sponsor submitted justifications for not submitting an absolute bioavailability study and a PK study investigating the effect of renal impairment on the pharmacokinetics of sonidegib. In addition, the sponsor indicated that dedicated DDI clinical studies to investigate the effects of hepatic impairment and co-administration of esomeprazole (PPI increasing gastric pH);¹⁵ on the pharmacokinetics of sonidegib, and to investigate the effects of co-administration of sonidegib on the pharmacokinetics of warfarin (CYP2B6 substrate) and bupropion (CYP2D6 substrate) were underway or planned at the submission date. No clinical DDI studies investigating the effect of sonidegib on substrates of BCRP-mediated efflux transport appear to be underway or planned.

In vitro human biomaterial studies report that sonidegib is absorbed by passive diffusion, is moderately to highly permeable, and is unlikely to be a substrate for the active gastrointestinal efflux transporters P-gp, MRP2 or BCRP. Sonidegib is poorly soluble in water. It has pH-dependent solubility *in vitro*, becoming poorly soluble as pH increases with a maximum solubility at pH 2. Based on its low solubility and moderate to high permeability sonidegib can be classified as a BCS class II compound.¹⁶

The submission included no absolute oral bioavailability study. The sponsor stated that such a study could not be undertaken in humans because sonidegib was insoluble in 'a large number of potential vehicles' making it impossible 'to prepare an IV injectable form of the drug. However, it is noted that an IV injectable solution was prepared for use in the nonclinical studies in intact animals (rat, dog, mini-pig), and it unclear why this solution was unsuitable for use in humans

In the absence of an absolute bioavailability study, the sponsor attempted to estimate the absolute oral bioavailability of sonidegib based on clinical data from Study A2110. This study showed that the mean absorption of sonidegib was 6% to 7% of a single oral dose of radiolabelled (¹⁴C)-sonidegib 800 mg in healthy male subjects (n = 6). In addition, data from Study A2114 showed that the AUC_{0-∞} and C_{max} values of sonidegib were 7.4 fold and 7.8 fold higher, respectively, in the fed state compared to the fasted state in healthy subjects (n = 12) following administration of a single 800 mg dose of sonidegib. Based on the AUC_{0-∞} data from Study A2114 the sponsor estimates that the maximum absolute oral bioavailability of sonidegib can be no higher than 14%. In the fasted state, the median T_{max}

¹⁵ pH = Negative logarithm of hydrogen ion concentration

¹⁶ Biopharmaceutical Classification System (BCS) Class II: A substance with high permeability and low solubility.

in both Study A2110 and Study A2114 was approximately 2 hours across the administered sonidegib single-dose range (200 mg to 1200 mg).

The bioavailability of an oral suspension of sonidegib 200 mg (single-dose) was 1.61 fold greater (based on $AUC_{0-\infty}$) relative to a sonidegib CSF capsule 200 mg (single-dose) identical to the final marketing image (FMI) formulation apart from the capsule shell not having an imprint (A2114). This result suggests that the sonidegib capsule proposed for marketing is not optimally formulated, most probably due to the low solubility of the solid form of the drug. The bioavailability of the sonidegib CSF capsule formulation was greater than the bioavailability of each of two tablet formulations, suggesting that the capsule formulation may be a preferable formulation for oral administration than either of the two tablet formulations used in Study A2114.

Food (high-fat) had a marked effect on the oral bioavailability of sonidegib (single-dose 800 mg, 4 x 200 mg CSF capsules). The $AUC_{0-\infty}$ and C_{max} values of sonidegib were 7.4 fold and 7.8 fold higher, respectively, when sonidegib was administered in the fed compared to the fasted state (A2114). The median T_{max} was 2.1 hours in the fasting state and increased to 5.0 hours in the fed state. The apparent clearance after oral administration (CL/F) of sonidegib was markedly lower in the fed compared to the fasted state (10.8 L/h versus 84.0 L/h, respectively), while the terminal half-life remained relatively constant in the fed and fasted states (290 hours versus 271 hours, respectively). The marked difference in exposure to sonidegib between the fasted and fed states support the sponsor's recommendation that sonidegib be administered on an empty stomach at the same time each day.

Exposure to sonidegib was less than dose proportional over the dose ranges tested. Following both single and multiple doses across the ranges of 100 mg to 3000 mg qd and 250 mg to 750 mg twice daily (bd) in patients with cancer (advanced solid tumours), a power model demonstrated less than dose proportional increases in C_{max} and AUC values (X2101). The popPK model steady-state exposure estimates in the total subject population were approximately 2 fold greater for the 800 mg qd dose compared to the 200 mg qd dose, indicating less than dose proportionality.

In the popPK model, the estimated geometric mean accumulation ratio based on the AUC_{0-24h} at steady state relative to Day 1 was 19.4 (% coefficient of variation (CV) = 109) in cancer patients and 5.68 (%CV = 104) in healthy volunteers. The ratios indicate that sonidegib undergoes substantial accumulation following repeated dosing, which is most likely to be a function of its long terminal half-life. The greater accumulation in cancer patients compared to healthy volunteers reflects the lower clearance in cancer patients than in healthy volunteers.

Sonidegib was extensively distributed into the extravascular tissues following oral administration. In the popPK model, the estimated apparent steady-state volume of distribution (V_{ss}/F) was 9166 L (%CV = 71.1%) in cancer patients and 8569 L (%CV = 97.9%) in healthy volunteers. In humans, sonidegib was highly bound to plasma proteins (> 97%), and was not concentration dependent over the range tested (1 to 2500 ng/mL at 37°C) (Report DMPK R0700955-03). *In vitro*, sonidegib strongly binds to both human serum albumin and human alpha1-acid glycoprotein (Report DMPK R1100368). The totality of the available *in vitro* human and animal data suggest that sonidegib has little or no distribution to red blood cells (DMPK R0700955-03). In patients with NBCCS (that is, Gorlin syndrome), sonidegib was shown to distribute to the skin following treatment with sonidegib 400 mg qd, and the steady-state level of sonidegib in the skin was 6 fold higher than in plasma (Study B2209).

In the absorption, distribution, metabolism and excretion (ADME) and mass balance study in healthy male subjects (n = 6), the elimination of absorbed sonidegib occurred almost exclusively by metabolism, and no unchanged sonidegib was detected in the urine

(Study A2110). Over the time period 0 to 540 hours following oral administration of a radioactively labelled single-dose of sonidegib (800 mg), total recovery of the radioactivity in the faeces and urine was approximately 93%, with the majority being recovered in the faeces (approximately 92%) and the small remainder being recovered in the urine (approximately 1.2%). Nearly all recovered sonidegib in the faeces was accounted for by unabsorbed sonidegib (approximately 89%), with metabolites of sonidegib accounting for the small remainder (approximately 3%). The sponsor estimates that if biliary elimination and/or direct intestinal secretion back into the intestinal lumen occur, then these mechanisms can account for no more than 12% of the unchanged sonidegib recovered in the faeces. The radioactivity recovered in the urine (approximately 1.2%) appears to be accounted for exclusively by metabolites of sonidegib as no unchanged sonidegib was detected in the urine.

The available data in humans indicate that sonidegib is predominantly eliminated by hepatic clearance, with renal clearance of the unchanged drug having a minimal role. Based on estimates of maximum absolute oral bioavailability of 6% (Study A2110) and 14% (Study A2114) the sponsor estimates that hepatic clearance is 10.2 L/h (That is, 10% of hepatic blood flow) and 23.8 L/h (That is, 24% of hepatic blood flow), respectively. These estimates are based on assumptions relating to the blood/plasma sonidegib concentration ratio, liver blood flow, and the average body weight of subjects in Study A2110. The estimated values for hepatic clearance are considered to be low to moderate, relative to hepatic blood flow, and suggest that sonidegib is unlikely to undergo significant first-pass hepatic clearance.

In the human biomaterial study (Report DMPK-R0800034), it was reported that that hepatic oxidative microsomal metabolism of sonidegib was primarily mediated by CYP3A4, and that sonidegib was not metabolized by CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP2J2, CYP4F2, or CYP4F12. Furthermore, the metabolism of sonidegib was reported not to be inhibited by CYP2D6, CYP1A2, CYP2C8, CYP2C9, or CYP2B6/CYP2C19 inhibitors. In addition, sonidegib was reported to be not metabolised by FMO1, FMO3 or FMO5.

The *in vivo* metabolism of sonidegib was assessed in the ADME study in healthy male subjects (Study A2110). In plasma, unchanged sonidegib was the major radiolabelled component, accounting for approximately 36.4% of the AUC_{0-504h} of radioactivity. The major circulating metabolite of the parent drug was the amide hydrolysis product M48 (LGE899), accounting for approximately 15.4% of the AUC_{0-504h} of radioactivity. Other circulating metabolites of note included the morpholine oxidation products M16 (LNC119) and M25 (LMT326) accounting together for approximately 14.1% of the AUC_{0-504h} of radioactivity, the morpholine dehydrogenation product M50 accounting for ~4% of the AUC_{0-504h} of radioactivity and the acyl glucuronide M47e accounted for ~ 3% of AUC_{0-504h} of radioactivity. Other identified metabolites in plasma accounted for < 3% of AUC_{0-504h} of radioactivity, and represented mainly products of oxidation in the morpholine part of the molecule. Unidentified metabolites in the plasma accounted for approximately 13.6% of the AUC_{0-504h} of radioactivity.

The metabolites of sonidegib identified in the faeces and urine over the 0 to 540 hour collection interval accounted for 3.2% and 1.2% of the oral dose, respectively (Study A2110). There were numerous metabolites identified in faeces, with the morpholine oxygenation product M31 being the most prominent (0.749% of dose in faeces 0 to 504 hours) followed by the morpholine dehydrogenation product M50 and the pyridine oxidation product M43 (LNM147). In the urine, the acyl glucuronide M47e (CMN964) metabolite accounted for most of the radioactivity in urine (0.908% of dose in urine 0 to 504 hours), while other metabolites were present in only trace amounts. Based on the metabolites identified in urine and faeces, the estimated contributions of the different classes of metabolic pathways to the total metabolic clearance of sonidegib can be

quantified as follows: 50% oxidation in morpholine part; 25% amide hydrolysis; 10% oxidation in pyridine part; and minor contributions by oxidations in the biphenyl part and by N-dearylation at the amide nitrogen. Less than 1% of the dose was accounted for by unidentified trace components.

The pharmacological activity of four human metabolites identified in plasma (LGE899, LMT326, LMV128, LNC119) were assessed in Study RD-2013-50348. The four metabolites were approximately 4 fold to 90 fold less active than the parent drug and represented less than 40% of sonidegib exposure. Therefore, the sponsor considers that the parent drug is the major contributor to the overall pharmacological activity of sonidegib.

The submitted data included limited PK data relating specifically to the target population of patients with advanced laBCC or mBCC treated with sonidegib 200 mg qd. The pivotal Phase II Study A2201 included PK data showing that steady-state sonidegib and LGE899 (metabolite) trough plasma concentration (C_{\min}) were obtained by Week 17 following administration of sonidegib 200 mg qd, with the geometric means (geometric CV%) being 689 ng/mL (64%) and 75 ng/mL (65%), respectively. The trough (C_{\min}) metabolite ratio for LGE899 (versus sonidegib) remained relatively stable during treatment, with geometric ratios for the 200 mg qd dose ranging from 0.16 to 0.24.

In the popPK analysis, the pharmacokinetics of sonidegib differed between cancer patients ($n = 351$) and healthy subjects ($n = 85$). In particular, the estimated geometric mean apparent clearance (CL/F) was 3.5 fold higher in healthy subjects compared to cancer patients (35.2 L/h versus 10.0 L/h, respectively), and the estimated geometric mean terminal half-life ($T_{1/2}$, beta) was notably shorter (8.65 days versus 28.3 days, respectively). In addition, the estimated time to reach 80% steady state was notably shorter in healthy subjects compared to cancer patients (18.3 days versus 63.6 days, respectively). The estimated geometric mean accumulation ratio (AUC_{0-24h}) was notably greater in patients with cancer compared to healthy subjects (19.4 versus 5.68, respectively). Overall, it appears that the difference in the PK parameters between cancer patients and healthy volunteers might be accounted for by a combination of factors including differences in (1) the content of the administered meals, (2) the relationship between meal-times and dosing, (3) the duration of dosing, (4) the mean age, and (5) baseline hepatic impairment.

The popPK analysis in cancer patients ($n = 351$) included an assessment of the effects of various covariate factors on exposure to sonidegib. Of the assessed factors, co-administered PPI/H2-antagonists and mild baseline hepatic impairment decreased sonidegib exposure (AUC_{0-24h}). The observed result for patients with hepatic impairment is paradoxical as it can be predicted that hepatic impairment will increase sonidegib exposure. The sponsor considers that confounding factors in the analysis of patients with mild hepatic impairment may have influenced the results. Covariate factors found not to have potentially clinically significant effects on sonidegib exposure (AUC_{0-24h}) in cancer patients included race (Japanese versus Caucasian), gender, body-weight, baseline renal function, and age (≥ 65 versus < 65 years).

In the popPK analysis, the CV% of steady-state sonidegib AUC_{0-24h} in patients on 200 mg qd was estimated to be 66%, while the CV% of steady state C_{\max} and C_{\min} were 62% and 69%, respectively. The results indicate that there is marked inter-subject variability in the steady-state PK parameters of sonidegib in cancer patients. There were no data on the intra-subject PK variability of sonidegib.

The clinical drug-drug interaction Study (A2108) in healthy subjects showed that exposure to sonidegib increased significantly when single-dose sonidegib 800 mg was co-administered with the CYP3A4 inhibitor ketoconazole 200 mg bd for 14 days (C_{\max} by 1.49 fold; AUC_{0-240h} by 2.25 fold) and decreased significantly when co-administered with the CYP3A4 inducer rifampicin 600 mg qd for 14 days (C_{\max} by 54%; AUC_{0-240h} by 72%). There

were no clinical data investigating the effects of the 200 mg dose of sonidegib on the PK of CYP3A4 inhibitors or inducers, but simulated data suggests that the effects of 200 mg are likely to be consistent with the effects of 800 mg observed in Study A2108. The results of Study A2108 indicate that co-administration of sonidegib and strong CYP3A4 inhibitors or strong CYP3A4 inducers should be avoided.

The human biomaterial studies indicated that, *in vitro*, sonidegib is a strong competitive inhibitor of both CYP2B6 and CYP2C9. No dedicated clinical studies investigating the PK effects of co-administration of sonidegib and substrates of these two CYP enzymes were submitted, but such studies are underway or planned. The co-administration of sonidegib with CYP2B6 or CYP2C9 substrates should be undertaken cautiously due to the potential for increased exposure to the substrates. The pop-PK analysis showed that co-administration of PPI/histamine receptor H₂-antagonists reduced the bioavailability of sonidegib, presumably due to increasing gastric pH thereby lowering the solubility and subsequent absorption of sonidegib. No dedicated clinical studies investigating the effects of co-administration of sonidegib and PPI/H₂-antagonists were submitted, but a study with the PPI esomeprazole is planned.

In the human biomaterial studies, sonidegib was reported not to be a time-dependent inhibitor of CYP1A2, CYP2C9, CYP2D6, or CYP3A4 enzymes (DMPK R0700986), nor was it reported to be an inducer of CYP1A2, CYP2B6, CYP2C9, or CYP3A4 enzymes (DMPK R1200636). In the human biomaterial studies, sonidegib was reported not to be an inhibitor of the OATP uptake transporters OATP1B1 and OATP1B3 (DMPK R1200563), the organic anion transporters (OAT) OAT1 and OAT3 (DMPK R1200564), or the organic cation transporters (OCT) OCT1 and OCT2 (DMPK R1200565).

In the human biomaterial studies, sonidegib was reported not to be a substrate for the active gastro-intestinal drug transporters P-gp, MRP2 or BCRP (DMPK R0700984, DMPK R1300665), nor to be an inhibitor of P-gp mediated efflux (DMPK R0700988) or MRP2-mediated efflux (DMPK R0800540) probe substrates. However, sonidegib was reported to inhibit BCRP-mediated efflux of a probe substrate, suggesting that sonidegib has the potential to inhibit BCRP *in vivo*. No clinical studies investigating the effects of co-administration of sonidegib and BCRP transporter substrates were submitted, and no information regarding planned studies could be identified in the submitted data package.

There were minor differences in the pharmacokinetics of sonidegib based on age, gender, and ethnicity (Japanese, Caucasian), but these differences are considered to be clinically insignificant. There were no significant differences in the pharmacokinetics of sonidegib based on weight.

Sonidegib may cause embryofetal death or severe birth defects when administered to pregnant women. The safety threshold for plasma sonidegib concentration based on an embryofetal development study in rabbits was defined as 3 pg/mL. Simulations from the full popPK model predicted that more than 95% of female patients will reach plasma levels below 3 pg/mL at 20 months after drug discontinuation. The sponsor states that women of child bearing potential must be instructed to use a highly effective method of contraception while taking sonidegib. In addition, contraception must be continued for 20 months after ending treatment. The sponsor is requested to comment on the possibility of women patients who wish to become pregnant 20 months after discontinuing treatment having their plasma sonidegib concentration measured prior to attempting to become pregnant.

Simulations from the full popPK model were also used to predict the medians and 90% prediction intervals of sonidegib concentrations in healthy female partners of male patients after use of condoms for 2, 6, 12, and 18 months post-drug discontinuation. After 2 months of condom use post-drug discontinuation after reaching steady-state sonidegib plasma concentrations, approximately 10% of healthy female partners were predicted to

have concentrations above 3 pg/mL and at 6 months post discontinuation < 5% of healthy female partners were predicted to have sonidegib concentrations above 3 pg/mL. Based on this recommendation the sponsor proposes that sexually active males being treated with sonidegib must use a condom, regardless of vasectomy status, during intercourse and for 6 months after ending treatment to prevent exposure of female sexual partners of child-bearing potential. The sponsor is requested to comment on the possibility of women who wish to become pregnant 6 months after their male partner discontinues treatment having their plasma sonidegib concentration measured prior to attempting to become pregnant.

Pharmacodynamics

Studies providing pharmacodynamic data

The submission included three reports providing pharmacodynamic (PD) data: a QT analysis report; an exposure-efficacy report; and an exposure-CK report.

PK-QTc relationship

Overview of submitted data

Non-clinical cardiovascular safety pharmacology studies did not show an increase in QTc;^{4,14} or an increase in cardiovascular toxicity at plasma concentrations up to 25 fold higher than those anticipated at steady-state in patients taking 200 mg qd. The sponsor did not undertake a 'thorough QT/QTc study meeting the relevant TGA adopted guideline relating to the clinical evaluation of QT/QTc interval prolongation and pro-arrhythmic potential for non-antiarrhythmic drugs (CHMP/ICH/2/04)'. The sponsor commented that multiple-dose administration of sonidegib in healthy volunteers would not be ethical due to the adverse drug reactions observed after multiple-dose administration in cancer patients (for example, muscle symptoms with or without CK elevation). Furthermore, the sponsor notes that, despite the 7 fold increase in exposure with food, a single dose administered with a high-fat meal to healthy volunteers cannot cover the entire exposure range observed in cancer patients due to drug accumulation following multiple-dose administration. Therefore, reproducing the upper range of steady-state exposure of sonidegib observed in cancer patients after repeated 200 mg qd doses is not feasible with a single-dose in healthy volunteers. Conducting a 'thorough QT/QTc study' in healthy volunteers at exposures lower than the steady-state exposure expected in cancer patients would not allow meaningful assessment of the QT prolongation risk. It is considered that the sponsor's justification for not undertaking a 'thorough QT/QTc study' is reasonable.

Exposure-efficacy report

Overview

The submission included an Exposure-efficacy Report dated 01 April 2014. The report included an analysis of the exposure-efficacy relationship using Week 5 sonidegib C_{min} data from the pivotal Phase II Study A2201 as the exposure measure and the confirmed objective response rate (ORR), progression-free survival (PFS), and time to tumour response (TTR) as the efficacy measures.

The exposure-efficacy analyses were reported in the PK/FAS;¹⁷ (n = 191) and the PK/pEAS;¹⁸ (n = 141). In the pivotal Study A2201, the protocol specified primary analysis population was the pEAS and the protocol specified supportive analysis population was the FAS. The pEAS and the FAS populations in the pivotal study are discussed later in this

¹⁷ FAS = full analysis set

¹⁸ pEAS = Primary efficacy analysis set

CER. The median age of the patients in the PK/FAS was 64.9 years (range: 24.0, 92.0) and in the PK/pEAS was 66.4 years (range: 24.0, 90.0).

The PK/FAS analysis set included all patients in the full analysis set (FAS) with a Week 5 (W5) evaluable trough concentration (C_{min}). The FAS included all patients who had been assigned study treatment, regardless of whether or not they had received the study drug. A C_{min} value was evaluable if the patient had taken the same sonidegib dose for at least 15 consecutive days prior to the PK sample, did not vomit within 4 hours of drug administration on the day prior to the PK sample, and the concentration did not meet exclusion criteria.

Exposure-CK report

Overview

The submission included an exposure-CK report, dated 1 April 2014, analysing the relationship between sonidegib plasma exposure and occurrence of Grade 3 or 4 CK elevations in pooled data from four cancer patient studies (Studies A2201, X2101, X1101, and B2209). The analyses used logistic regression models with addition of pre-specified covariates in the final model, if identified as being significant in preliminary models.

The analysis was undertaken in the PK/CK data set, which included 336 cancer patient pooled from the four studies. The demographic characteristics of these 336 patients were similar to those for 341 patients from the same four studies included in pooled PK/ECG analysis set described above. The PK/CK analysis set included all patients with at least one post-dose CK assessment and at least one of the following exposure parameters: Cycle 1 Day 15 AUC_{0-24h} (that is, C1D15 AUC); C1D15 C_{max} ; or C2D1 C_{min} .

The endpoint used for the analysis was the occurrence of a CK elevation of Grade ≥ 3 (using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03) over the course of the study, defined as yes or no. The CTCAE V4.03 CK criteria are as follows: Grade 0 \leq upper limit of normal (ULN); Grade 1 $>$ ULN to 2.5 x ULN; Grade 2 $>$ 2.5 to 5 x ULN; Grade 3 $>$ 5 to 10 x ULN; Grade 4 $>$ 10 x ULN.

CK elevations were determined from the laboratory test, not from reported adverse events. CK assessments $>$ 30 days after the last dose of the study drug were excluded. Each patient had only one endpoint for this analysis (CK \geq Grade 3, yes or no) occurring during the study and \leq 30 days after the last dose. For patients with Grade 3 or 4 CK elevation, the time to the first Grade 3 or 4 CK elevation (in days) was determined from the start of continuous qd or bd dosing (that is, excluding the PK run-in period in Studies X2101 and X1101). In addition, for all patients the grade of the baseline CK assessment (if available) and grade of the worst post-dose CK assessment were determined.

Evaluator's conclusions on pharmacodynamics

No clinically significant effect was observed on the QTcF;¹⁹ interval at the proposed sonidegib dose of 200 mg qd. The PK-QTcF relationship was investigated using central tendency analysis on data from the pivotal Phase II Study A2201, PK- Δ QTcF modelling in the PK-ECG subgroup in the pivotal Phase II Study A2201, PK- Δ QTcF modelling in pooled data from four studies in cancer patients, and PK- Δ QTcF modelling in pooled data from four studies in healthy volunteers. The analytical methods were well described and are well known and accepted techniques for assessing the effect of medicines on the QTcF interval. The results were consistent for the different analytical methods used and are considered to be reliable. A 'thorough QT/QTc' study in healthy volunteers meeting the

¹⁹ QTcF = QT corrected for heart rate according to formula of Fridericia

relevant TGA adopted guideline;²⁰ was not undertaken. The justification provided by the sponsor for not undertaking such a study is considered to be acceptable.

No exposure-efficacy relationship was observed for sonidegib 200 mg qd and 800 mg qd on ORR, PFS, or TTR in the PK/FAS and PK/pEAS data from the pivotal Phase II Study A2201. Logistic regression modelling (W5 C_{min} versus ORR), Cox regression modelling (W5 C_{min} versus PFS), and Kaplan-Meier plots (W5 versus time to event endpoints) were used to investigate the exposure-efficacy relationship. The statistical methods are standard for analyses of the type undertaken and were well described. The results were consistent for each of the outcomes tested and are considered to be reliable.

There was a positive relationship between Grade 3 or 4 CK elevations and exposure (C1D15 AUC, C1D15 C_{max} , and C2D1 C_{min}). The risk of experiencing a Grade 3 or 4 CK elevation was notably greater with the 800 mg qd dose of sonidegib compared to the 200 mg qd dose. In the C2D1 C_{min} analysis, sex was identified as a risk factor for Grade 3 or 4 CK elevation with a lower risk for female patients than for male patients. The relationship between Grade 3 or 4 elevation and exposure was investigated using logistic regression models incorporating pre-specified co-variates (if identified as being significant). The statistical methods are standard for analyses of the type undertaken and were well described. The results were consistent for each of the relationships tested and are considered to be reliable.

Dosage selection for the pivotal studies

The submission included one, pivotal Phase II clinical efficacy and safety Study A2201. The sonidegib doses selected for the pivotal study were 200 mg qd and 800 mg qd.

Information presented in for Study A2201 and the Clinical Overview indicates that the sonidegib doses selected for the pivotal study were based on data from Study X2101.

Study X2101 was a Phase I, multi-national, multi-centre, open-label, dose-escalation trial in patients with advanced solid tumours sponsored, undertaken from 06 April 2009 to 20 February 2012. The primary objective of the study was to determine the maximum tolerated dose (MTD) of single agent sonidegib when administered orally qd 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.

A total of 103 patients were enrolled in the study at the following dosages: 6 at 100 mg qd; 6 at 200 mg qd; 5 at 400 mg qd; 26 at 800 mg qd; 11 at 1000 mg qd; 9 at 1500 mg qd; 10 at 3000 mg qd; 14 at 250 mg bd; 8 at 400 mg bd; and 8 at 750 mg bd. The MTDs for sonidegib were 800 mg qd and 250 mg bd. The MTDs were based on the Bayesian logistic regression model (BLRM) used during the dose-escalation phase for dose level selection and determination of the MTD, and review of safety data by the investigators and Novartis personnel.

Four (4) dose limiting toxicities (DLTs) occurred in 1 patient in the 800 mg qd group (4.8% (1/21)) in Cycle 1; 1 x AST increased, 1 x CK increased, 1 x CK/MB increased, and 1 x myoglobin increased. No DLTs occurred in the 250 mg bd group (0/12) in Cycle 1. Grade 3 or 4 CK elevations were not observed with 800 mg qd or 250 mg bd. No DLTs or Grade 3 or 4 CK elevations were observed in the 200 mg qd group (0/6).

The PK data (single-dose) at C1D15 demonstrated that the mean \pm standard deviation (SD) C_{max} values for 200 mg bd, 250 mg bd and 800 mg bd were 269 ± 163 ng/mL, 807 ± 353 ng/mL, and 840 ± 457 ng/mL, respectively, and the mean \pm SD AUC_{0-24h} values were 5916 ± 3886 ng.hr/mL, 12781 ± 6351 ng.hr/mL, and 14495 ± 4781 ng.hr/mL,

²⁰ CHMP/ICH/2/04 Note for guidance on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for nonantiarrhythmic drugs

respectively. The mean \pm SD steady state C_{\min} values for 800 mg qd and 250 mg bd were similar (1050 ± 788 and 1159 ± 567 ng/mL, respectively). There were no steady-state data in this study for the 200 mg qd dose.

The two doses selected for the pivotal Phase II trial were 200 mg qd and 800 mg qd. In the Clinical Overview (Dose-selection rationale) it is stated that the clinical data from Study X2101 suggested that 'sonidegib doses of ≥ 200 mg/day, which had demonstrated antitumor activity in the rat and medulloblastoma (MB) efficacy model, were also associated with preliminary antitumor activity in recurrent MB and advanced BCC. The 200-mg once-daily regimen was selected for evaluation in the registration study on the basis that it represented the lowest dose level tested that demonstrated evidence of antitumor activity (with exposure in the predicted efficacious range). The highest, well-tolerated, biologically-active dose of sonidegib was 800 mg, administered once daily on a continuous-dosing schedule. Twice-daily dosing was not associated with a clinically significant advantage over once-daily administration, resulting in higher systemic exposure relative to the equivalent once-daily regimen and an increased tendency to cause dose-limiting toxicities (DLTs). Steady-state AUC was 18 to 30% higher with 400 mg and 750 mg bid dosing than with the equivalent once daily dose'. Overall, the clinical rationale for selecting the dosage used in the pivotal Phase II Study A2201 is considered to be reasonable.

Efficacy

Studies providing efficacy data

Study A2201; pivotal efficacy study

Study design, objectives, locations and dates

The pivotal study is an ongoing, Phase II, randomised, double-blind study of the efficacy and safety of two doses of sonidegib (200 mg qd and 800 mg qd) in patients with locally advanced basal cell carcinoma (laBCC) or metastatic basal cell carcinoma (mBCC). The study included 230 randomised patients (194 with laBCC and 36 with mBCC), randomised 1:2 to sonidegib 200 mg qd ($n = 79$) or 800 mg qd ($n = 151$).

The study was undertaken in 58 enrolling centres in 12 countries: Australia (2 centres), Belgium (2 centres), Canada (2 centres), France (5 centres), Germany (10 centres), Greece (1 centre), Hungary (2 centres), Italy (1 centre), Spain (3 centres), Switzerland (3 centres), United Kingdom (7 centres), and the United States (21 centres). The first patient visit was on 20 July 2011 and the data cut-off date for the efficacy analysis was 28 June 2013 (that is after all patients had reached the Week 24 visit or had discontinued from the study). The full clinical study report (CSR) study provided in the submission is dated 3 April 2014.

The study is sponsored by the sponsor in the USA. The study is being conducted in compliance with Good Clinical Practice (GCP), including the archiving of essential documents, and according to the ethical principles of the Declaration of Helsinki. The study protocol and all amendments have been reviewed by an Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for each enrolling centre. Informed consent in writing was obtained from each patient before any protocol specified procedures were conducted.

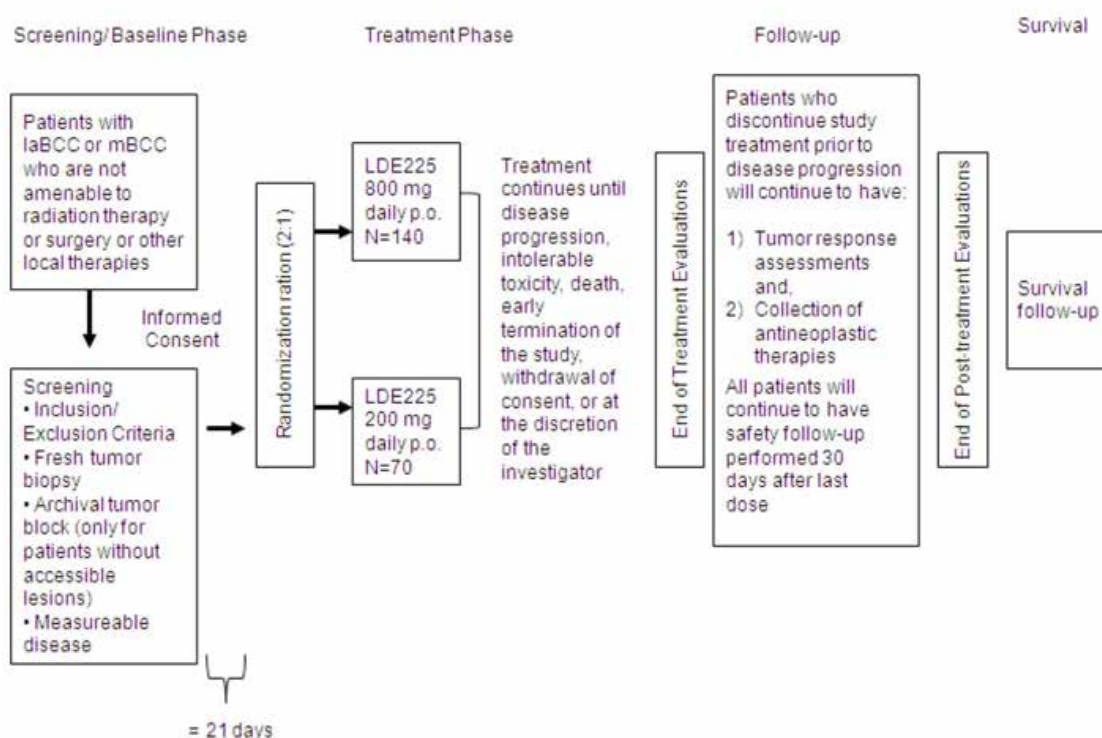
Objectives

The primary objective was to evaluate the efficacy of sonidegib as measured by the objective response rate (ORR) assessed by central review according to modified Response Evaluation Criteria in Solid Tumours (mRECIST) in patients with laBCC, and Response Evaluation Criteria in Solid Tumours 1.1 (RECIST 1.1) in patients with mBCC.

The key secondary objectives were to determine the duration of objective tumour response (DoR) and the rate of complete response (CR) as assessed by central review according to mRECIST in patients with laBCC and according to RECIST 1.1 in patients with mBCC. There were a large number of other secondary objectives, and a smaller number of exploratory objectives.

The pivotal study was a multicentre, adaptive, randomised, double-blind, Phase II efficacy and safety study designed to evaluate two doses of sonidegib for the treatment of patients with laBCC or mBCC. Eligible patients were randomly assigned in a 1:2 ratio to treatment with sonidegib 200 mg or sonidegib 800 mg on a continuous once-daily (qd) dosing schedule. The study design is presented schematically in the Figure 2 below.

Figure 2: Schematic of the study design (Study A2201)



Screening/Baseline assessments (including baseline radiological assessments) were performed ≤ 21 days after study enrolment. During the treatment phase, assessments were undertaken every 2 weeks from Week 1 to Week 17 (inclusive), and then every 4 weeks from Week 17 to Week 157 (inclusive), then every 12 weeks from Week 169 onwards. Visits occurring ± 3 days from the scheduled visit dates were not considered to be protocol deviations. Study treatment continued until disease progression, intolerable toxicity, withdrawal of consent, death, or at the discretion of the investigator. The end of treatment visit was scheduled within 21 days after the decision to discontinue treatment. Following progression, or after study treatment discontinuation, patients were followed every 3 months for survival. However, tumour evaluations were not to exceed 12 months after discontinuation of treatment. Tumour evaluations were allowed for patients who discontinued treatment due to adverse events until disease progression.

Evaluator's conclusions on efficacy

The efficacy data supporting the proposed indication at the proposed dose is limited to one, ongoing, pivotal Phase II, multinational, multicentre, randomised, double-blind, uncontrolled Study A2201. The absence of a control arm in the pivotal study introduces a

degree of uncertainty to the interpretation of the efficacy data. It is accepted that an appropriate active control arm for treatment of the proposed indication was not available at the time of protocol development and initiation of the pivotal study. However, in the absence of a suitable active-control it is considered that it would have been reasonable to have designed and undertaken a placebo-controlled study.

The study included 230 patients, 79 randomised to sonidegib 200 mg qd and 151 randomized to 800 mg qd. The number of patients treated with the proposed dose of 200 mg qd for the proposed indication is limited to 79 patients treated for a median of 8.9 months (range: 1.3, 21.4). The study randomised patients in a 2:1 ratio to 800 mg qd (n = 151) and 200 mg qd (n = 79) on the assumption that the higher dose would be more efficacious than the lower dose. However, the efficacy data showed that the observed differences between the two doses were not clinically meaningful, while the safety data of the 200 mg qd dose was stated by the sponsor to offer 'a more manageable safety profile' than the 800 mg qd dose. Therefore, the sponsor is seeking approval of the 200 mg qd dose for the proposed indication, but not the 800 mg qd dose.

Of the 230 randomised patients, 194 had laBCC (66 (200 mg qd), 128 (800 mg qd)) and 36 had mBCC (13 (200 mg qd), 23 (800 mg qd)). The PI indicates that 16 patients had a diagnosis of Gorlin syndrome (15 laBCC, 1 mBCC). The sponsor has been requested to confirm the number of patients with Gorlin Syndrome in the pivotal study.

ORR results pivotal study (primary efficacy endpoint)

The protocol specified primary efficacy endpoint in the pivotal study was the ORR, per central using mRECIST for laBCC and RECIST 1.1 for mBCC, undertaken when all patients had been treated for at least 24 weeks or had discontinued treatment. The protocol specified that the primary analysis was in the pEAS and the supportive analysis was in the FAS.

In the pEAS, the confirmed ORR via central review in all patients in the 200 mg qd treatment arm was 36.4% (20/55) (95% confidence interval (CI): 23.8, 50.4), and 33.6% (39/116) (95% CI: 25.1, 43.0) in the 800 mg qd treatment arm; $\Delta = -2.7\%$ (95% CI: -18.73, 12.45).

In the FAS, the confirmed ORR via central review in all patients in the 200 mg qd treatment arm was 41.8% (33/79) (95% CI: 30.8, 53.4), and 32.5% (49/151) (95% CI: 25.1, 40.5) in the 800 mg qd treatment arm; $\Delta = -9.3\%$ (95% CI: -22.77, 3.93).

In both the pEAS and the FAS, the result for both treatment arms met the pre-specified threshold criteria for clinical relevance of point-estimate for the ORR of $\geq 30\%$ with lower bound 95% CI of $\geq 20\%$. However, while the ORR for laBCC patients met the clinical relevance criteria for both treatment arms in both the pEAS and the FAS, the ORR for mBCC failed to meet the clinical relevance criteria for both treatment arms. The sponsor states that potential explanations for the lower response rates in patients with mBCC include the heterogeneity and aggressiveness of the disease, the extent of tumour burden, and the location of the metastatic lesions.

In the pEAS, waterfall plots showed that 96.9% and 94.6% of evaluable patients with laBCC experienced a reduction in tumor size in the 200 mg qd and 800 mg qd treatment arms, respectively, based on photographic evaluation. In the pEAS, waterfall plots showed that 91.7% and 84.2% of evaluable patients with mBCC experienced a reduction in tumour size in the 200 mg qd and 800 mg qd treatment arms, respectively, based on any imaging modality. In the FAS, corresponding waterfall plots showed that 92.3% and 90.1% of evaluable patients with laBCC experienced a reduction in tumour size in the 200 mg qd and 800 mg qd treatment arms, respectively, and 91.7% and 84.2% of evaluable patients with mBCC experienced a reduction in tumor size in the 200 mg qd and 800 mg qd treatment arms, respectively.

Secondary efficacy endpoint analyses of the ORR per investigator assessment in the pEAS and FAS were supportive of the corresponding results observed for the ORR per central review. The ORRs were higher per investigator assessment than per central review in both the pEAS and FAS. The agreement rates between the investigator and the central review were moderate for both analysis sets.

Results for key secondary efficacy endpoints (duration of response and complete remission rate) in the pivotal study

The median DoR times per central review in both the pEAS (primary analysis) were not-estimable in responders in the laBCC, mBCC, and all patient groups treated with 200 mg qd. In the pEAS, the percentage of responders censored in the laBCC, mBCC, and all patient groups were 83.3% (15/18), 100% (2/2) and 85.0% (17/20), respectively, in the 200 mg qd treatment arm. The event-free probability for the DoR at 12 months was not-estimable for the laBCC, mBCC, and all patient groups in the 200 mg qd treatment arm. It is difficult to meaningfully interpret the DoR data in the absence of an appropriate control arm.

The complete response rate (CRR) per central review in the 200 mg treatment arm in the pEAS (primary analysis) in the laBCC, mBCC and all patient groups was 4.8% (2/42) (95% CI: 0.6, 16.2), 0%, and 3.6% (2/55) (95% CI: 0.4, 12.5), respectively. The CRR values per central review in both the pEAS and FAS were low for the 200 mg qd treatment arm. The sponsor attributes the low CRR to a number of factors including, stringent response criteria for complete histological clearance with laBCC, the magnitude of the lesions at baseline, and the high proportion of patients in the mBCC cohort with distant metastases. However, the sponsor considers that the overall disease control rates (CR+PR+SD)²¹ were strongly indicative of treatment benefit despite the low CRRs (that is, 92.7% (51/55) and 91.1% (72/79) per central review in all patients in the 200 mg qd treatment arm, pEAS and FAS, respectively).

Secondary efficacy endpoints of regulatory interest (progression free survival and overall survival) in the pivotal study

The median PFS per central review in the 200 mg qd treatment arm for the pEAS was not-estimable for the laBCC patient group and 13.1 (95% CI: 5.6, 13.1) months for the mBCC patient group, with respective censoring rates of 88.1% (37/42) and 69.2% (9/14). The estimated event-free probability at 12 months was 83.6% (95% CI: 58.9, 94.1) in the laBCC group and 64.9% (95% CI: 24.9, 87.4) in the mBCC group in the 200 mg qd treatment arm.

The median overall survival (OS) in all patients in the FAS was not-estimable in both the 200 mg qd and 800 mg qd treatment arms at the cut-off date of 28 June 2013. Death due to any cause was reported in 2.5% (2/79) patients in the 200 mg treatment arm and 6.0% (9/151) of patients in the 800 mg treatment arm. In the 200 mg qd treatment arm, the median OS values in the laBCC and mBCC patient groups were not-estimable, and 1 death was reported in the laBCC patient group (1.5%, 1/66) and 1 death was reported in the mBCC patient group (7.7%, 1/13). In the 800 mg qd treatment arm, the median OS values in the laBCC and mBCC patient groups were not-estimable, and 7 deaths were reported in the laBCC patient group (5.5%, 7/128) and 2 deaths were reported in the mBCC patient group (8.7%, 2/23).

Results for the pre-planned sensitivity analysis from the pivotal study

The pivotal study included a pre-planned sensitivity analysis in laBCC patients, applying similar methodology to that used in the vismodegib Erivance trial. In the laBCC group treated with sonidegib 200 mg qd, different mRECIST definitions used in the sensitivity analysis compared to the primary analysis resulting in higher numbers of patients with an overall objective response and a complete response being reported in the sensitivity

²¹ CR+PR+SD = complete response + partial response + stable disease

analysis compared to the primary analysis. Consequently, in laBCC patients treated with sonidegib 200 mg qd, both the ORR and the CRR were notably higher in the sensitivity analysis compared to the primary analysis (for example, in the pEAS the respective ORRs were 52.4% (22/42) and 42.9% (18/42), and the respective CRRs were 16.7% (7/4) and 4.8% (2/42)). In the mBCC group treated with sonidegib 200 mg qd, the same response RECIST 1.1 criteria were used for both analyses and, consequently, the results of the sensitivity and primary analyses were identical. The results of the sensitivity analyses in the pEAS and the FAS for sonidegib 200 mg qd and vismodegib 150 mg qd are summarised below.

Table 8: Clinical Overview; Best overall response from the sonidegib sensitivity analysis and the vismodegib trial (Erivance), per central review and independent review, respectively

	Sonidegib 200 mg		Vismodegib 150 mg	
	laBCC N=42	mBCC N=13	laBCC N=63	mBCC N=33
Primary efficacy analysis set (pEAS)				
Objective response rate, n (%)	22 (52.4)	2 (15.4)	27 (42.9)	10 (30.3)
95% CI	(36.4, 68.0)	(1.9, 45.4)	(30.5, 56.0)	(15.6, 48.2)
Best overall response, n (%)				
Complete response	7 (16.7)	0	13 (20.6)	0
Partial response	15 (35.7)	2 (15.4)	14 (22.2)	10 (30.3)
Disease stabilization	17 (40.5)	10 (76.9)	24 (38.1)	21 (63.6)
Disease progression	0	0	8 (12.7)	1 (3.0)
Unknown	3 (7.1)	1 (7.7)	0	0
Missing	0	0	4 (6.3)	1 (3.0)
	laBCC N=66	mBCC N=13	laBCC N=71	mBCC N=33
Full analysis set (FAS)				
Objective response rate, n (%)	36 (54.5)	2 (15.4)	27 (38.0)	10 (30.3)
95% CI	(41.8, 66.9)	(1.9, 45.4)	(26.8, 50.3)	(15.6, 48.7)
Best overall response, n (%)				
Complete response	10 (15.2)	0	13 (18.3)	0
Partial response	26 (39.4)	2 (15.4)	14 (19.7)	10 (30.3)
Disease stabilization	24 (36.4)	10 (76.9)	Unavailable	Unavailable
Disease progression	1 (1.5)	0	Unavailable	Unavailable
Unknown	5 (7.6)	1 (7.7)	Unavailable	Unavailable

Pre-planned sensitivity analysis applying the methodology used for the Erivance study

Results for cross-study comparison provided in the clinical overview

The submission included a cross-study comparison of the results from Study A2201 for patients treated with sonidegib 200 mg qd and the results of the registration study for vismodegib 150 mg qd. The results of the cross-study comparison suggest that, based on the ORR, sonidegib 200 mg qd is likely to be at least as efficacious as vismodegib 150 mg qd in patients with laBCC and less efficacious in patients with mBCC.

Safety

Studies providing safety data

The submission included an integrated Summary of Clinical Safety (SCS). The key safety data in this summary were based on 293 patients from three studies identified as the pooled data set (Studies A2201 and X2101) and the supportive data (Study X1101). The SCS pool included all available safety data in adult patients from Studies A2201 and X2101. The safety data from Study X1101 was not included in this pool due to differences in study design, the patient population treated, and the potential differences in the tolerability of sonidegib in Japanese patients.

Table 9: Clinical studies including in the summary of safety; 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

The SCS pool included safety data on 272 patients who received ≥ 1 dose of study drug, 229 patients from Study A2201 and 43 patients from Study X2101. Therefore, as 84.2% (229/272) of the total number of patients in the SCS pool is derived from the pivotal Phase II Study A2101, the evaluation of safety in the clinical evaluation report [not included with this AusPAR] primarily focuses on the safety data from the pivotal study. Overall, the safety data from the SCS pool provided no significant additional information to that provided from the pivotal Study A2201. In addition, safety data from 21 Japanese patients from Study X1101 have been examined, but are considered to add no additional information to that provided from the 229 predominantly Caucasian patients in the pivotal Study A2201.

Pivotal Study A2201; clinical safety data

Safety assessments

The safety set (n = 229) included all patients who received at least one dose of study drug. Safety assessments consisted of regular monitoring and recording all adverse events (AE), including serious adverse events (SAE), laboratory haematology parameters, laboratory clinical chemistry parameters, and ECGs, and the routine monitoring of vital signs and physical condition. Approximately 60 patients (identified sequentially at enrollment) underwent additional ECG evaluations at Week 17.

AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology (version 16.1) and toxicity was assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03. The occurrence of AEs was sought by non-directive questioning of the patient at each visit during the study and 30 days after the last dose of study drug. AEs could also be volunteered by the patient during and between visits, or identified through physical examination, laboratory test results, or other assessments.

Laboratory assessments were undertaken by a central laboratory. Central laboratory results were used to determine patient eligibility for the study, to randomise the patient, and to make dose adjustment decisions (except in medical emergencies where local laboratory results could be used). Abnormal laboratory values or test results constituted AEs only if they fulfilled at least one of the following criteria: induced clinical signs or symptoms; considered to be clinically significant; required concomitant therapy or procedures; or required changes in study treatment.

Patient exposure

Patients received treatment with sonidegib 200 mg qd (as 1 x 200 mg capsule + 3 matching placebo capsules) or sonidegib 800 mg qd (as 4 x 200 mg capsules). Dose modifications and delays for suspected treatment-related toxicities were allowed. The duration of exposure of patients in the safety set is summarised below.

Table 10: Study A2201; Duration of exposure (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		
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

The mean \pm SD actual dose intensities were 180.7 ± 34.30 mg/day (range: 27.5, 246.6 mg/day) in the 200 mg qd treatment arm and 678.2 ± 283.91 mg/day (range: 237.2, 3500.0 mg/day) in the 800 mg/day treatment arm. The corresponding mean \pm SD relative dose intensities were $90.3 \pm 17.5\%$ and $84.8 \pm 35.49\%$ for the 200 mg qd and 800 mg qd treatment arms, respectively. The percentage of patients with relative dose intensities $> 90\%$ was 72.2% ($n = 57$) and 52.7% ($n = 79$) in the 200 mg qd and 800 mg qd treatment arms, respectively. The cumulative dose, dose intensity, and relative dose intensity data for the safety set are summarised in Table 11.

Table 11: Study A2201; Cumulative dose, dose intensity, and relative dose intensity of study drug (safety set)

Exposure variable	Sonidegib 200 mg N=79	Sonidegib 800 mg N=150
Cumulative dose (mg)^a		
n	79	148 ^b
Mean (standard deviation)	50973.0 (24897)	148288.0 (107413)
Median	45200.0	126900.0
Minimum, maximum	8200.0, 129657.0	12800.0, 454400.0
Average daily dose (mg)^c		
n	79	148 ^b
Mean (standard deviation)	184.7 (32.72)	717.1 (273.19)
Median	198.1	781.4
Minimum, maximum	28.1, 246.6	249.7, 3500.0 ^d
Actual dose intensity (mg/day)^e		
n	79	148 ^b
Mean (standard deviation)	180.7 (34.30)	678.2 (283.91)
Median	194.3	734.7
Minimum, maximum	27.5, 246.6	237.2, 3500.0
Relative dose intensity (%)^f		
n	79	148 ^b
Mean (standard deviation)	90.3 (17.15)	84.8 (35.49)
Median	97.2	91.8
Minimum, maximum	13.8, 123.3	29.6, 437.5
Relative dose intensity, n (%)^g		
<70	9 (11.4)	42 (28.0)
70-90	13 (16.5)	27 (18.0)
>90	57 (72.2)	79 (52.7)

^a Cumulative dose = total of active dose taken during the study.

^b Exposure data for 2 patients cannot be summarized due to missing drug accountability data.

^c Average daily dose = cumulative dose / number of dosing days, drug free day(s) are not counted.

^d Maximum value is erroneous; this resulted from a discrepancy between the drug accountability and dose administration records

^e Actual dose intensity (DI) = cumulative dose / duration of exposure

^f Relative dose intensity (%) = (DI/PDI)*100. Planned dose intensity (PDI) is 200 mg per day or 800 mg per day based on the treatment group.

^g Relative dose intensity = (Cumulative dose (mg)/Duration of exposure (day))/(Cumulative planned dose (mg)/Duration of exposure (day))*100.

Planned dose intensity (PDI) is 200 mg per day or 800 mg per day based on the treatment arm

Dose reductions were reported in 13.9% (n = 11) of patients in the 200 mg qd treatment arm compared to 30.0% (n = 45) of patients in the 800 mg qd treatment arm. Dose interruption were reported in 62.0% (n = 49) of patients in the 200 mg qd treatment arm compared to 60.7% (n = 91) of patients in the 800 mg qd treatment arm. AEs were the most common reason for dose interruption, and were reported in 27.8% (n = 22) and 44.0% (n = 22) of patients in the 200 mg qd and 800 mg qd treatment arms, respectively. Dose errors were also reported frequently in both the 200 mg qd and 800 mg qd treatment arms, 27.8% (n = 22) and 28.0% (n = 42), respectively. Dosing errors were typically attributed to single doses of the study drug being missed.

Based on the 'rule of threes', the safety set of 229 exposed patients is sufficient to detect adverse drug reactions occurring with an incidence of $\geq 1.3\%$ with 95% certainty. However, the safety set is too small to reliably detect adverse drug reactions occurring with an incidence of $\leq 1\%$ (that is, uncommon, rare and very rare adverse drug reactions according to CIOMS III conventions). The median duration of exposure in the sonidegib 200 mg qd treatment arm was 8.9 months compared to 6.5 months in the 800 mg qd treatment arm. This shorter exposure in the 800 mg qd treatment arm was attributed to early discontinuation as the result of AEs and not to progressive disease. In the sonidegib 200 mg qd treatment arm, 43 patients (54.4%) were exposed for ≥ 8 months and 21 patients (26.6%) for ≥ 12 months. In the sonidegib 800 mg qd treatment arm, 55 patients (36.7%) were exposed for ≥ 8 months and 28 patients (18.7%) for ≥ 12 months.

Laboratory tests

Haematology

Haematological abnormalities of any grade occurred less commonly in the 200 mg qd treatment arm than in the 800 mg qd treatment arm, and nearly all commonly occurring haematological abnormalities were Grade 1/2 events in both treatment arms. The two most commonly occurring haematological abnormalities reported in $\geq 20\%$ of patients in both treatment arms were decreased haemoglobin levels and decreased lymphocyte count. The results for selected haematology abnormalities are summarised below.

Table 12: Study A2201; Selected haematology abnormalities (worst value on study) (safety set)

Laboratory parameter	Sonidegib 200 mg N=79		Sonidegib 800 mg N=150	
	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)

Table 13: Study A2201; Shift tables for haemoglobin (decreased) and lymphocytes (decreased) in the sonidegib 200 mg qd treatment arm (n = 79) (safety set)

Haemoglobin decreased								
Treatment	Baseline	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Sonidegib 200 mg (N=79)	Grade 0	65 (82.3)	57 (87.7)	5 (7.7)	3 (4.6)	0	0	0
	Grade 1	12 (15.2)	2 (16.7)	10 (83.3)	0	0	0	0
	Grade 2	2 (2.5)	0	1 (50.0)	1 (50.0)	0	0	0
	Total	79 (100.0)	59 (74.7)	16 (20.3)	4 (5.1)	0	0	0

Lymphocytes decreased								
Treatment	Baseline	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Sonidegib 200 mg (N=79)	Grade 0	71 (89.9)	58 (81.7)	9 (12.7)	3 (4.2)	1 (1.4)	0	0
	Grade 1	6 (7.6)	2 (33.3)	2 (33.3)	2 (33.3)	0	0	0
	Grade 2	2 (2.5)	0	0	2 (100.)	0	0	0
	Total	79 (100.0)	60 (75.9)	11 (13.9)	7 (8.9)	1 (1.3)	0	0

Clinical chemistry

At least one clinical chemistry abnormality was reported in nearly all patients in both treatment arms. In the sonidegib 200 mg qd treatment arm clinical chemistry abnormalities reported in $\geq 20\%$ of patients were increased serum creatinine levels (92.4%), increased cholesterol levels (70.9%), increased CK levels (57.0%), increased glucose levels (46.8%), increased lipase level (39.2%), decreased magnesium levels (31.6%), increased calcium levels (20.3%), and decreased glucose levels (20.3%). In the 200 mg qd treatment arm, increased ALT and AST levels were reported in 17.7% and 15.2% of patients, respectively, and increased alkaline phosphatase levels were reported in 17.7% of patients. Increased amylase levels were reported in 13.9% of patients of patients in the 200 mg qd treatment arm. The results for selected clinical chemistry abnormalities are summarised below.

Table 14: Study A2110; Selected clinical chemistry abnormalities (worst value on study) (safety set)

Laboratory parameter	Sonidegib 200 mg N=79		Sonidegib 800 mg N=150	
	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)

Table 15: Study A2201; Shift tables for selected clinical chemistry abnormalities in the sonidegib 200 mg qd treatment arm (n = 79) (safety set)

Parameter	Shift tables							
	Baseline	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Creatinine increased	Grade 0	72 (91.1)	4 (5.6)	67 (93.1)	1 (1.4)	0	0	0
	Grade 1	7 (8.9)	2 (28.6)	4 (57.1)	1 (14.3)	0	0	0
	Total	79 (100.0)	6 (7.6)	71 (89.9)	2 (2.5)	0	0	0
Cholesterol increased	Grade 0	40 (50.6)	23 (57.5)	17 (42.5)	0	0	0	0
	Grade 1	38 (48.1)	0	31 (81.6)	7 (18.4)	0	0	0
	Grade 2	1 (1.3)	0	1 (100.0)	0	0	0	0
	Total	79 (100.0)	23 (29.1)	49 (62.0)	7 (8.9)	0	0	0
Glucose increased	Grade 0	65 (82.3)	40 (61.5)	23 (35.4)	2 (3.1)	0	0	0
	Grade 1	7 (8.9)	2 (28.6)	4 (57.1)	1 (14.3)	0	0	0
	Grade 2	6 (7.6)	0	2 (33.3)	2 (33.3)	2 (33.3)	0	0
	Grade 3	1 (1.3)	0	0	0	1 (100.0)	0	0
	Total	79 (100.0)	42 (53.2)	29 (36.7)	5 (6.3)	3 (3.8)	0	0
CK increased	Grade 0	71 (89.9)	32 (45.1)	28 (39.4)	7 (9.9)	3 (4.2)	1 (1.4)	
	Grade 1	3 (3.8)	1 (33.3)	2 (66.7)	0	0	0	
	Missing	5 (6.3)	1 (20.0)	2 (40.0)	1 (20.0)	0	1 (20.0)	
	Total	79 (100.0)	34 (43.0)	32 (40.5)	8 (10.1)	3 (3.8)	2 (2.5)	
Lipase increased	Grade 0	75 (94.9)	47 (62.7)	15 (20.0)	6 (8.0)	6 (8.0)	1 (1.3)	0
	Grade 1	1 (1.3)	1 (100.0)	0	0	0	0	0
	Grade 2	2 (2.5)	0	0	0	2 (100.0)	0	0
	Grade 3	1 (1.3)	0	1 (100.0)	0	0	0	0
	Total	79 (100.0)	48 (60.8)	16 (20.3)	6 (7.6)	8 (10.1)	1 (1.3)	0

Increased serum creatinine levels (all grades) were reported in 92.4% and 92.7% of patients in the sonidegib 200 mg qd mg and 800 mg qd treatment arms, respectively. The Clinical Overview notes that further evaluation revealed that the high percentages resulted from the implementation of the CTCAE guidance (Version 4.03), where the definition of Grade 1 includes any increase from baseline to > 1 to 1.5 fold. Consequently, for many patients post-treatment serum creatinine levels would still be within the normal range for this parameter. The Clinical Overview also notes that no intervention was required for the high serum creatinine levels.

In the 200 mg qd treatment arm, of the 72 patients with baseline creatinine Grade 0, 4 (5.6%) remained at Grade 0, 67 (93.1%) shifted to Grade 1, 1 shifted to Grade 2 and no patients shifted to Grade 3 or Grade 4. Of the 7 (8.9%) patients with baseline creatinine Grade 1, 6 (28.6%) shifted to down to Grade 0, 4 (57.1%) remained at Grade 1, 1 shifted to Grade 2, and no patients shifted to Grade 3 or 4. The sponsor is requested to provide baseline and post-baseline mean, median and ranges for serum creatine levels for patients in the 200 mg and 800 mg qd treatment arms.

Review of the System Organ Class (SOC) 'renal and urinary disorders' (irrespective of causality) identifies 8 (10.1%) patients in the 200 mg qd treatment arm with an event (all Grade 1/2) and 14 (9.3%) patients in the 800 mg qd treatment arm with at least one event (2 (1.3%) patients with Grade 3/4 events). In the 8 patients in the 200 mg qd treatment arm, the 'renal and urinary disorders' AEs were haematuria (n = 3, 3.8%), chromaturia (n = 2, 2.5%), dysuria (n = 2, 2.5%), pollakiuria (n = 2, 1.3%), and renal failure (n = 1, 1.3%). In the 14 patients in the 800 mg treatment arm, the 'renal and urinary disorders' were pollakiuria (n = 4, 2.7%), acute renal failure (n = 2, 1.3%), haematuria (n = 2, 1.3%), nocturia (n = 2, 1.3%), and 1 (0.7%) each for toxic nephropathy, dysuria, renal impairment, renal pain, urinary incontinence, and urinary retention.

Vital signs, physical findings, and other safety related observations

Vital signs and weight change

No appreciable change in mean systolic or diastolic blood pressure was recorded at any time during the study in either treatment group. In the 200 mg qd treatment arm, weight loss of $\geq 10\%$ from baseline was reported in no patients (0/7) exposed for < 4 months, 10.3% (3/29) of patients exposed for 4 to < 8 months, 22.7% (5/22) of patients exposed for 8 to < 12 months, and 23.8% (5/21) of patients exposed for ≥ 12 months.

Electrocardiogram (ECG)

The results of the PK/QTc analysis undertaken in approximately 60 patients at Week 17 have been discussed in the Pharmacodynamics section of this AusPAR. The results discussed below relate to the safety set (n = 229).

In the safety data, no AEs with preferred terms of 'electrocardiogram QT prolonged' or 'torsades de pointes' were reported in patients in either the 200 mg qd or 800 mg qd treatment arms. No Grade 3/4 AEs or SAEs of QT prolongation were reported in either treatment arm. No cardiac abnormalities of note were reported at the time an abnormal QTc interval was noted on ECG. No action in relation to the study drug was needed, and no patient discontinued study drug as a result of QTc prolongation.

Three (3) patients in the 800 mg qd treatment arm experienced a post-baseline QTcF > 480 ms, 1 of whom also had a post-baseline QTcF > 500 ms. One (1) patient in the 200 mg qd treatment arm experienced a post-baseline QTcF > 500 ms. No associated cardiac-related AEs were reported in either of the patients with post-baseline QTcF prolongations > 500 ms. Increases from baseline > 30 ms were reported in 7.6% of patients in the 200 mg qd group and 14.4% of patients in the 800 mg qd group. No increases from baseline in QTcF > 60 ms were observed in either treatment arm. Other ECG abnormalities, most notably sinus bradycardia, ST-T depression, and T-wave changes, were also observed. Although the frequencies of some ECG abnormalities were relatively high, the clinical significance of these events is unclear as the incidence of severe cardiac events was low. In the 200 mg qd treatment arm there were 5 (6.3%) patients reporting cardiac disorders, including 1 patient with a Grade 3 event (atrial fibrillation) with all other events being Grade 1/2. In the 800 mg qd treatment arm there were 20 patients (13.3%) reporting cardiac disorders, with 4 patients reporting Grade 3/4 events (1 each for angina pectoris, atrial fibrillation, bradycardia, left bundle branch block, congestive cardiac failure).

In order to better understand potential associations between ECG abnormalities, cardiac events, and sonidegib, the sponsor reported that the safety database was reviewed and all patients with an ECG abnormality at any time on study and all reported cardiac events at any time on study were evaluated. The sponsor stated that no apparent trends were observed, and cardiac events were found in isolated cases only.

It is not clear from the study report whether the investigation of the torsades de pointes/QT prolongation referred to MedDRA Standardised MedDRA Query (SMQ) results. The sponsor should clarify this matter.

Other safety related topics

Muscle-related toxicities

The sponsor considers that muscle-related AEs reported in patients treated with sonidegib represent the most important clinical issue identified in the pivotal Study A2201. In the 200 mg qd treatment arm, AEs of CK increased (all grades) were reported in 29.1% (n = 23) of patients in the 200 mg qd treatment arm, including 6.3% (n = 5) of patients with Grade 3/4 CK increases. In the 800 mg qd treatment arm, AEs of CK increased (all grades) were reported in 37.3% (n = 56) of patients, including 12.7%

(n = 19) of patients with Grade 3/4 increases. In the 200 mg qd treatment arm, rhabdomyolysis was reported in 1 (1.3%) patient while in the 800 mg qd treatment arm rhabdomyolysis was reported in 5 (3.3%) patients.

In June 2013, a case of rhabdomyolysis with associated renal failure was reported with sonidegib in an on-going drug-drug interaction Study A2112. As a result, the sponsor reviewed all AE reports involving muscle symptoms in 938 subjects (313 healthy volunteers and 625 patients) treated with sonidegib as of 15 August 2013. The search included the broader SMQ for rhabdomyolysis, the preferred term 'muscle spasms, plus all-grade CK elevations.

Furthermore, the sponsor convened an Independent Safety Review and Adjudication Committee consisting of three independent experts to: review all safety data with muscle events across the sonidegib program, including rhabdomyolysis and CK elevations of all grades, with/without muscle symptoms and with/without renal impairment, based on a safety pooling analysis across the sonidegib program; provide a clear definition of rhabdomyolysis; confirm or adjudicate cases (if any) with rhabdomyolysis; characterize the population at risk of muscular toxicity; and recommend measures for patient management and risk mitigation. The Committee's report was dated 25 November 2013.

Following an initial review of the data, the Committee determined that the focus of the review should be on patients with reported CK elevations > 10 x ULN or reported cases of rhabdomyolysis, taking into account prior medical history and confounding factors. The Committee considered that low-grade CK elevation were not associated with an increased risk of muscular events and, therefore, decided not to adjudicate these cases. The Committee reviewed cases for muscle-associated symptoms (subsequently defined as myalgia, muscle spasms or cramps, and myopathy (muscle weakness)) and muscle injury attributed to CK elevation. The committee also reviewed the association between cases of CK elevation and hospitalisations for intravenous hydration, acute renal failure and death. The Committee identified 53 patients meeting its criteria for review.

The Committee restricted the term rhabdomyolysis to its 'clinical application' of CK elevation > 10 fold the pre-treatment or baseline level associated with a 1.5 fold increase in serum creatinine from baseline. Of the 53 patients evaluated by the Committee, only 1 patient had a case of rhabdomyolysis meeting the definition. The investigator-reported cases of rhabdomyolysis identified in the pivotal Study A2201 were not confirmed by the Committee, based on the Committee's definition of rhabdomyolysis. However, the Committee acknowledged that the use of IV hydration in patients in the pivotal study with CK elevations may have prevented impending rhabdomyolysis. In the one investigator-reported case of rhabdomyolysis in the 200 mg qd treatment arm, the patient did not experience further Grade \geq 2 muscle-related AEs following treatment interruption and re-challenge with the same dose. Of the 5 patients in the 800 mg qd treatment arm with investigator-reported cases of rhabdomyolysis, only 1 patient discontinued treatment due to CK elevation.

The Committee identified that the majority of patients with sonidegib induced muscle injury experienced symptoms, most often muscle spasms or cramps, preceding the elevated CK levels. However, in some cases CK elevation was not preceded by muscle symptoms, and these cases were defined by the Committee as 'asymptomatic myositis'. Of the cases of CK elevation reviewed by the Committee, about 60 percent received hydration or were hospitalized for IV hydration symptoms or had documented myoglobinuria. The Committee devised a treatment algorithm to minimise the risk of serious muscle-related acute renal injury associated with sonidegib, and this algorithm has been included by the sponsor in the proposed PI.

Secondary malignancies

Seven (7) cases of squamous-cell carcinoma (including 1 case of Bowen's disease) were reported in the pivotal study: 3 (3.8%) patients in the 200 mg qd treatment arm and 4 (2.7%) in patients in the 800 mg qd treatment arm. Other secondary malignancies reported in the study included 2 cases of malignant melanoma, 2 cases of prostate cancer, and single cases of B-cell lymphoma, brain neoplasm, transitional cell carcinoma, lung neoplasm, nasal neoplasm, and vulval cancer. The sponsor reported that no obvious pattern was evident with regard to timing or type of malignancy. The significance of the secondary malignancies has not yet been established. Overall, the SOC of 'neoplasms benign, malignant and unspecified (including cysts and polyps)' were reported in a total of 22 (9.6%) patients, including 8 (10.1%) patients in the 200 mg qd treatment arm and 14 (9.3%) patients in the 800 mg qd treatment arm.

Safety issues with the potential for major regulatory impact

Liver toxicity

The available evidence from the pivotal Study A2201 suggests that sonidegib 200 mg qd is unlikely to be hepatotoxic in the proposed patient population. In patients treated with 200 mg qd, the SOC of 'hepatobiliary disorders' included only 1 (1.3%) patient with 1 AE (biliary duct stone). In the SOC of 'investigations' in patients treated with 200 mg qd, the AE of ALT increased was reported in 1 (1.3%) patient (Grade 3), the AE of AST increased was reported in 1 (1.3%) patient (Grade 3), the AE of alkaline phosphatase increased was reported in 1 (1.3%) patient (Grade 1), the AE of gamma-glutamyl transferase increase was reported in 1 patient (Grade 1), and there were no reports of the AE of total bilirubin increased.

In patients treated with 200 mg qd, clinical chemistry abnormalities (laboratory tests) included 14 (17.7%) patients with ALT increased (including 2 (2.5%) with Grade 3/4 events), 12 (15.2%) patients with AST increased (including 2 (2.5%) with Grade 3/4 events), 14 (7.7%) patients with alkaline phosphatase increased (all Grade 1/2 events), and 5 (6.3%) patients with bilirubin increased (all Grade 1).

Renal toxicity

The available evidence from the pivotal Study A2201 suggests that sonidegib 200 mg qd is unlikely to demonstrate renal toxicity in the proposed patient population. The significance of the high proportion of patients in the pivotal study with post-baseline increased serum creatinine levels has been discussed above.

Haematological toxicity

The available evidence from the pivotal Study A2201 suggests that sonidegib 200 mg qd is unlikely to demonstrate haematological toxicity in the proposed patient population. Shifts in haematological parameters (clinical laboratory) have been discussed above and do not give rise to concern. In the 200 mg qd treatment arm, anaemia and iron deficiency anaemia were reported as AEs (irrespective of causality) in 2 patients (1 x Grade 1, 1 x Grade 2) and 1 patient (1 x Grade 1), respectively. There were no other 'blood and lymphatic disorders' (SOC) reported in the 200 mg qd treatment arm.

Serious skin reactions

In the pivotal Study A2201, 'skin and subcutaneous tissues disorders' (SOC) were reported in 64.6% (n = 51) of patients in the 200 mg qd treatment arm. There were 36 (45.6%) patients with Grade 1 events, 14 (17.7%) patients with Grade 2 events, and 1 (1.3%) patient with a Grade 3 event. The most commonly reported events ($\geq 2\%$ of patients) in decreasing order of frequency were alopecia (43.0%, n = 34), pruritus (6.3%, n = 5), hyperhidrosis (3.8%, n = 3), madarosis (3.8%, n = 3), rash (2.5%, n = 2), papule (2.5%,

n = 2), hair colour changes (2.5%, n = 2), and hair growth abnormal (2.5%, n = 2). The one Grade 3 event was alopecia. There were no reports of Stevens-Johnson syndrome or toxic epidermal necrolysis in either the 200 mg qd or 800 mg qd treatment arms.

Cardiovascular safety

The available evidence from the pivotal Study A2201 suggests that sonidegib 200 mg qd is unlikely to be causally associated with adverse cardiovascular events in the proposed patient population. Available data indicate that sonidegib is not associated with QT prolongation, and no case of QT prolongation with clinically relevant consequences has been reported. No cases of ventricular arrhythmia or torsades de pointes and no deaths associated with QT prolongation have been reported in the sonidegib clinical development program.

No clinically relevant effects were seen on the QTcF interval in patients in the 200 mg qd or 800 mg qd treatment arms in the pivotal study. No cases of 'electrocardiogram QT prolonged or 'torsades de pointes' (as preferred terms) were reported in either treatment group in the pivotal study. No clinically significant risks of QTc prolongation were identified in the PK-QT analysis at therapeutic or supra-therapeutic exposures to sonidegib.

In the pivotal Study A2201, 'cardiac disorders' (SOC) were reported in 5 (6.3%) patients in the 200 mg qd treatment arm, and consisted of one AE each of atrial fibrillation, angina pectoris, AV block first degree, sinus arrhythmia, sinus bradycardia, and supra ventricular extrasystole. 'Vascular disorders' (SOC) were reported in 11 (13.9%) patients in the 200 mg qd treatment arm, and the only AEs occurring in ≥ 2 patients were hypertension (n = 5, 6.3%) and hypotension (n = 2, 2.5%). All other AEs in this treatment group were reported once only.

Unwanted immunological events

There were no 'immune disorders' (SOC) reported in the pivotal Study A2201 in patients in the sonidegib 200 mg qd treatment arm, while the AE of seasonal allergy was reported in 3 (2.0%) patients in the 800 mg qd treatment arm. No cases of anaphylaxis or angioedema have been reported in the sonidegib clinical development program.

Other safety issues

Safety in special populations

Age

The SCS included a comparison of AEs (irrespective of causality) with an incidence of at least 10% in both the sonidegib 200 mg qd and 800 mg qd treatment arms by age group (< 65 years and ≥ 65 years) from the pivotal Study A2201.

AEs (irrespective of causality) in patients treated with 200 mg qd were reported in 90.6% of patients < 65 years and 97.9% of patients ≥ 65 years. AEs (irrespective of causality) reported in $\geq 20\%$ of patients in either age group (< 65 years (n = 32) versus ≥ 65 (n = 47) years) in the 200 mg qd treatment arm, by decreasing order of frequency in the younger age group were: muscle spasms (53.1% versus 46.8%); dysgeusia (40.6% versus 36.2%); alopecia (37.5% versus 46.8%); CK increased (37.5% versus 23.4%); nausea (28.1% versus 36.2%); fatigue (28.1% versus 29.8%); headache (25.0% versus 8.5%); myalgia (25.0% versus 14.9%); diarrhoea (18.8% versus 27.7%); and decreased appetite (15.6% versus 21.3%).

In the pivotal study, AEs (irrespective of causality) reported more commonly ($\geq 10\%$) in patients aged < 65 compared to patients aged ≥ 65 years in the 200 mg qd treatment arm were: CK increased (37.5% versus 23.4%, $\Delta = 14.1\%$); headache (25.0% versus 8.5%, $\Delta = 16.5\%$); and myalgia (25.0% versus 14.9%, $\Delta = 10.1\%$). In the pivotal study, no AEs

(irrespective of causality) in the 200 mg qd treatment arm were reported more commonly ($\geq 10\%$) in patients aged ≥ 65 years compared to patient aged < 65 years.

It is considered that the observed differences in the AE profiles (irrespective of causality) of patients aged < 65 years compared to patients aged ≥ 65 years in the 200 mg qd treatment arm do not warrant dosage adjustment based on age.

Sex

The SCS included a comparison of AEs (irrespective of causality) with an incidence of at least 10% in both the sonidegib 200 mg qd and 800 mg qd treatment arms by sex from the pivotal Study A2201.

AEs (irrespective of causality) in patients treated with 200 mg qd were reported in 91.7% of males and 100% of females. AEs (all causality) reported in $\geq 20\%$ of patients by sex (males (n = 48) versus females (n = 31)) in the 200 mg qd treatment arm, by decreasing order of frequency in males were: muscle spasms (52.1% versus 45.2%); CK increased (35.4% versus 19.4%); dysgeusia (35.4% versus 41.9%); alopecia (33.3% versus 58.1%); fatigue (29.2% versus 29.0%); nausea (25.0% versus 45.2%); diarrhoea (22.9% versus 25.8%); weight decreased (20.8% versus 35.5%); decreased appetite (20.8% versus 16.1%); myalgia (16.7% versus 22.6%); and arthralgia (6.3% versus 22.6%).

In the pivotal study, there was one AE (irrespective of causality) reported more commonly ($\geq 10\%$) in males compared to females treated with sonidegib 200 mg qd (CK increased 35.4% versus 19.4%, $\Delta = 20.0\%$). In the pivotal study, AEs (irrespective of causality) reported more commonly ($\geq 10\%$) in females compared to males treated with 200 mg qd were: alopecia (58.1% versus 33.3%, $\Delta = 24.8\%$); nausea (45.2% versus 25.0%; $\Delta = 20.2\%$); weight decreased (35.5% versus 20.8%, $\Delta = 14.7\%$); and arthralgia (22.6% versus 6.3%, $\Delta = 16.3\%$).

In the pivotal study, commonly reported AEs (irrespective of causality) occurred notably more commonly in females than in males in the 200 mg qd treatment arm. However, it is considered that the observed differences in the AE profiles do not warrant dosage adjustment based on sex.

Race

The SCS included a comparison of AEs (irrespective of causality) with an incidence of at least 10% in both the sonidegib 200 mg qd and 800 mg qd treatment arms race (Caucasian versus non-Caucasian) from the pivotal Study A2201.

It is considered that the imbalance in patient numbers between the two racial groups in the 200 mg qd treatment arm is too large to allow meaningful comparison (that is the, number of Caucasian patients approximately 9 fold greater than non-Caucasian patients (n = 71 versus n = 8, respectively)).

Geographical region

The SCS included a comparison of AEs (irrespective of causality) in three different geographical regions in both the sonidegib 200 mg qd and 800 mg qd treatment arms from the pivotal Study A2201. In the 200 mg qd treatment arm, the number of patients from Australia (n = 5) was considered to be too small to allow meaningful comparison with patients from Europe (n = 45) and North America (n = 29).

AEs (irrespective of causality) in patients treated with 200 mg qd were reported in 91.1% of patients in the European region and 100% of patients from the North American region. AEs (irrespective of causality) reported in $\geq 20\%$ of patients from either region (Europe (n = 45) versus North America (n = 29)), treated with 200 mg qd, by decreasing order of frequency in the European group were: alopecia (51.1% versus 24.1%); muscle spasms (51.1% versus 48.3%); dysgeusia (44.4% versus 31.0%); weight decreased (33.3% versus 17.2%); fatigue (31.1% versus 24.1%); diarrhoea (26.7% versus 20.7%); nausea (26.7%

versus 48.3%); headache (24.4% versus 3.4%); CK increased (22.2% versus 37.9%); decreased appetite (20.0% versus 20.7%); myalgia (20.0% versus 10.3%)

There were some differences in the AEs profiles between patients treated and European sites and patients treated at US sites in the 200 mg qd treatment arm. However, the differences are considered not to be clinically meaningful.

laBCC compared to mBCC

The SCS included a comparison of AEs (irrespective of causality) in the laBCC and mBCC groups in both the sonidegib 200 mg qd and sonidegib 800 mg qd treatment arms from the pivotal Study A2201.

In the sonidegib 200 mg qd treatment arm, AEs were reported in 93.9% (62/66) of patients with laBCC and 100% (13/13) of patients with mBCC. AEs (irrespective of causality) reported in $\geq 20\%$ of patients in either strata (laBCC versus mBCC) in the 200 mg qd treatment arm, by descending order of frequency in the laBCC group were: muscle spasms (50.0% versus 46.2%); alopecia (43.9% versus 38.5%); dysgeusia (40.9% versus 23.1%); nausea (31.8% versus 38.5%); CK increased (27.3% versus 38.5%); fatigue (27.3% versus 38.5%); weight decreased (27.3% versus 23.1%); diarrhoea (21.2% versus 38.5%); myalgia (18.2% versus 23.1%); and decreased appetite (13.6 versus 46.2%).

Commonly occurring AEs (irrespective of causality) in the 200 mg qd treatment arm reported more frequently ($\geq 10\%$) in patients with laBCC than in patients with mBCC were dysgeusia, cough, and hypertension. Commonly reported AEs (irrespective of causality) in the 200 mg qd treatment arm occurring more frequently ($\geq 10\%$) in patients with mBCC than in patients with laBCC were CK increased, fatigue, diarrhoea, decreased appetite, back pain, musculoskeletal pain, paraesthesia, and hyperhidrosis.

Pregnancy and lactation

The Summary of Clinical Safety reports that, in animal studies, sonidegib was embryotoxic, fetotoxic and teratogenic. The drug also inhibited fertility in female rats, but not in male rats. There were no data on excretion of sonidegib in human breast milk.

Safety related to drug-drug interactions

Muscle toxicity

The pivotal Phase II Study A2201 excluded patients who were receiving drugs recognized to cause rhabdomyolysis. However, if it was essential that the patient stay on a statin to control hyperlipidaemia, pravastatin could be used 'with extra caution'. Consequently, the study included limited data on muscle symptoms and CK elevations in patients who had taken statins in combination with sonidegib. The results for the analysis in the sonidegib 200 mg qd treatment arm are summarised in the table below.

Table 16: Study A2201; Statins and muscle symptoms and CK elevations (safety set)

Adverse Event		On any statin (n=8)	Not on a statin (n=71)	Pravastatin (n=5)	On other statins (n=3)
Muscle symptoms	All grades	5 (62.5%)	42 (59.2%)	5 (100%)	1 (33.3%)
	Grade 3-4	0	3 (4.2%)	0	0
CK elevation	All grades	5 (62.5%)	40 (56.3%)	3 (60.0%)	2 (66.7%)
	Grade 3-4	0	5 (7.0%)	0	0

The sponsor comments that 'an analysis of patient taking statin in conjunction with sonidegib has shown no difference in muscle-related symptoms or Grade 3 or 4 CK elevation compared to those not on statins'. However, it is considered that the data relating to muscle symptoms and CK elevations with co-administered sonidegib 200 mg qd and statins are too limited to conclude that the two drugs can be safely used in combination for the proposed indication.

Increased exposure of sonidegib resulting from DDI interactions

Sonidegib is primarily metabolized by CYP3A4. The PK DDI data indicated that co-administration of sonidegib with strong CYP3A4 inhibitors should be avoided due to the risk of increased systemic exposure to sonidegib.

Post marketing data

Not applicable to this submission.

Evaluator's overall conclusions on clinical safety

The safety profile of sonidegib for the proposed indication is based on one pivotal Study A2201 in which 229 patients were exposed to the drug, including 79 exposed to the proposed dose of 200 mg qd for a median duration of 8.9 months (range: 1.3, 21.4) and 150 exposed to 800 mg qd for a median duration of 6.5 months (range: 0.1, 19.1). There were no long-term safety data in the submission. In the 200 mg qd treatment arm (n = 79), 43 patients (54.4%) were exposed for ≥ 8 months and 21 (26.6%) patients were exposed for ≥ 12 months. In the 800 mg qd treatment arm (n = 150), 55 patients (36.7%) were exposed for ≥ 8 months and 28 (18.7%) patients were exposed for ≥ 12 months. The safety profile of sonidegib 200 mg qd was notably superior to sonidegib 800 mg qd, but significant safety concerns are still associated with the lower dose. The conclusions on the clinical safety of sonidegib for the treatment of the proposed indication discussed below focuses on the sonidegib 200 mg qd treatment arm from the pivotal Study A2201.

Nearly all patients in the 200 mg qd treatment arm experienced at least one AE irrespective of causality (94.9%, n = 75), and nearly all patients (86.1%, n = 68) had at least one AE that was suspected by investigators to be related to treatment with the study drug. AEs (irrespective of causality) were primarily Grade 1/2 events, with Grade 3/4 events being reported in 30.4% (n = 24) of patients. AEs suspected to be related to the study were primarily Grade 1/2 events, with Grade 3/4 events being reported in 22.8% (n = 18) of patients.

In the 200 mg qd treatment arm, the most commonly occurring AEs (irrespective of causality) reported in $\geq 20\%$ of patients in descending order of frequency were muscle spasms (49.4%), alopecia (43.0%), dysgeusia (38.0%), nausea (23.9%), CK increased (29.1%), fatigue (29.1%), weight decreased (26.6%), and diarrhoea (24.1%). The most commonly occurring Grade 3/4 events (irrespective of causality) reported in $\geq 2\%$ of patients in the 200 mg qd treatment arm in descending order of frequency were CK increased (6.3%), lipase increased (5.1%), muscle spasms (2.5%), asthenia (2.5%), and hypertension (2.5%).

AEs of special interest (irrespective of causality) reported in $\geq 20\%$ of patients in the 200 mg qd treatment arm in decreasing order of frequency were muscle-related (myopathy/rhabdomyolysis) (63.3%, n = 53), alopecia (46.8%, n = 37), nausea and/or vomiting (43.0%, n = 34), decreased appetite and/or weight loss (38.0%, n = 30), dysgeusia (38.0%, n = 30), fatigue (asthenia)/lethargy (36.7%, n = 29), and diarrhoea (24.1%, n = 19). AEs of special interest (irrespective of causality) in the 200 mg qd treatment arm were predominantly Grade 1/2 events, with Grade 3/4 events reported in $\geq 2\%$ of patients being muscle-related (8.9%, n = 7), nausea and/or vomiting (3.8%, n = 3), and fatigue (asthenia)/lethargy (2.5%, n = 2). Nearly all of the patients in the 200 mg qd treatment arm group had at least one AE of special interest that was suspected by investigators to be related to the study drug.

The total number of patients in the 200 mg qd treatment arm discontinuing to due to AEs (irrespective of causality) was 17 (21%), including 14 (18%) patients discontinuing due to AEs of special interest. AEs of special interest (irrespective of causality) leading to

treatment discontinuation in the 200 mg qd treatment arm were muscle-related (4 patients, 5.1%), decreased appetite and/or weight loss (3 patients, 3.8%), nausea and/or vomiting (2 patients, 2.5%), dysgeusia (2 patients, 2.5%), fatigue (asthenia)/lethargy (2 patients, 2.5%), and alopecia (1 patient, 1.3%).

In the 200 mg qd treatment arm, 31.6% (n = 25) of patients required dose adjustment and/or temporary dose interruption to manage AEs. The most commonly occurring AEs (irrespective of causality) requiring dose adjustment and/or temporary dose interruption reported in $\geq 2\%$ of patients in the 200 mg qd treatment group in decreasing order of frequency were CK increased (6.3%), lipase increased (5.1%), nausea (3.8%), diarrhoea (2.5%), fatigue (2.5%), and viral gastroenteritis (2.5%).

In the 200 mg qd treatment arm, 83.5% (n = 66) of patients had AEs (irrespective of causality) requiring additional medications or therapies. The most commonly occurring AEs (irrespective of causality) requiring additional medications or therapies reported in $\geq 5\%$ of patients in the 200 mg qd treatment arm in decreasing order of frequency were muscle spasms (20.4%), diarrhoea (13.9%), nausea (12.7%), headache (12.7%), urinary tract infection (7.6%), pneumonia (6.3%), arthralgia (6.3%), hypertension (6.3%), decreased appetite (5.1%), bronchitis (5.1%), and back pain (5.1%).

In the 200 mg qd treatment arm, no deaths occurred in patients while on-treatment (that is, up to 30 days after the end of treatment), while in the 800 mg qd treatment arm 4 deaths (2.7%) occurred in patients on-treatment. The 4 on-treatment deaths in the 800 mg qd treatment were considered by the investigators to be unrelated to the study drug, with 2 of the deaths being attributed to the underlying malignancy and the other 2 deaths being related to cardiac disorders in patients with pre-existing risk cardiac factors. As of the cut-off date for the pivotal study (28 June 2013), there had been a total of 11 deaths (that is, on-treatment plus off-treatment), 2 (2.5%) in the 200 mg qd treatment arm (1 x laBCC (1.5%) and 1 x mBCC (7.7%) patient) and 9 (6.0%) in the 800 mg qd treatment arm (7 x laBCC (5.5%) and 2 x mBCC (8.7%)).

In the 200 mg qd treatment arm, SAEs (irrespective of causality) were reported in 11 (13.9%) patients, and each event was reported only once. Suspected study drug related SAEs were reported in 3 (3.8%) patients in the 200 mg qd treatment arm (1 x CK increased, 1 x rhabdomyolysis, 1 x syncope).

The clinical chemistry abnormality of particular concern in the 200 mg qd treatment arm was increased CK (45 patients (57.0%), including 5 patients (6.3%) with Grade 3 or 4 increases). CK shifts from baseline Grade 0 (n = 71) to post-baseline increase levels Grade 1, 2, 3, or 4 occurred in 39.4% (20/71), 9.9% (2/71), 4.2% (3/71) and 1.4% (1/71) of patients, respectively.

In the 200 mg qd treatment arm, CK increases categorized as AEs (all grades) were reported in 29.1% (n = 23) of patients, including 6.3% (n = 5) of patients with Grade 3/4 events. There was one case of rhabdomyolysis in 1 (1.3%) patient treated in the 200 mg qd treatment arm, but this case was not confirmed by the Independent Safety Review and Adjudication Committee. Following treatment interruption and re-challenge with the same dose this patient did not experience further Grade ≥ 2 muscle-related AEs.

Other clinical chemistry abnormalities of potential concern reported in the 200 mg qd treatment arm included hypercholesterolaemia (56 patients (70.9%), all Grade 1/2 events), hyperglycaemia (37 patients (46.8%), including 3 patients (3.8%) with Grade 3/4 increases), and increased lipase (31 patients (39.2%), including 9 patients (11.4%) with Grade 3 or 4 increases).

In the 200 mg qd treatment arm, the majority of patients at baseline had Grade 0 glucose levels (82.3%, n = 85), while baseline Grade 0 and Grade 1 (elevations) cholesterol levels were reported in 50.6% (n = 40) and 48.1% (n = 38) of patients. Review of the medical

histories of patients in the 200 mg qd treatment arm revealed that type 2 diabetes was reported in 5 (6.3%) patients, diabetes mellitus in 2 (2.5%) patients, hypercholesterolaemia in 13 (16.5%) patients, hyperlipidaemia in 7 (8.9%) patients, and dyslipidaemia in 2 (2.5%) patients. The increased glucose and cholesterol levels identified as laboratory abnormalities do not appear to result in corresponding clinically significant AEs. The significance of the increased glucose and cholesterol levels observed in laboratory tests is unclear.

In the 200 mg qd arm, lipase shifts from baseline Grade 0 (n = 75) to post-baseline increased levels Grades 1, 2, 3, or 4 occurred in 20.0% (15/75), 8.0% (6/75), 8.0% (6/25), and 1.3% (1/75), respectively. There were no AEs of pancreatitis associated with increased lipase levels, although increases in lipase levels were associated with non-specific gastrointestinal symptoms. The significance of the increased lipase levels observed in laboratory tests is unclear.

The clinical chemistry abnormality of increased serum creatinine level was reported in 92.4% (n = 73) of patients in the sonidegib 200 mg qd treatment arm. However, the sponsor indicates that this was due to implementation of the CTCAE guidance (version 4.03), where the definition of Grade 1 includes any increase from baseline (>1 to 1.5 fold increase). This definition was likely to include patients in whom post-baseline shifts in serum creatinine levels remained within the normal range. Review of 'renal and urinary disorders' (SOC) reported in the 200 mg qd treatment arm did not identify any significant AEs. In the 200 mg qd treatment arm, creatinine increased was reported as an AE in 2 (2.5%) patients.

The post-baseline haematology laboratory results in the 200 mg qd treatment arm showed that haemoglobin levels were reduced in 25.3% (n = 20) of patients, lymphocytes were reduced in 24.1% (n = 19) of patients, neutrophils were reduced in 7.6% (n = 6) of patients, leukocytes were reduced in 6.3% (n = 5) of patients, and platelets were reduced in 6.3% (n = 5) of patients. These laboratory abnormalities were not reflected in 'blood and lymphatic system disorders', where only 3 (3.8%) patients in the 200 mg qd treatment arm reported AEs (related to anaemia).

Other safety issues of concern associated with sonidegib treatment include: fetotoxicity and teratogenicity, with consequent risks to women of child-bearing potential treated with the drug and women of child-bearing potential who are sexual partners of men treated with the drug; the potential for increased exposure when administered with strong CYP3A4 inhibitors; the potential for increased muscle toxicity when administered with statins and other drugs with a known risk of myopathy; the potential for increased exposure in patients with hepatic impairment given that the drug is metabolised and primarily cleared by the liver; limited information in races other than Caucasians; and the potential risk of secondary malignancies.

The Clinical Overview included a comparison between sonidegib 200 mg qd and vismodegib 150 mg qd relating to AEs reported in at least 5% of patients. In general, the comparison favoured patients treated with sonidegib 200 mg qd compared to patients treated with vismodegib 150 mg qd. However, the incidence of all BCC patients discontinuing due to AEs was notably higher with sonidegib 200 mg qd in the pivotal Study A2201 than with vismodegib 150 mg qd in the pivotal Study SHH4776g (Vismodegib AUSPAR) (21.5% (17/79) versus 11.5% (12/104), respectively).

First round benefit-risk assessment

First round assessment of benefits

In the pivotal Phase II Study A2201, the primary benefit of sonidegib 200 mg qd was an ORR meeting the pre-specified criteria for clinical significance, with the ORR being assessed per central review according to mRECIST in patients with laBCC and to RECIST 1.1 in patients with mBCC. The ORR in the 200 mg qd treatment arm was 36.4% (20/55) (95% CI: 23.8, 50.4) in the primary analysis (pEAS) and 41.8% (33/79) (95% CI: 30.8, 53.4) in the supportive analysis (FAS). In both analyses, the ORR met the pre-specified criteria for clinical significance (that is, point estimate \geq 30%, lower bound 95% CI \geq 20%). However, the absence of a control arm in the pivotal study introduces a degree of uncertainty into the assessment of the benefit of sonidegib 200 mg qd for treatment of the proposed indication. In addition, the primary analysis of the ORR was undertaken when all patients were followed for at least 24 weeks (unless discontinued earlier), and there were no data in the submission confirming the long-term durability of the response. The final analysis in the pivotal study is planned for Week 78.

In the primary analysis (pEAS), the benefit of sonidegib 200 mg qd based on the ORR per central review and pre-specified criteria for clinical significance was observed in patients with laBCC (42.9% (18/42) (95% CI: 27.7, 59.0)), but not in patients with mBCC (15.4% (2/13) (95% CI: 1.9, 45.4)). The ORR results for laBCC and mBCC observed in the primary analysis (pEAS) were consistent with the corresponding results observed in the supportive analysis (FAS).

The DoR, per central review according to mRECIST in patients with laBCC and to RECIST 1.1 in patients with mBCC, was a key secondary efficacy endpoint in the pivotal study. In all patients in the 200 mg qd treatment arm, the median DOR in responders was not-estimable in both the primary analysis in the pEAS (85% censoring rate, 17/20) and the supportive analysis in the FAS (87.9% censoring rate, 29/33). In the 200 mg treatment arm, the median DoR per central review in the pEAS (primary analysis) and the FAS (supportive analysis) was not-estimable in both patients with laBCC and patients with mBCC. In the absence of a control arm it is difficult to meaningfully interpret the DoR results.

The CRR, per central review according to mRECIST in patients with laBCC and to RECIST 1.1 in patients with mBCC, was a key secondary efficacy endpoint in the pivotal study. In all patients in the 200 mg qd treatment arm, the CRR was 3.6% (2/55) (95% CI: 0.4, 12.5) in the pEAS (primary analysis) and 2.5% (2/79) (95% CI: 0.3, 8.8) in the FAS (supportive analysis). In the 200 mg qd treatment arm, the CRR in the pEAS (primary analysis) was 4.8% (2/42) (95% CI: 0.6, 16.2) in patients with laBCC and 0% (0/13) in patients with mBCC. In the 200 mg qd treatment arm, the CRR in the FAS (supportive analysis) was 3.0% (2/66) (95% CI: 0.4, 10.5) in patients with laBCC and 0% (0/13) in patients with mBCC. Based on the CRR results, the benefits of treatment with 200 mg qd are considered to be poor in all patients with BCC.

The median PFS, per central review according to mRECIST in patients with laBCC and to RECIST 1.1 in patients with mBCC, was a secondary efficacy endpoint in the pivotal study. The median PFS in the 200 mg qd treatment arm (pEAS) was not-estimable in patients with laBCC (censoring rate 88.1%, 37/42) and 13.1 months (95% CI: 5.6, 13.1) in patients with mBCC (censoring rate 69.2%, 9/13). The median PFS in the 200 mg qd treatment arm (FAS) was not-estimable in patients with laBCC (censoring rate 89.4%, 59/66) and 13.1 months (95% CI: 5.6, 13.1) in patients with mBCC (censoring rate 69.2%, 9/13).

The median OS (FAS), a secondary efficacy endpoint in the pivotal study, was not-estimable in patients in the 200 mg qd treatment arm in the total population, with 97.5%

(77/79) of patients being censored. In the absence of a control arm it is difficult to meaningfully interpret the PFS and OS results.

Exploratory patient-reported outcomes showed that the majority of patients treated with sonidegib 200 mg qd experienced maintenance and/or improvement in their health status, functioning, and disease-related symptoms.

First round assessment of risks

The assessment of the risks of sonidegib 200 mg qd for the treatment of the proposed indication is based on the safety data from 79 patients in the pivotal Phase II Study A2201 who were treated for a median duration of 8.9 months (range 1.3, 21.4 months). The long-term risks of treatment with sonidegib 200 mg qd for the proposed indication are unknown. The long-term safety data from the pivotal study for sonidegib 200 mg qd were limited to 21 (26.6%) of patients exposed for ≥ 12 months. The lack of long-term safety data is a concern, because treatment with sonidegib 200 mg qd is being proposed to continue for as long as clinical benefit is observed, or until unacceptable toxicity develops.

The risk of a patient with advance BCC treated with sonidegib 200 mg qd experiencing an AE is very high. In the pivotal study, nearly all patients treated with sonidegib 200 mg qd experienced at least one AE irrespective of causality (94.9%, n = 75), and the majority of patients reported at least one AE that was suspected to be study drug related (86.1%, n = 68). While the majority of AEs experienced by patients in the 200 mg qd treatment arm were Grade 1/2 events, a significant proportion of patients experienced Grade 3/4 events (30.4%, n = 24 (irrespective of causality) and 22.8%, n = 18 (study drug related)).

The major risks of treatment with sonidegib 200 mg qd were muscle-related events (myopathy/rhabdomyolysis), alopecia, nausea and/or vomiting, decreased appetite and/or weight loss, dysgeusia, fatigue (asthenia)/lethargy, and diarrhoea. The AEs of special interest (irrespective of causality) reported in $\geq 20\%$ of patients in the 200 mg qd treatment arm in decreasing order of frequency were muscle-related (myopathy/rhabdomyolysis) (63.3%, n = 53), alopecia (46.8%, n = 37), nausea and/or vomiting (43.0%, n = 34), decreased appetite and/or weight loss (38.0%, n = 30), dysgeusia (38.0%, n = 30), fatigue (asthenia)/lethargy (36.7%, n = 29), and diarrhoea (24.1%, n = 19). The AEs of special interest in the 200 mg qd treatment arm were predominantly Grade 1/2 events, and Grade 3/4 events reported in $\geq 2\%$ of patients were muscle-related (8.9%, n = 7), nausea and/or vomiting (3.8%, n = 3), and fatigue (asthenia)/lethargy (2.5%, n = 2). Nearly all of the AEs of special interest in the 200 mg qd treatment arm were suspected by investigators to be related to the study drug.

Overall, preferred term AEs (irrespective of causality) reported in $\geq 20\%$ of patients in the 200 mg qd treatment arm, in decreasing order of frequency, were muscle spasms (49.4%), alopecia (43.0%), dysgeusia (38.0%), nausea (23.9%), CK increased (29.1%), fatigue (29.1%), weight decreased (26.6%), and diarrhoea (24.1%). The most commonly occurring Grade 3/4 events (irrespective of treatment) reported in $\geq 2\%$ of patients in the 200 mg qd treatment arm in descending order of frequency were CK increased (6.3%), lipase increased (5.1%), muscle spasms (2.5%), asthenia (2.5%), and hypertension (2.5%).

In the pivotal study, there was a significant risk of AEs leading to treatment discontinuation in patients in the 200 mg qd treatment arm. AEs (irrespective of causality) leading to treatment discontinuation in the 200 mg qd treatment arm were reported in 21% (n = 17) of patients. The majority of AEs leading to discontinuation (14/17 patients) in the 200 mg qd treatment arm were related to the events of special interest: that is, muscle-related (4 patients, 5.1%); decreased appetite and/or weight loss (3 patients, 3.8%); nausea and/or vomiting (2 patients, 2.5%); dysgeusia (2 patients, 2.5%); fatigue (asthenia)/lethargy (2 patients, 2.5%); and alopecia (1 patient, 1.3%).

In the pivotal study, there were significant risks of dose adjustments and/or temporary dose interruptions needed to manage AEs in patients in the 200 mg qd treatment arm (31.6%). AEs (irrespective of causality) requiring dose adjustment and/or temporary dose interruption reported in $\geq 2\%$ of patients in the 200 mg qd treatment arm, in decreasing order of frequency, were CK increased (6.3%), lipase increased (5.1%), nausea (3.8%), diarrhoea (2.5%), fatigue (2.5%), and viral gastroenteritis (2.5%).

There were significant risks in the pivotal study of additional medications or therapies needed to manage AEs in patients in the 200 mg qd treatment arm (83.5%). AEs (irrespective of causality) requiring additional medications or therapies reported in $\geq 5\%$ of patients in the 200 mg qd treatment arm, in decreasing order of frequency, were muscle spasms (20.4%), diarrhoea (13.9%), nausea (12.7%), headache (12.7%), urinary tract infection (7.6%), pneumonia (6.3%), arthralgia (6.3%), hypertension (6.3%), decreased appetite (5.1%), bronchitis (5.1%), and back pain (5.1%).

No deaths on-treatment were reported in patients treated in the 200 mg qd treatment arm, and 2 deaths were reported up to the date of data cut-off. In patients in the 200 mg qd treatment arm, SAEs (irrespective of causality) were reported in 13.9% (n = 11) of patients and drug related SAEs were reported in 3.8% (n = 3) of patients (1 x CK increased, 1 x rhabdomyolysis, 1 x syncope).

The risk of experiencing an increased CK level (laboratory abnormality) was high in patients in the 200 mg qd treatment arm (45 patients (57.0%), including 5 patients (6.3%) with Grade 3 or 4 increases). In the 200 mg qd treatment arm, CK elevations were reported as AEs (all grades) in 29.1% (n = 23) of patients, with Grade 3/4 increases being reported 6.3% (n = 5) of patients. The majority of patients with Grade ≥ 2 CK elevations experienced muscle symptoms (mostly spasms or cramps) preceding the CK elevation.

The median time to onset of Grade ≥ 2 CK elevation was 10.6 weeks (range: 2, 32 weeks) in the 200 mg qd treatment arm, and the median time to resolution (Grade ≤ 1) of Grade ≥ 2 CK elevations in this treatment arm following interruption of treatment was 9 days (95% CI: 8, 14), with 10/13 patients shifting to normalization or Grade 1. In the 200 mg qd treatment arm, the median time to onset of Grade 3/4 CK elevations was not-estimable, while the median time to resolution of Grade 3/4 CK elevations following interruption of treatment was 8 days (95% CI: 4, not estimable (NE)), with 4/5 patients shifting to Grade 1 or normalization. There was one case of rhabdomyolysis reported in the 200 mg qd treatment arm, but this was not confirmed by the Independent Safety Review and Adjudication Committee. The patient with rhabdomyolysis in the 200 mg qd treatment was re-challenged with the same dose and did not experience further Grade ≥ 2 muscle-related AEs,

The risks of other significant clinical chemistry abnormalities in patients in the 200 mg qd treatment arm included hypercholesterolaemia (70.9%), hyperglycaemia (46.8%), and increased lipase (39.2%). The significance of these risk is unknown. However, they do not appear to translate into significant AEs. The most frequently reported Grade 3/4 clinical chemistry abnormalities occurring in $\geq 2\%$ of patients in the 200 mg qd treatment arm were increased lipase (11.4%), CK (6.3%), increased glucose (3.8%), increased potassium (3.8%), increased AST (2.5%), increased ALT (2.5%) and increased amylase (1.3%).

The risk of decreased haemoglobin levels and decreased lymphocytes detected by laboratory testing was high in patients in the 200 mg qd treatment arm (25.3% and 24.1%, respectively), with all events being Grade 1/2 apart from one Grade 3/4 event for decreased lymphocytes in 1 (1.3%) patient. However, the risk of 'blood and lymphatic disorders' (SOC) was low in patients in the 200 mg qd treatment arm, with only 3 (3.8%) patients reporting these disorders (2 x anaemia, 1 x iron deficiency anaemia).

Other safety risks associated with sonidegib treatment include: fetotoxicity and teratogenicity, with consequent risks to women of child-bearing potential treated with the

drug and women of child-bearing potential who are sexual partners of men treated with the drug; the potential for increased exposure when administered with strong CYP3A4 inhibitors; the potential for increased muscle toxicity when administered with statins and other drugs with a known risk of myopathy; the potential for increased exposure in patients with hepatic impairment given that the drug is metabolized and primarily cleared by the liver; limited information in races other than Caucasians; and the potential risk of secondary malignancies. Further potential risks of treatment with sonidegib include treatment resistance, and disease rebound following cessation of treatment.

First round assessment of benefit-risk balance

The benefit-risk balance of sonidegib 200 mg qd, given the proposed usage, is considered to be unfavourable. It is considered that the totality of the risks associated with treatment with sonidegib 200 mg qd outweigh the potential, but unconfirmed, benefits of the drug for the proposed indication.

In the pivotal Study A2110, the primary benefit of sonidegib 200 mg qd for treatment of the proposed indication was an ORR per central review of 36.4% (20/55) (95% CI: 23.8, 50.4) in the primary analysis (pEAS) and 41.8% (33/79) (95% CI: 30.8, 53.4) in the supportive analysis (FAS). In both the pEAS and the FAS, the ORR per central review met the pre-specified criteria for clinical significance (that is, point-estimate \geq 30% with lower bound 95% CI of \geq 20%). However, the absence of a control arm in the pivotal study introduces a degree of uncertainty into the interpretation of the clinical significance of the observed ORR benefit. In addition, the primary analysis of the ORR was undertaken when all patients had been followed for at least 24 weeks unless discontinued earlier, and there were no data in the submission confirming the long-term durability of the response. Furthermore, subgroup analyses of the ORR per central review in both the pEAS and FAS demonstrated that, while the ORR met the criteria for clinical significance in patients with laBCC, the ORR failed to meet the criteria in patients with mBCC. Therefore, there are no data in the submission demonstrating that sonidegib 200 mg qd is efficacious for the treatment of patients with mBCC.

One of the main risks of treatment with sonidegib 200 mg qd for patients with the proposed indication was the high rate of patient discontinuation due to adverse events (irrespective of causality) observed with the regimen. The total number of patients in the sonidegib 200 mg qd treatment arm discontinuing due to AEs (irrespective of causality) was 17 (21.5%), including 14 (17.7%) patients discontinuing due to AEs of special interest. AEs of special interest (irrespective of causality) leading to treatment discontinuation were muscle-related (4 patients, 5.1%), decreased appetite and/or weight loss (3 patients, 3.8%), nausea and/or vomiting (2 patients, 2.5%), dysgeusia (2 patients, 2.5%), fatigue (asthenia)/lethargy (2 patients, 2.5%), and alopecia (1 patient, 1.3%).

The concern relating to the benefit-risk balance for 200 mg qd for the treatment of patients with advanced BCC can be illustrated by a simple comparison of benefits and risks in the FAS in the pivotal study. In the FAS, 41.8% (33/79) of patients in the 200 mg qd treatment arm obtained a clinically significant benefit based on the ORR per central review when all patients had been followed for at least 24 weeks unless discontinued earlier, following 24 weeks of treatment, while 20.3% (16/79) of patients discontinued treatment prematurely due to AEs (irrespective of causality) with 1 patient being lost to follow up. Therefore, based on the ORR the benefit of treatment was observed in approximately 4 out of 10 patients, while the risk of discontinuing due to an AE was observed in approximately 2 out of 10 patients.

In addition to the high rate of discontinuations due to AEs, other risks considered to shift the benefit risk balance towards unfavourable for patients treated with 200 mg qd include: the high rate of patients that experience at least one AE (all grades) that was

suspected to be drug, including the high rate of Grade 3/4 events (22.8%, 18/79); the high rate of muscle related AEs suspected to be drug related (58.2%, 46/79); the high rate of alopecia related AEs suspected to be drug related (41.8%, 33/79); the high rate of dysgeusia related AEs suspected to be drug related (34.2%, 27/79); the high rate of fatigue (asthenia)/lethargy related AEs suspected to be drug related (25.3%, 20/79); and the high rate of diarrhoea related AEs suspected to be drug related (13.9%, 11/79).

An additional significant risk associated with sonidegib 200 mg qd for the treatment of the proposed indication shifting the benefit-risk balance to unfavourable include the potential for fetotoxicity and teratogenicity associated with pregnancy in women of child-bearing potential treated with the drug and women of child-bearing potential who are the sexual partners of men treated with drug.

First round recommendation regarding authorisation

It is considered that the efficacy of the proposed dose of sonidegib 200 mg qd for the proposed indication has not been satisfactorily established. Therefore, it is recommended that the submission to approve sonidegib for the treatment of adult patients with laBCC who are not amenable to curative surgery or radiation therapy, or with mBCC, should be rejected. The reasons for this recommendation are discussed in the following paragraphs.

The efficacy of the proposed dose for the proposed indication was based on 24 week, uncontrolled data in 79 patients in the pivotal Phase II Study A2201. The primary efficacy endpoint was the ORR per central review, and in both the pEAS (primary analysis) and the FAS (supportive analysis) the endpoint met the pre-specified criteria for clinical significance. However, interpretation of the clinical significance of the ORR data in the pivotal study is uncertain in the absence of a control arm. Therefore, it is considered that the results should be confirmed in a Phase III study comparing sonidegib 200 mg qd with vismodegib 150 mg qd. Furthermore, there were no data in the submission on the long-term durability of the objective response. The absence of long-term efficacy data is considered to be a significant deficiency, given that the sponsor recommends that treatment with sonidegib should continue for as long as clinical benefit is observed or until unacceptable toxicity develops. Therefore, it is considered that the durability or the response should be confirmed with long-term data. In addition, there are no controlled data on whether the ORR after all patients had been observed for at least 24 weeks (unless discontinued earlier) translates into clinically meaningful outcomes (that is, increase in PFS and/or increase in OS).

In both the pEAS and the FAS, the subgroup analysis of the ORR per central review in the pivotal Phase II Study A2201 demonstrated that the endpoint meet the pre-specified criteria for clinical significance for patients with laBCC using mRECIST treated with sonidegib 200 mg qd, but not for patients with mBCC using RECIST 1.1. Therefore, there are no data in the submission supporting the efficacy of sonidegib 200 mg qd for the treatment of mBCC, which is one of the proposed indications.

The two key pre-specified secondary efficacy endpoints in the pivotal Phase II Study A2201 of DoR per central review and CRR per central review are considered to provide limited support for the efficacy of sonidegib 200 mg qd for the proposed indication. The median DoR per central review in the pEAS was not-estimable in patients with laBCC using mRECIST or mBCC using RECIST, with 83.3% (15/18) of responders being censored in the laBCC group and 100% (2/2) of responders being censored in the mBCC group. The clinical significance of the results for the DoR cannot be meaningfully interpreted in the absence of a control arm. The CRR per central review was notably low in both the pEAS and FAS in patients with laBCC using mRECIST (4.8%, 2/42 in the pEAS and 3.0%, 2/66, in the FAS), and in patients with mBCC using RECIST 1.1 (0%, 0/13 in the pEAS and the FAS).

The CRR rates are low in patients with laBCC; no complete responses were observed in patients with mBCC.

In the pivotal Phase II Study A2201, the median PFS per central review in the pEAS in the sonidegib 200 mg treatment arm was not-estimable in patients with laBCC using mRECIST (censoring rate 88.1%, 37/42) and 13.1 months (95% CI: 5.6, 13.1) in patients with mBCC using RECIST 1.1. The median PFS per central review in the FAS in the sonidegib 200 mg qd treatment arm was not-estimable in patients with laBCC using mRECIST (censoring rate 89.4%, 59/66) and 13.1 months (95% CI: 5.6, 13.1) in patients with mBCC using RECIST 1.1. The median OS (FAS) was not-estimable for sonidegib 200 mg qd in the total population, with 97.5% (77/79) of patients being censored. In the absence of a control arm it is difficult to meaningfully interpret the PFS and OS results.

The benefit-risk balance for the sonidegib 200 mg qd is unfavourable for the reasons discussed above.

Clinical questions and second round evaluation

The questions are presented in bold italics with the sponsors response and the evaluation of the response presented following each question.

General questions

Question 1

Does the sponsor intend to undertake a Phase III study comparing the efficacy and safety of sonidegib 200 mg qd and vismodegib 150 mg qd for the treatment of adult patients with advanced BCC? If not, please justify the decision.

Sponsor's response

At the current time, no head-to-head comparative study is planned.

It is important to note that no established effective systemic treatments were available for patients with locally advanced BCC (laBCC) or metastatic BCC (mBCC) when the protocol for Study CLDE225A2201 was implemented (2011). In addition, placebo was not considered as an option due to the severity of the disease and the preliminary efficacy in BCC observed in Study CLDE225X2101. As a consequence, the proposed study design and selection of control arm are considered to be appropriate. Objective response rate is an accepted and well-recognized endpoint in oncology studies (FDA 2007, EMA 2012); it is defined as the proportion of patients with tumour/lesion size reduction of a predefined amount for a minimum period of time. The FDA has generally defined ORR as the sum of partial response (PR) and complete response (CR) rates and this is consistent with that adopted for the sonidegib pivotal registration study. When defined in this manner, ORR is a direct measure of a drug's antitumor activity. As objective responses can be directly attributed to the administered drug, single-arm studies can be used to evaluate ORR in patients with refractory tumours where available therapies are limited. The significance of the ORR is subsequently assessed by its magnitude and duration, and ORR has formed the basis for the approval of several drugs and biologics for the treatment of various skin cancers.

laBCC that is not amenable to further surgery or radiation is a rare condition and mBCC is extremely rare. It is recognised that the optimal dataset to compare efficacy and safety of sonidegib 200 mg and vismodegib 150 mg would be a long-term controlled study with no option for crossover following treatment failure. However, difficulties in conducting comparative studies in this limited population need to be acknowledged.

Also, the challenge of a rapidly changing treatment landscape often precludes the design of meaningful head-to-head trials. For example, a number of studies are ongoing with vismodegib, aiming at further optimizing tolerability and efficacy of this drug.

With such clinical development ongoing, a head-to-head study (which will be ongoing for many years) may ultimately not provide the desired answer, simply because the treatment practice and recommendation for optimal use of the drugs that have been compared has changed in the meantime.

It is not uncommon in drug development that agents with a similar mode of action become available within a relative short time period. It typically takes many years until the place of a drug in physicians' armamentarium is established, during which strengths and weaknesses of similar drugs become apparent, without a head-to-head study ever being conducted.

With the above considerations in mind, the sponsor does not intend to undertake a Phase III study comparing the efficacy and safety of sonidegib 200 mg qd and vismodegib 150 mg qd for the treatment of adult patients with advanced BCC.

Evaluator's comments

This response is satisfactory. The development programs of vismodegib and sonidegib have run concurrently. Due to commercial implications of a direct comparison, it is likely to be left to non-industry clinical groups to perform such a test.

Question 2

Does the sponsor intend submitting long-term efficacy and safety data for sonidegib 200 mg qd? If not, please justify the decision.

Sponsor's response

The sponsor wishes to submit long-term efficacy and safety data for sonidegib 200 mg qd. In fact, three separate analyses of the data from Study CLDE225A2201 (hereafter Study A2201) have been conducted:

- Pre-specified primary efficacy analysis (6 month analysis), corresponding to a 28 June 2013 data cut-off, when all patients had received treatment for ≥ 24 weeks or had discontinued therapy. Efficacy and safety data from this 6-month analysis were submitted to TGA together with original dossier.
- 12-month analysis, corresponding to a 31 December 2013 data cut-off, when all patients had received treatment for ≥ 50 weeks or had discontinued therapy.
- 18-month analysis, corresponding to a 11 July 2014 data cut-off, when all patients had received treatment for ≥ 78 weeks or had discontinued therapy. As discussed with the Delegate. The efficacy and safety data from the 12-month analysis and 18-month analysis are submitted in this response.

Evaluator's comments

The sponsor's response is noted.

Pharmacokinetics

Question 1

The sponsor provided a justification for not providing an absolute bioavailability study in humans based on the insolubility of sonidegib in a large number of vehicles making it impossible to prepare an intravenous formulation for use in such a study. However, it is noted that the intravenous pharmacokinetics of sonidegib were examined in three nonclinical species (rat, dog, and mini-pig). The sponsor appears to

have used a radiolabelled (¹⁴C) intravenous solution of sonidegib in these studies. Please explain why an intravenous formulation of sonidegib could be prepared for the nonclinical studies, but not for an absolute bioavailability study in humans.

Sponsor's response

Preclinical Studies R0700684-01, R1100218, R0900883-01 and R1100451, required the administration of only low doses of the ¹⁴C IV formulation; typically 1 to 2 mg/kg, allowing thereby the use of a 1 mg/mL solution.

An IV formulation providing a similar exposure like a 200 mg oral dose would require a higher concentration in the solution, and thus would not be feasible. This is particularly the case since the vehicle used for the preclinical IV formulations contains 25 to 30% ethanol, 40% captisol, 30 to 35% pH 6.0 buffer or water. Since the amount of an organic co-solvent in an injectable vehicle should generally not exceed 20%, such a formulation would not be suitable for a human study.

Evaluator's comments

The justification for not performing an absolute bioavailability study is satisfactory.

Question 2

In the human biomaterial study (Study DMPK R08003232), sonidegib was reported to inhibit BCRP-mediated efflux, suggesting that the drug has the potential to inhibit BCRP in vivo. No clinical studies investigating the effects of co-administration of sonidegib and BCRP transporter substrates were submitted, and no information regarding planned studies could be identified in the submitted data package. Does the sponsor intend to undertake a clinical DDI study investigating co-administration of sonidegib and a probe substrate for the BCRP efflux transporter? If not, please justify the decision.

Sponsor's response

The sponsor does not plan for a BCRP clinical DDI study. Even though sonidegib has been shown to be an inhibitor of BCRP activity *in vitro* with an estimated IC₅₀ value of approximately 1.5 µM, the systemic inhibition of BCRP activity (that is, in the liver) is unlikely. This is because the clinically relevant unbound (plasma) drug concentrations are well below this estimated value. Inhibition of BCRP in the intestine is theoretically possible if the entire orally administered dose is available to interact with BCRP. However, this is an unlikely scenario due to the limited solubility of sonidegib and due to the potential interaction of the soluble portion with matrix components.

Furthermore, the vast majority of the known BCRP substrates (methotrexate, mitoxantrone, imatinib, irrinotecan, lapatinib, topotecan), excluding statins, are anti-cancer agents. None of these anti-cancer agents are used in the treatment for advanced BCC, and are therefore not expected to be used in combination with sonidegib.

The sponsor has proposed labelling cautioning and advising prescribers to monitor closely those patients taking statins due to overlapping muscle toxicity. Therefore, a clinical DDI study with a BCRP substrate is not expected to result in any further prescribing recommendations for patients with advanced BCC being treated with sonidegib.

Evaluator's comments

This explanation is satisfactory, however, the wording of the PI has been commented upon.

Question 3

Please provide a table comparing the baseline demographics of the patients in PK/ECG analysis set and the total patient population in the pivotal Study A2201. Are the patients in the PK/ECG analysis set reflective of the total patient population?

Sponsor's response

Baseline characteristics were generally similar for patients in the FAS and the PK/ECG set and were well balanced between the sonidegib 200 mg and 800 mg arms in both analysis sets.

Evaluator's comments

The data provided demonstrates generally similar baseline characteristics between the FAS and PK/ECG sets.

Efficacy

Question 1

In the clinical study report for Study A2201, the investigational plan section 9.2 states 'a sample size of approximately 210 patients (with laBCC or mBCC) was considered to be adequate for a non-comparative analysis of the efficacy and safety of sonidegib in each dose group, with additional exploratory assessments of the impact of therapy through PRO measures'. The sponsor is requested to reconcile this sample size calculation (that is, 420 subjects in total 210 in each dose group) with the adequacy of the actual numbers of patients that were recruited, with an explanation of the consequent certainty, and generalisability, of the efficacy outcomes observed.

Sponsor's response

Study A2201 is designed to have 210 patients randomised (that is, in the FAS), in order to achieve 150 patients in the pEAS. A 2:1 randomisation ratio was adopted between the 800 mg and 200 mg arm, resulting in 140 and 70 patients in the FAS on the 800 mg and 200 mg dose, respectively. In the pEAS, this resulted in 100 patients and 50 patients in the 800 mg and 200 mg arm, respectively. This sample size is considered adequate for a non-comparative analysis of the efficacy and safety of sonidegib in each dose group.

The clinical study report has a general introduction and therefore only the total number of patients in FAS was mentioned. Further details are provided in another section of the study protocol (sample size calculation).

The investigational plan section and sample size calculation section of the study protocol provide further rationale for the sample size. The protocol table provides decision operating characteristics for each arm based on the planned sample size of 50 and 100 pEAS patients in the 200 mg and 800 mg arm, respectively. If 800 mg had been terminated at the interim futility analysis, and only 200 mg had been carried forward, then the sample size for it would have increased to 100 pEAS patients. This condition's operating characteristics is also provided in the table of the study protocol.

The sample size in each arm provides good control of type I (false-positive) error rate for the primary endpoint, for example, the type I error rate is only 0.3% for the 800 mg arm (n = 100), and 2.4% for the 200 mg arm (n = 50), or 0.5% for the 200 mg arm (n = 100) if the true ORR on the respective arms is 20% or less.

Evaluator's comments

This response is satisfactory

Question 2

In the pivotal Study A2201, the predominant histopathological subtype, per central review, was reported as 'undetermined' in a notable proportion of patients in the total population in both the FAS (27.4%) and the pEAS (26.3%). Please comment on this observation.

Sponsor's response

It is important to emphasise that all patients randomised in Study A2201 were confirmed as having BCC at baseline by investigators. Histopathological subtype of aggressive versus non-aggressive was a stratification factor during randomization for laBCC patients. As per randomisation stratification, every laBCC patient was classified as aggressive or non-aggressive. That is, no patient had a value of undetermined histology. All analyses by histopathological subtype were based on the stratification value used in randomisation.

In addition to that, the fresh tumour biopsies (collected at screening) or the archival tumour specimens were collected for central histological confirmation of diagnosis and histological subtyping. This step was added with the protocol amendment. The data field 'predominant histology/cytology' in the listing is used to summarise the histopathological subtype per central review in the tables, that is BCC-basosquamous (metatypic or keratonizing), BCC-infiltrative, BCC-superficial, BCC-nodular.

Among these subtypes, BCC-nodular and BCC-superficial were pre-specified as 'non-aggressive', while BCC-basosquamous (metatypic or keratonizing) and BCC-infiltrative as 'aggressive'. If all the baseline samples for a patient had 'predominant histology/cytology' blank, then the subtype is derived as 'undetermined'. If all the baseline samples are not done or not available, then the patient is presented in the table as 'Missing'.

In the 18 month analysis (cut off 11 July 2014), there are 63 patients in the FAS who had 'undetermined' histology/cytology. A total of 73 baseline samples were collected for these patients. Note a patient could have multiple samples but all of them had 'predominant histology/cytology' field blank (derived as 'undetermined').

Evaluator's comments

The evaluator notes that all patients had a confirmed diagnosis of BCC at baseline, which directly corresponds to the indication sought.

Question 3

In the pivotal Study A2201, a sensitivity analysis in patients with laBCC comparing best overall response per central review using 'updated' mRECIST between sonidegib and vismodegib was undertaken applying similar methodology to that used in the Erivance trial. Please provide a tabulated summary comparing best overall response definitions used in the primary and sensitivity analyses of patients with laBCC treated with sonidegib. Please explain why the term 'updated' was used to describe the mRECIST in the sensitivity analysis of patients with laBCC.

Sponsor's response

In collaboration with the US FDA, the sponsor developed a modified RECIST guideline (termed mRECIST) to assess responses in laBCC in Study A2201, which included evaluation by an independent review committee (IRC).

Following the approval of vismodegib in the USA in January 2012, an interpretation of the future results of the ongoing Study A2201 in the context of approved agents (that is, vismodegib) became of interest. While acknowledging the limitations and difficulties of cross-study comparisons, introduction of 'vismodegib-like' criteria allowed for such an interpretation. Therefore, a pre-specified sensitivity analysis was included in the statistical analysis plan.

In the absence of a well-established name for the vismodegib mRECIST criteria, the sponsor chose to call these 'updated mRECIST' or 'sensitivity analysis per updated mRECIST' in order to differentiate them from those used in Study A2201. However, the choice of the word 'updated' was ultimately arbitrary.

The mRECIST criteria, as used in Study A2201 are in essence, as per vismodegib-like updated mRECIST criteria, a negative histology could 'override' a PR-result (or in certain cases even a stable disease (SD)-result) per magnetic resonance imaging (MRI) or photograph, leading to a composite overall response of complete response (CR).

In contrast, per mRECIST used for sonidegib, a CR could in principle only be achieved if supported by CR by both MRI and photography, classifying thereby many responders as PR that would otherwise have been CR by updated mRECIST.

In addition, vismodegib-like updated mRECIST criteria allow concluding a composite PR, when MRI is PR or better, but photo only shows SD; this is not allowed in mRECIST which concludes a composite SD for such scenarios.

In conclusion, the vismodegib-like updated mRECIST criteria will conclude more responders, and especially more CRs.

Evaluator's comments

This response is satisfactory.

Question 4

The sponsor is kindly requested to present an update to the following efficacy parameters: overall response rate, duration of response, progression-free survival, time to response and overall survival for both the subjects with locally advanced and metastatic BCC.

Sponsor's response

The sponsor provided the following updated efficacy information.

Table 17: Efficacy overview per central review, 200 mg, FAS

	6 month			18 month		
	laBCC N=66	mBCC N=13	combined N=79	laBCC N=66	mBCC N=13	combined N=79
Objective response rate, n (%)	31 (47.0)	2 (15.4)	33 (41.8)	37 (56.1)	1 (7.7)	38 (48.1)
95% CI	(24.6, 59.7)	(1.9, 45.4)	(30.8, 53.4)	(43.3, 68.3)	(0.2, 36.0)	(26.7, 59.6)
Best overall response, n (%)						
Complete response	2 (3.0)	0	2 (2.5)	3 (4.5)	0	3 (3.8)
Partial response	29 (43.9)	2 (15.4)	31 (39.2)	34 (51.5)	1 (7.7)	35 (44.3)
Disease stabilization	29 (43.9)	10 (76.9)	39 (49.4)	23 (34.8)	11 (84.6)	34 (43.0)
Disease progression	1 (1.5)	0	1 (1.3)	1 (1.5)	0	1 (1.3)
Unknown	5 (7.6)	1 (7.7)	6 (7.6)	5 (7.6)	1 (7.7)	6 (7.6)
Duration of response						
No. of events*	4	0	4	10	0	10
No. censored	27	2	29	27	1	28
Median (95% CI) (mo)	NE	NE	NE	NE	NE	NE
Event-free probability (%), (95% CI)						
12 months	65.9 (25.7, 88.0)	NE	66.7 (26.1, 88.6)	65.6 (43.2, 81.0)	100.0 (NE)	67.0 (45.2, 81.8)
Progression-free survival						
No. of events*	7	4	11	15	6	21
No. censored	59	9	68	51	7	58
Median (95% CI) (mo)	NE	13.1 (5.6, 13.1)	NE	22.1 (NE)	13.1 (NE)	22.1 (NE)
Progression-free survival probability (%), (95% CI)						
12 months	83.5 (84.8, 92.9)	64.9 (24.9, 87.4)	80.2 (83.5, 89.8)	82.2 (87.0, 90.8)	58.9 (23.4, 82.5)	78.2 (84.4, 87.1)
Time to tumor response						
Median (95% CI) (mo)	3.9 (3.6, 4.2)	4.6 (1.6, 7.4)	3.9 (3.6, 4.2)	4.0 (3.8, 5.6)	1.6 (NE)	4.0 (3.7, 5.6)
Overall Survival						
No. of patients who died, %	1 (1.5)	1 (7.7)	2 (2.5)	3 (4.5)	3 (23.1)	6 (7.6)
	laBCC N=66	6 month mBCC N=13	combined N=79	laBCC N=66	18 month mBCC N=13	combined N=79
No. censored, %	65 (98.5)	12 (92.3)	77 (97.5)	63 (95.5)	10 (76.9)	73 (92.4)
Median OS (mo)	NE	NE	NE	NE	NE	NE
OS rate, % (95% CI)						
12 months	100 (NE)	87.5 (38.7, 98.1)	97.8 (85.3, 99.7)	100 (NE)	90.9 (50.8, 98.7)	98.5 (89.7, 99.8)

*Full analysis set included all randomized patients. *Event refers to disease progression or death due to any reason. CI: confidence interval. NE: not estimable. Sources:

Evaluator's comments

The updated efficacy information is noted.

Safety

Question 1

Please provide mean (SD), median, and range (max, min) values for serum creatinine levels (baseline and post-baseline) for patients in the 200 mg qd and 800 mg qd treatment arms from the pivotal Study A2201.

Sponsor's response

In Study A2201, median serum creatinine values at baseline were 80.0 µmol/L with sonidegib 200 mg and 81.0 µmol/L with sonidegib 800 mg. The median worst post-baseline values for serum creatinine were 92.0 µmol/L and 94.0 µmol/L with sonidegib 200 mg and 800 mg, respectively, reflecting a median of 1.2 fold increase in the worst fold change from baseline.

In summary, the majority of patients experienced clinically insignificant increases in creatinine from baseline and further evaluation of these data indicated that the majority of them are still within normal range. There were 2 patients who had worsening of creatinine to Grade 3, however both patients had plausible confounders. The current labelling lists Grade 1 and 2 serum creatinine increased with the frequency of very common. The sponsor will continue to monitor for cases of serum creatinine elevations going forward in both the ongoing studies as well in the post-marketing period.

Evaluator's comments

At the proposed dose of sonidegib 200 mg daily, the estimated increase in serum creatinine was 0.7 to 1.6 fold from baseline. A Grade 1 post-baseline increase in serum creatinine was observed in 7 patients (9.6%), and a Grade 2 post-baseline increase was observed in 1 patient (1.4%).

There was a similar proportion of patients that experienced a post-baseline increase in serum creatinine for those exposed to 200 mg daily and 800 mg daily, reflecting a lack of dose-response for this adverse event.

Question 2

Please comment on the clinical significance of the high proportion of patients with post-baseline hyperglycaemia (clinical laboratory results) in both the 200 mg qd and 800 mg qd treatment arms from the pivotal Study A2201. Is there any evidence that sonidegib increases blood glucose levels to clinically significant concentrations in a clinically meaningful proportion of patients, and if so did these patients require additional therapies?

Sponsor's response

There is no consensus in the literature with regard to the role of the Hh pathway, and whether a relation between disrupted Hh signalling and development of type 2 diabetes exists. Pre-clinically, there were no adverse histopathology findings on the pancreas or in glucose blood levels.

The high proportion of patients with post-baseline hyperglycaemia (clinical laboratory results) in both the 200 mg and 800 mg groups using 18 month analysis data (cut off 11 July 2014) is mainly due to a shift to low grades in both dosage groups:

- Number (%) of patients shifted to a worsened post-baseline grade in glucose, 200 mg (n = 79)
 - grade-0 to grade-1: 25 (31.6%)
 - grade-0 to grade-2: 3 (3.8%)
 - grade-1 to grade-2: 1 (1.3%)
 - grade-2 to grade-3: 2 (2.5%)
- Number (%) of patients shifted to a worsened post-baseline grade in glucose, 800 mg (n = 150)
 - grade-0 to grade-1: 41 (27.3%)
 - grade-0 to grade-2: 15 (10.0%)
 - grade-0 to grade-3: 1 (0.7%)
 - grade-1 to grade-2: 4 (2.7%)
 - grade-2 to grade-3: 1 (0.7%)

The majority of these shifts were not considered adverse events by the investigator and very infrequently was any medication taken to treat these conditions. Thus, these laboratory shifts were not considered clinically significant.

Furthermore, a search of the safety data in Study A2201 through 11 July 2014 has revealed that there have not been any AE reports of either worsening glycaemic control or new onset diabetes.

In summary, based on an evaluation of the data in totality, the sponsor is not of the view that sonidegib increases blood glucose levels to clinically significant concentrations in a

clinically meaningful proportion of patients. However, the sponsor will continue to monitor for cases of blood glucose elevations going forward in both the ongoing studies as well in the post-marketing period.

Evaluator's comments

There does not appear to be a dose-dependent relationship for hyperglycaemia. Given the incidence of BCC and diabetes mellitus increases with increasing age, it is not unexpected that worsening blood sugar was observed in the Sonidegib development program, but this does not confirm a causal relationship.

Question 3

Please comment on the clinical significance of the high proportion of patients with post-baseline hypercholesterolaemia (clinical laboratory results) in both the 200 mg qd and 800 mg qd treatment arms from the pivotal Study A2201. Is there any evidence that sonidegib increases serum cholesterol to clinically significant concentrations in a clinically meaningful proportion of patients, and did these patients require any additional therapies?

Sponsor's response

Pre clinically, in female rats there were moderate increases in cholesterol (1.4 to 1.8 fold) at exposures 3 to 25 fold the clinical exposure. In dogs, cholesterol elevations were seen in both sexes in the 13-week study where 2 fold elevations in cholesterol occurred at exposures approximately 4 fold of that in clinical setting. The highest elevations were seen in the 26 week study where 50% of the high dose dogs were euthanised moribund. Cholesterol was elevated by approximately 2.8 fold at exposures greater than 17 fold of that in the clinical setting. Hypercholesterolemia in the rat and the dog is not considered adverse. Humans carry the majority of their cholesterol (> 50%) with LDL, while in the dog and the rat, > 90% of cholesterol is carried with HDL, thus translatability is very limited.

The high proportion of patients with post-baseline hypercholesterolaemia (clinical laboratory results) in both the 200 mg and 800 mg groups using 18 month analysis data (cut off 11 July 2014) is mainly due to a shift to low grades in both dosage groups with no shift to Grade 3 or Grade 4:

Number (%) of patients shifted to a worsened post-baseline grade in cholesterol, 200 mg (n = 79):

- grade-0 to grade-1: 17 (21.5%)
- grade-1 to grade-2: 7 (8.9%)

Number (%) of patients shifted to a worsened post-baseline grade in cholesterol, 800 mg (n = 150):

- grade-0 to grade-1: 38 (25.3%)
- grade-1 to grade-2: 4 (2.7%)

The majority of these shifts were not considered adverse events by the investigator and only 1 patient received treatment for elevated cholesterol. Furthermore, only 3 patients reported cholesterol-related AEs. Thus, these laboratory shifts were not considered clinically significant. The few patients receiving concomitant medications and experiencing AEs are described further herein.

A search of the laboratory data in Study A2201 through 11 July 2014 revealed that there were no patients who had clinically significant post-baseline hypercholesterolaemia that is, worsening of cholesterol from baseline to Grade 3/4. A search of the AE data revealed that there were 3 patients (5 records) in total on 200 mg and 800 mg who had either

'blood cholesterol increased' or 'hypercholesterolaemia'. All these events were Grade-1 or Grade-2, without significant increase of blood cholesterol compared to baseline. No medication was given to treat the events:

In summary, based on an evaluation of the data in totality, the sponsor is not of the view that sonidegib increases cholesterol to clinically significant levels in a clinically meaningful proportion of patients. However, the sponsor will continue to monitor for cases of elevated cholesterol going forward in both the ongoing studies as well in the post-marketing period.

Evaluator's comments

The incidence of worsening of hypercholesterolemia to Grade 0 or 1 was comparable between the patients exposed to 200 mg and 800 mg sonidegib. (The sponsor is also proposing to include a statement in the PI regarding the potential interaction between HMG-CoA reductase inhibitors and sonidegib in relation to muscle symptoms).

Question 4

It is not clear from the pivotal Phase II study safety report A2201 whether investigation of the torsades de pointes/QT prolongation in the safety set relate to SMQ results. Please clarify this matter. Please provide a tabulated summary of 'torsades de pointes/QT prolongation (SMQ)' using narrow and broad search terms (MedDRA SMQs Version 15.0).

Sponsor's response

The sponsor confirms that the risk of 'electrocardiogram QT prolongation/torsades de pointes' was evaluated using a broad MedDRA search. This included the following: Torsades de pointes/QT prolongation (broad SMQ), convulsion (narrow SMQ), bradyarrhythmias (including conduction defects and disorders of sinus node function; broad SMQ) as well as Preferred Terms (PTs) of bradycardia, electrocardiogram RR interval prolonged, heart rate decreased, syncope and arrhythmia.

For the 18 month data, the risk of 'electrocardiogram QT prolongation/torsades de pointes' via SMQ search is summarised in the SCS Addendum. As a conservative approach, the sponsor always used the broad SMQ search in order to capture and analyse any events in this category. Please also note for the 18-month reporting, MedDRA version 17.1 is used.

Evaluator's comments

The incidence of individual causes of events in the 'torsades de pointes/QT prolongation' category is low and does not yield a discernible pattern, or apparent dose-dependence.

Question 5

The sponsor is kindly requested to report the proportion of subjects that had both troponin and CK-MB assay, and the results of testing, following any grade, and Grades 3 or 4, elevation in CK in the pivotal Study A2201.

What is the sponsors' explanation for the elevations in serum troponin reported for three subjects in Study A2201 (1.3% of all subjects)? Can the sponsor confirm the absence of chronic low-grade toxicity to cardiac muscle, potentially resulting in impaired cardiac function, with cumulative Odomzo exposure given that functional echocardiography was not routinely performed in this study?

Sponsor's response

As of the 18 month analysis, there are a total of 48 patients in the 200 mg arm and 100 patients in the 800 mg arm, who had a post baseline serum CK level at Grade 1 or above, regardless of their baseline level. Among these patients, the availability of CK-MB and

troponin I level on the same day of CK measurement (as summarised in the table below). Please note troponin T is measured very scarcely in this trial and therefore not considered for this summary. If a patient had multiple CK elevations reported as different grades, this patient is counted once in each of the grade reported. If a patient had multiple CK elevations of the same grade, as long as the patient had CK-MB (and/or troponin I) at one of these elevations, then he/she is counted as having CK-MB (and/or troponin I), and he/she is counted only once under that grade.

Table 18: Summary of CK-MB and troponin data availability on the same day of CK elevation (18 month analysis, safety set)

Data availability on the same day of CK	Any CK elevation post baseline, regardless of baseline grade					
	Grade 1	Grade 2	Grade 3	Grade 4	Any grade	Grade 3/4
200 mg	N=47	N=11	N=5	N=2	N=48	N=6
CK-MB	45	11	5	2	46	6
Troponin I	44	11	4	2	45	5
CK-MB and troponin I	44	11	4	2	45	5
800 mg	N=92	N=38	N=20	N=11	N=100	N=25
CK-MB	84	28	18	11	93	23
Troponin I	84	27	18	11	93	23
CK-MB and troponin I	84	27	18	11	93	23

N is the number of patients with a post baseline elevation in CK of the respective grade

The details of CK, CK-MB, troponin T, and troponin I are presented in the SCS addendum for each patient. Also summarised below is the review of CK-MB/CK ratio and troponin levels based on these data.

The CK-MB/CK ratio and troponin levels were measured after screening and when clinically indicated. The CK-MB/CK ratio was <5% in all 157 patients who had both CK-MB and CK reported (regardless whether CK was elevated or not) after initiating treatment with sonidegib with the exception of 2 patients [information redacted] on a single occasion; however, CK, troponin I, and consequent ECGs were normal for both of these patients.

Only 3 patients had a doubling in troponin I levels, two patients [information redacted] who received sonidegib 200 mg and the third patient [information redacted] who received sonidegib 800 mg.

In summary, the available data suggest that CK elevations seen with sonidegib originate from skeletal muscle, and that treatment with sonidegib is unlikely to be associated with myocardial injury.

Measurement of CK-MB has been superseded by troponin I in the clinical evaluation of cardiac ischaemia/infarction. Although the majority of CK-MB elevation may be from cardiac muscle, it is also present in skeletal muscle, rendering it incompletely specific. From the data presented, in patients who experienced an elevation in CK-MB, the majority had a concomitant clinically insignificant elevation in troponin I concentration. Among the three patients with a doubling of troponin I concentration in association with an elevation of CK-MB, only one had clinical features suggestive of myocardial ischaemia.

Evaluator's comments

The evaluator concurs with the sponsors' opinion that the origin of CK-MB observed is likely to be from skeletal rather than cardiac muscle.

Question 6

What is the sponsors' explanation for the elevations in serum troponin reported for three subjects in Study A2201 (1.3% of all subjects)? Can the sponsor confirm the absence of chronic low-grade toxicity to cardiac muscle, potentially resulting in impaired cardiac function, with cumulative Odomzo exposure given that functional echocardiography was not routinely performed in this study?

Sponsor's response

The sponsor thoroughly evaluated all available nonclinical and clinical data in collaboration with two independent cardiologists, to assess any potential effect of sonidegib on cardiac muscle.

As discussed in the Preclinical Pharmacology Written Summary, cardiovascular safety was extensively evaluated in dedicated telemetry studies as well as in multiple-dose dog studies with exposures exceeding the clinical exposure with no risks identified. Histopathologic evaluation of hearts from rat and dog studies up to 6 months in duration did not show any changes associated with sonidegib. Separate studies with cardiomyocytes were not conducted as no findings in skeletal or cardiac muscle were found in the rat and dog studies.

Recent internal data indicate that the effects of sonidegib on skeletal muscle cells can dissociate inhibition of the Smoothed (Smo) pathway, as determined by Gli1 expression (a downstream target of Smo/Sonic Hedgehog (Hh) signaling), from creatine phosphokinase (CK) release, a sign of muscle pathology. It was observed that relatively lower concentrations of sonidegib, although still sufficient to cause complete inhibition of the Hh pathway, did not cause signs of cytotoxicity such as CK release. Only at substantially higher concentrations was CK release evident. These data suggest Gli-independent Hh responses along the line of the non-canonical pathway.

Furthermore, a microarray study was performed to determine differences in the pathways regulated by non-damage- and damage-inducing doses of sonidegib and the results were validated by subsequent quantitative polymerase chain reaction (qPCR) analysis. This analysis showed that several critical pathways are involved. Due to the complex interplay between these pathways, no clear hypothesis on the mechanism of muscle toxicity has emerged from these cellular experiments.

Changes in myoglobin levels have not been reported with other agents from the same class. In Study A2201, per protocol, myoglobin values were evaluated as clinically indicated or when cardiac involvement was suspected. A review and analysis of the reported myoglobin levels from Study A2201 was conducted in relation to abnormal cardiac enzymes, ECGs, and cardiac AEs reported around the time of the laboratory abnormalities.

Data showed that abnormal myoglobin levels were noted in only one patient treated with sonidegib 800 mg [information redacted]. This patient had a long-standing history of intermittent myalgia dating back to 1970. During the course of the study, this patient had multiple episodes of muscle-related events including an investigator-reported AE of rhabdomyolysis and plasma CK >45-times the upper limit of the normal range (ULN). Despite the elevated myoglobin levels, troponin-I levels collected at the same time remained within the normal range and the corresponding ECGs showed no impact on the myocardium, hence excluding any underlying cardiac aetiology. According to the literature, increased myoglobin levels are often seen in parallel with significant CK elevations and do not correlate to cardiac effect.

The sponsor initiated a thorough cardiac evaluation of sonidegib during the early development of the compound. In the Phase I Study X2101, CK and cardiac enzymes (CK-MB and troponin T) were measured for all patients. CK-MB levels were also measured

concurrently with total CK. To determine whether CK elevations were solely due to skeletal muscle injury, or whether the elevations might also indicate myocardial injury, CK-MB levels were evaluated in all patients with Grade ≥ 3 CK elevations. The rationale to focus on patients with Grade ≥ 3 CK elevations was that these patients had clear evidence of muscle injury, and if sonidegib affects both skeletal and cardiac muscle they may also have evidence of myocardial injury.

Overall, 11 patients in Study X2101 had a CK-MB measurement concurrent with a Grade 3-4 CK elevation. Among these patients, CK-MB was above the ULN for 9 patients. In the setting of high CK elevations resulting from skeletal muscle injury, the absolute CK-MB can be above the ULN in the absence of cardiac muscle injury and the CK-MB/CK ratio (expressed as a percentage) is often utilised to address this. The CK-MB/CK ratio was $< 5\%$ (that is, within the normal reference range) for all 9 patients with elevated absolute CK-MB indicating that this was not reflective of cardiac muscle injury.

Two patients had elevations in troponin T; this was Grade 3 in one patient and Grade 4 in the other. Both elevations occurred in the absence of ischemic ECG changes or AEs suggestive of cardiac ischemia or cardiac dysfunction.

Overall review of the AEs for these 11 patients did not reveal any clinical events indicative of cardiac muscle injury or heart failure.

A similar evaluation of relevant data from the pivotal registration study (Study A2201) was performed where the CK-MB/CK ratio and troponin levels were measured after screening and when clinically indicated. Please refer to the response to Question 5 for a discussion of this evaluation from Study A2201. Serious and fatal cardiac-related events have been reported with other Hh-pathway inhibitors, these events are not entire. In the pivotal Study A2201, 3 cases of cardiac death on-treatment were reported with sonidegib 800 mg as of the 11 July 2014 cut-off date. These cases were adjudicated by independent cardiac experts. A review of the data for these patients revealed that all were > 80 -years-old and had cardiac comorbidities at baseline. A cardiac cause of death was ruled out in two of the cases, although a possible relationship to study drug for the third case [information redacted] could not entirely be excluded due to lack of relevant clinical information reported at the time of death. Furthermore, the treating physicians did not suspect a relationship to the study drug in any of the cases.

Evaluator's comments

Among the three patients with elevations of Troponin, all had pre-existing cardiac disease. Troponin I and T found in cardiac myocytes are commonly measured to determine if myocardial necrosis has occurred. However, these troponin sub-types may also be more rarely systemically released as a result of other clinical conditions, including pulmonary embolism, sepsis and renal failure. From the data presented, there is no currently identifiable causal link between Sonidegib exposure and cardiac infarction measurable by increased serum troponin.

Evaluation of data presented in addition to the responses to questions

In agreement with the Delegate for the submission, the sponsor presented 12 and 18 month follow-up efficacy and safety data from Study A2201.

The 18 month cut-off of 11 June 2014 represents an overall median duration of follow-up of 26.3 months with overall exposure to sonidegib of 207.2 patient-years. The mean (stSD) duration of exposure in months increased was 12.9 (7.57) for sonidegib 200 mg and 9.8 (8.30) for sonidegib 800 mg. Median relative dose intensity was 96.8% for sonidegib 200 mg and 90.7% for sonidegib 800 mg, again indicating better tolerability in the 200-mg arm.

At the time of the 18 month analysis, 54 patients (68.4%) in the sonidegib 200-mg arm and 65 patients (43.3%) in the sonidegib 800-mg arm had cumulative exposures exceeding 8 months.

At the 18 month cut-off, the majority of patients (87% overall) were not continuing treatment. The reasons for treatment discontinuation are shown in table below.

Table 19: FAS patient disposition

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)

Overall, the most common reasons for treatment cessation were adverse events (33.9%), progressive disease (20%), withdrawal by subject (16.1%) and physician decision (9.6%). This pattern of reasons for discontinuation was similar between the 200 mg and 800 mg dose groups. A negligible proportion of patients had ceased treatment throughout the study owing to protocol violations.

The results of the primary efficacy end-point, ORR, at the primary analysis time-point and 18-month follow-up are comparable. The point estimates of ORR for all patients (mBCC and laBCC) are higher at the 18-month time-point for the 200 mg and 800 mg cohorts. However, the 95% confidence intervals of the ORR% overlap between time-points

Table 20: Objective response rate (central review) for the laBCC and mBCC pEAS cohorts combined

	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	
	All patients		All patients		All patients	
	Sonidegib 200 mg N=55	Sonidegib 800 mg N=116	Sonidegib 200 mg N=55	Sonidegib 800 mg N=116	Sonidegib 200 mg N=55	Sonidegib 800 mg N=116
Objective Response Rate (ORR: CR+PR)						
n (%)	20 (36.4)	39 (33.6)	25 ^a (45.5)	47 (40.5)	24 ^b (43.6)	48 (41.4)
95% CI (%)	(23.8, 50.4)	(25.1, 43.0)	(32.0, 59.4)	(31.5, 50.0)	(30.3, 57.7)	(32.3, 50.9)
Diff. between tmt groups %	-2.7		-4.9		-2.3	
95% CI (%)	(-18.73, 12.45)		(-21.07, 11.00)		(-18.45, 13.56)	
Best Overall Response, n (%)						
CR, n (%)	2 (3.6)	0	2 (3.6)	1 (0.9)	2 (3.6)	1 (0.9)
95% CI	(0.4, 12.5)	(0.0, 3.1)	(0.4, 12.5)	(0.0, 4.7)	(0.4, 12.5)	(0.0, 4.7)
PR	18 (32.7)	39 (33.6)	23 ^a (41.8)	46 (39.7)	22 ^b (40.0)	47 (40.5)
SD	31 (56.4)	54 (46.6)	26 (47.3)	51 (44.0)	27 (49.1)	50 (43.1)
PD	0	1 (0.9)	0	2 (1.7)	0	2 (1.7)
UNK	4 (7.3)	22 (19.0)	4 (7.3)	16 (13.8)	4 (7.3)	16 (13.8)

The results of the pEAS population are similar to those seen in the centrally reviewed FAS population. The ORRs per central review were 48.1% (95% CI: 36.7, 59.6) and 41.1% (95% CI: 33.1, 49.3) for the combined laBCC and mBCC cohorts in the sonidegib 200 mg, and 800 mg arms, respectively.

The 18-month follow-up ORR for the laBCC and mBCC cohorts according to dose exposure is shown below in the table.

Table 21: ORR in centrally reviewed FAS populations, 18-month follow-up

	laBCC	mBCC
200mg sonidegib	56.1% (95% CI: 43.3, 68.3)	7.7% (95% CI: 0.2, 36.0)
800mg sonidegib	45.3% (95% CI: 36.5, 54.3)	17.4% (95% CI: 5.0, 38.8)

The ORR in the pEAS populations for the primary analysis and follow-up periods are shown in the table below.

Table 22: Best overall response summary table per central review using mRECIST for laBCC and RECIST 1.1 for mBCC (pEAS)

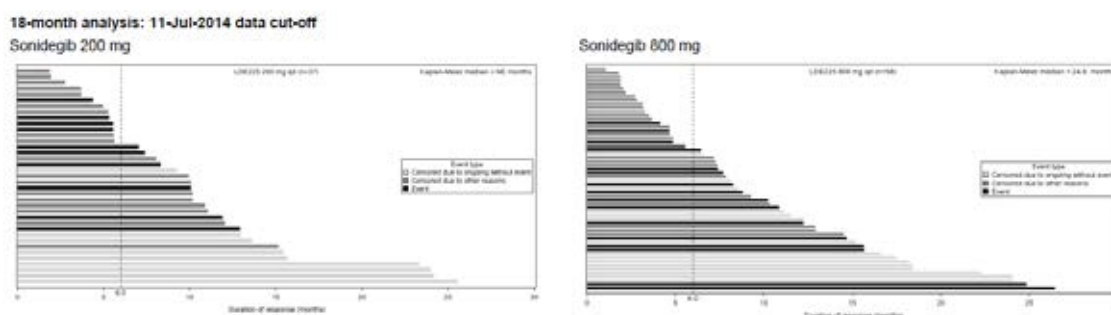
	Primary analysis: 28-Jun-2013 data cut-off				12-month analysis: 31-Dec-2013 data cut-off				18-month analysis: 11-Jul-2014 data cut-off			
	laBCC		mBCC		laBCC		mBCC		laBCC		mBCC	
	Sonidegib 200 mg N=42	Sonidegib 800 mg N=93	Sonidegib 200 mg N=13	Sonidegib 800 mg N=23	Sonidegib 200 mg N=42	Sonidegib 800 mg N=93	Sonidegib 200 mg N=13	Sonidegib 800 mg N=23	Sonidegib 200 mg N=42	Sonidegib 800 mg N=93	Sonidegib 200 mg N=13	Sonidegib 800 mg N=23
Objective Response Rate (ORR: CR+PR)												
n (%)	18 (42.9)	35 (37.6)	2 (15.4)	4 (17.4)	24 (57.1)	43 (46.2)	1 ^a (7.7)	4 (17.4)	23 ^b (54.8)	44 (47.3)	1 (7.7)	4 (17.4)
95% CI (%)	(27.7, 59.0)	(27.8, 48.3)	(1.9, 45.4)	(5.0, 38.8)	(41.0, 72.3)	(35.8, 56.9)	(0.2, 36.0)	(5.0, 38.8)	(38.7, 70.2)	(36.9, 57.9)	(0.2, 36.0)	(5.0, 38.8)
Diff. between tmt groups %	-5.2		2.0		-10.9		9.7		-7.5		9.7	
95% CI (%)	(-23.68, 12.69)		(-28.76, 27.53)		(-28.75, 7.72)		(-19.96, 33.15)		(-25.50, 11.22)		(-19.96, 33.15)	
Best Overall Response, n (%)												
CR, n (%)	2 (4.8)	0	0	0	2 (4.8)	1 (1.1)	0	0	2 (4.8)	1 (1.1)	0	0
95% CI	(0.6, 16.2)	(0.0, 3.9)	(0.0, 24.7)	(0.0, 14.8)	(0.6, 16.2)	(0.0, 5.8)	(0.0, 24.7)	(0.0, 14.8)	(0.6, 16.2)	(0.0, 5.8)	(0.0, 24.7)	(0.0, 14.8)
PR	16 (38.1)	35 (37.6)	2 (15.4)	4 (17.4)	22 (52.4)	42 (45.2)	1 ^a (7.7)	4 (17.4)	21 ^b (50.0)	43 (46.2)	1 (7.7)	4 (17.4)
SD	21 (50.0)	39 (41.9)	10 (76.9)	15 (65.2)	15 (35.7)	34 (36.6)	11 (84.6)	17 (73.9)	16 (38.1)	33 (35.5)	11 (84.6)	17 (73.9)
PD	0	0	0	1 (4.3)	0	1 (1.1)	0	1 (4.3)	0	1 (1.1)	0	1 (4.3)
UNK	3 (7.1)	19 (20.4)	1 (7.7)	3 (13.0)	3 (7.1)	15 (16.1)	1 (7.7)	1 (4.3)	3 (7.1)	15 (16.1)	1 (7.7)	1 (4.3)

The primary outcome of Study A2201 was ORR. The ORR among the overall study population and the laBCC and mBCC patient cohorts seen at the 18-month follow-up time-point are comparable with the primary analysis, in both the FAS and pEAS populations. This additional data demonstrates a consistent effect and is supportive for sonidegib to be

registered for the proposed indication. At the proposed dose of 200 mg sonidegib, the ORR was approximately 7 fold higher in laBCC patients as compared to mBCC patients.

The secondary outcome of duration of response was reported for 67 patients with laBCC who were centrally assessed in the pEAS. The median duration of response was not estimable for patients in the 200mg group and was 24.8 months (95% CI 10.8, 26.4) for the 800mg group. Waterfall plots of duration of response in the responders in the FAS as seen in Figure 3 below.

Figure 3: Waterfall plot for duration of response per central review using mRECIST for laBCC cohort (all responders, FAS)



The secondary outcome of complete response rate was reported at the 18-month time-point for the FAS and pEAS populations.

Table 23: Complete response rate among laBCC and mBCC cohorts in the FAS and pEAS populations

		FAS	pEAS
200mg sonidegib	laBCC	4.5% (95% CI: 0.9, 12.7)	4.8% (95% CI: 0.6, 16.2)
	mBCC	0	0
800mg sonidegib	laBCC	0.8% (95% CI: 0.0, 4.3)	1.1% (95% CI: 0.0, 5.8)
	mBCC	0	0

The secondary outcomes of duration of response and complete response are consistent among the FAS and pEAS populations in those exposed to 200mg sonidegib. The complete response rate is low in the laBCC patients, and no mBCC patients experienced a CR.

18 month safety update

Among patients exposed to 200 mg sonidegib, the median duration of exposure increased from 8.9 months (range 1.3, 21.4) to 11.0 months (range 1.3, 33.5). For patients exposed to 800 mg, the median duration of exposure was 6.5 months (range 0.3 to 19.1) at the primary analysis as compared to 6.6 months (range 0.3, 31.5) at the 18-month follow-up cut-off.

The median dose intensity was 193.7mg/day (range 15.9 to 246.6) for the sonidegib 200mg cohort. Dose interruptions were reported in 68.4% of those in the 200mg cohort, with approximately two thirds of those having ≥ 2 events.

The sponsor reports that 'no new safety findings were evident with longer-term follow-up'. The pattern of adverse events was similar between the primary analysis and 18-month follow-up periods.

Second round benefit-risk assessment

Second round assessment of benefits

The efficacy of sonidegib in patients with laBCC and mBCC who have limited treatment options have been characterised in the 18-month follow-up data presented. The evaluator again notes that the trials of sonidegib were designed and run prior to the approval for vismodegib. The sponsor has provided an explanation for not performing a direct comparison of sonidegib and vismodegib in the future in their response.

For patients with laBCC treated with 200 mg sonidegib, the observed ORR was consistent with the data at primary analysis, with 56.1% of patients meeting this criterion. There majority of patients had either partial response or stable disease 50% and 38% of patients respectively. A best response of complete response was observed in 4.8% of patients.

Among the patients with mBCC treated with 200 mg sonidegib, no complete responders were identified, a partial response was observed in 1/13 patients (7.7%) and 11/13 patients (84.6%) had stable disease.

In the absence of a study of comparative efficacy, the 95% confidence interval for the ORR in the current submission is comparable with that in the currently approved PI for vismodegib, for both laBCC and mBCC patients:

Table 24: Comparative efficacy

	95% CI for ORR – sonidegib, 18-month follow-up, 200mg group	95% CI for ORR – vismodegib primary endpoint
laBCC	38.7% to 70.2%	30.5% to 56.0%
mBCC	0.2% to 36.0%	15.6% to 48.2%

The durability of response was not estimable for laBCC patients in the 200mg group.

Second round assessment of risks

In addition to the risks identified in the first round evaluation, the sponsor has presented data on the adverse events of special interest of: hypersensitivity-associated events, Grade 3 or 4 lipase elevation and QTcF prolongation. The reported incidence of second malignancy has not been compared with the background risk in sonidegib-unexposed individuals with BCC, nor presented according to duration of exposure to sonidegib.

Second round assessment of benefit-risk balance

Given the similarity of the primary efficacy end-point between the primary analysis and the 18-month time point, plus the similarity in estimated treatment effect in comparison with that for vismodegib, the overall risk-benefit is favourable.

Second round recommendation regarding authorisation

It is recommended that authorisation proceed for the proposed indication.

VI. Pharmacovigilance findings

Risk management plan

Summary of RMP evaluation²²

The sponsor submitted EU-RMP (version 1.0, data lock point 28 June 2013, dated 10 April 2014) and an Australian Specific Annex (version 1.0, release date 5 August 2014) in support of this application. In their response, the sponsor has submitted EU-RMP (version 2.0, data lock point 11 July 2014, dated 30 January 2015) and an Australian Specific Annex (version 2.0, release date 8 April 2015).

Table 25: Summary of key changes between EU RMP/ASA version 1.0 and EU RMP/ASA version 2.0

Summary of key changes	
Safety specification	<ul style="list-style-type: none"> • New important identified risk: Lipase/amylase increased • New important potential risks: Impaired fertility, post-natal development defects and fractures • New missing information: Female patients of childbearing potential taking concomitant oral contraceptives, carcinogenicity studies, patients with severe renal impairment and patients with anaemia. • Updated missing information: 'off-label use' changed to 'off-label use in patients with medulloblastoma, BCC appropriate for surgery or radiotherapy and other cancers', and 'patients with hepatic impairment' to 'patients with severe hepatic impairment'.
Pharmacovigilance activities	<ul style="list-style-type: none"> • New activities: Study A2201, Study CLDE225X2104 and Study CLDE225C2301
Risk minimisation activities	<ul style="list-style-type: none"> • Removed proposal for additional risk minimisation activities for identified risk 'myopathy'. • Added potential risk 'impaired fertility' to proposed additional risk minimisation activities. • Educational material details added including distribution strategy

²² Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Outstanding issues

Pharmacovigilance plan

Regarding the proposed 'enhanced surveillance program' for the risk of pregnancy exposure the sponsor should provide the following information:

- Describe how the sponsor will 'encourage HCP and patient reporting of exposure to sonidegib during pregnancy'.
- Describe how the sponsor will periodically remind prescribers and other health professionals of the importance of reporting pregnancy exposures and the required follow-up.
- Describe how the enhanced surveillance program will be conveyed in the educational program.
- Such information should be included in an update to the ASA.

Risk minimisation plan

Key to the success of the pregnancy prevention program is the implementation of education and facilitation of consent to avoid pregnancy exposure. The sponsor has proposed counselling forms for this purpose. Ideally, completion of these forms should be linked to supply of the medicine to ensure that patients have been appropriately informed and counselled regarding the risk of teratogenicity. The sponsor should provide the following information regarding the patient verification and counselling forms.

- Describe how the supply of sonidegib is linked to the successful completion of the verification forms. If these activities are not linked describe how the sponsor can be certain that a patient supplied with the medicine has been appropriately counselled of the risks (this is considered a key component of any pregnancy prevention program).
- The verification forms proposed for Australia should be submitted to the TGA for review.
- The distribution plan for the verification forms should be provided.
- Such information should be included in an update to the ASA.

As they comprise an important part of the risk minimisation plan for sonidegib, locally adapted educational materials should be provided to the TGA for review, preferably prior to approval.

The physician's survey, an activity to assess the effectiveness of educational materials is to be conducted in several European countries. Sonidegib is not yet approved in Europe. The sponsor should articulate a contingency plan for this activity to be conducted in Australia in the situation that sonidegib is approved in Australia but not in Europe in a timely fashion.

Outstanding PI recommendations to the delegate

The Delegate is advised that the vismodegib approved PI also contraindicates 'women of child-bearing potential, unless two reliable methods of contraception are being used'. It is recommended for regulatory consistency that similar restrictions apply for sonidegib.

It is recommended to the Delegate that the PI should contain a statement that the safety of long-term use has not yet been established.

New and outstanding recommendations from second round evaluation

Comments on the safety specification of the RMP

Clinical Evaluation Report

The safety specification in the draft RMP is satisfactory.

Nonclinical Evaluation Report

Results and conclusions drawn from the nonclinical program for sonidegib detailed in the sponsor's draft RMP are in general concordance with those of the nonclinical evaluator.

Proposed wording for conditions of registration

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

The sonidegib EU-RMP (version 2.0, data lock point 11 July 2014, dated 30 January 2015) and an Australian Specific Annex (version 2.0, release date 8 April 2015) to be revised to address the outstanding issues in this report should be implemented (see outstanding issues above).

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

Pharmaceutical chemistry/biological evaluation: The pharmaceutical chemistry evaluation was supportive of registration, notwithstanding minor amendments to the PI.

Nonclinical

There were no objections to registration on nonclinical grounds.

Summary of the nonclinical findings

- The primary pharmacology studies demonstrated sonidegib to have an inhibitory effect on the hedgehog signalling pathway *in vitro* and *in vivo*.
- Secondary off-target effects of sonidegib and its' major metabolite were considered unlikely.
- There was a potential for pro-arrhythmic effect as observed at supra-therapeutic concentration in hERG-transfected cells. No changes in dog ECG parameters were observed in the initial 13 weeks of daily dosing, but QRS increase of approximately 12% and QTc increase of approximately 7% were observed in the 26 week repeat dose toxicity study.
- Sonidegib was highly bound to human plasma proteins (97 to 98%). It is not distributed into red blood cells.
- The metabolism of sonidegib was primarily by oxidation/reduction with subsequent catalysis by CYP3A4. Sonidegib was not observed to be an inducer of any CYP

isoenzymes, but did inhibit CYP2B6 and CYP2C9. It was observed to inhibit BCRP. It is not transported into hepatocytes by OAT, OATP or OCT.

- The major primary metabolite, M48, was not pharmacologically active. The major route of excretion was in faeces, with a trivial amount in urine.
- Toxic effects of sonidegib seen in repeat-dose studies were consistent with the known sites of Hedgehog-dependent signalling; bone, teeth, GI tract, skin and reproductive tract.
- Concomitant sonidegib and simvastatin dosing in rats resulted in a synergistic increase in histological and biomarkers (AST and CK) of skeletal muscle injury.
- Sonidegib showed no evidence for induction of mutations in standard bacterial reverse mutation assays. The drug also showed no evidence for clastogenicity in both *in vitro* (human peripheral blood lymphocytes) and *in vivo* (rat bone marrow micronucleus) assays. Sonidegib was not tested for carcinogenicity.
- Female rat fertility was very sensitive to sonidegib (exposure ratio at NOAEL of approximately 0.003 for ≥ 6 weeks dosing), with evidence for induction of early resorptions. Embryofetal development in rabbits was also highly sensitive to sonidegib. External and skeletal malformations were found at the higher doses tested (exposure ratios > 0.05), whilst the incidence of skeletal variations was elevated after doses that did not produce detectable levels of sonidegib in the maternal circulation (exposure ratio $<< 0.0001$). The results suggest induction of both teratogenicity and fetotoxicity.
- Juvenile rats dosed orally with sonidegib for five weeks showed high sensitivity to toxic effects (exposure ratio at NOAEL of approximately 0.02 to 0.03). The spectrum of tissues showing test article-related changes was similar to that for adults (bone, teeth, and alimentary tract), but with the addition of minimal to moderate sciatic nerve fibre degeneration.
- Based on its fetotoxic and teratogenic effects, sonidegib is assigned Pregnancy Category X.¹²

Clinical

The clinical evaluator recommended approval of the submission following the second round of evaluation.

Pharmacology

The following data were provided for evaluation:

- Three clinical pharmacology studies in healthy volunteers
- Four Phase I/II studies of pharmacokinetics in patients with advanced solid tumours
- Five pooled analyses of PK-QTc, exposure-efficacy, exposure-CK, population PK and PK in Japanese versus non-Japanese patients.

Pharmacokinetics

No oral bioavailability study was performed due to the insolubility of sonidegib.

An estimate of bioavailability from a mass balance Study A2110 was approximately 6 to 7% of the oral dose.

A food-effect was observed, with $AUC_{0-\infty}$ and C_{max} 7.4 and 7.8 fold higher respectively in fed compared to fasted state. T_{max} was approximately 2 hours across the dose range studied in fasting state as compared to 5 hours in the fed state.

Sonidegib exposure was less than dose proportional over the dose ranges tested (2 fold increase in exposure between 200 mg and 800 mg)

Accumulation following repeat dosing is likely; the population PK analysis estimated the geometric mean accumulation ratio to be 19.4 (%CV = 109)

Sonidegib is primarily metabolised by CYP3A4. Sonidegib exposure was significantly increased with concomitant ketoconazole and decreased by concomitant rifampicin administration.

Effect of age, gender and weight

The population PK evaluation demonstrated no effect of age, gender or weight on the PK of sonidegib. The PI is appropriately worded.

Effect of ethnicity

Following single-dosage, Japanese patients had a higher mean exposure than Caucasian and Black subjects. However, from the population PK analysis, the clinical evaluator states that 'the estimated steady state exposure parameters were similar for Japanese and Westerner cancer patients'.

Renal impairment

Sonidegib is negligibly excreted by the renal route. A dedicated study was not performed. The population PK analysis, included patients with mild and moderate renal impairment. No dose adjustment is required, as stated in the PI.

Hepatic impairment

A dedicated study of patients with hepatic impairment was not performed. The population PK analysis permitted an assessment of the effect of mild hepatic impairment only. No conclusions can be drawn on the effect of moderate or severe hepatic impairment. The PI contains an appropriately worded statement.

Pharmacodynamics

No significant pharmacodynamic effect was observed on QTcF interval with 200 mg daily sonidegib administration. However, the sponsor's response did contain reports of patients experiencing. (see Safety discussion).

No exposure-efficacy relationship was observed on ORR, PFS or TTR in the pivotal study between 200 mg and 800 mg daily sonidegib; the proposed dose is 200 mg daily.

A positive relationship between Grade 3 or 4 elevations and exposure was observed between the two dose regimens studied.

Efficacy

Pivotal Study A2201 was a Phase II randomised double-blind study of efficacy and safety of two doses of sonidegib (200 mg or 800 mg daily, randomised 1:2 respectively) in patients with locally advanced (laBCC) or metastatic basal cell carcinoma (mBCC), not amenable to radiotherapy or surgery. Treatment was administered on an ongoing outpatient basis until patient-determined withdrawal or at the discretion of the investigator.

The schematic of the study design is shown in Figure 2 above.

Inclusion and exclusion criteria

The study included patients 18 years or older diagnosed with laBCC that was not amenable to radiation therapy, curative surgery, or other local therapies, or with mBCC. Only patients with histologically confirmed diagnoses of laBCC or mBCC were eligible for enrollment.

Patients with laBCC were also required to have measurable disease, defined as at least one lesion that could be accurately measured in at least one dimension ≥ 10 mm with magnetic resonance imaging (MRI) scan or on colour photographs. Patients with mBCC were also required to have measurable disease, defined as at least one non-nodal lesion that could 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 (that is, lymph node) ≥ 15 mm in short axis with spiral computerized tomography (CT) scan or MRI scan (irrespective of slice thickness).

All patients were required to have World Health Organization (WHO) performance status ≤ 2 (that is, able to carry out all normal activities without restriction (PS = 0), restricted in physically strenuous activity but ambulatory and able to carry out work (PS = 1), or ambulatory and capable of all self-care, unable to carry out any work, and up and about more than 50% of waking hours (PS = 2)). All patients were required to have adequate bone marrow, liver, and renal function meeting pre-specified criteria.

Analysis populations

The analysis populations comprised the FAS which was assessed according to treatment assignment. The primary efficacy analysis set is a subset of the FAS and included patients with laBCC with tumours that were adequately assessed by MRI or photography or both.

Disease characteristics of the total 230 patients within each analysis population are shown below.

Table 26: Study A2201 Full analysis set (FAS)

		Sonidegib 200 mg QD (n=79)	Sonidegib 800 mg QD (n=151)	Total (n=230)
laBCC	Total	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	Total	13 (16.5)	23 (15.2)	36 (15.7)

Table 27: Study A2201 Primary efficacy analysis set (pEAS)

		Sonidegib 200 mg QD (n=55)	Sonidegib 800 mg QD (n=116)	Total (n=171)
laBCC	Total	42 (76.4%)	93 (80.2%)	135 (78.9%)
	Aggressive histology	24 (43.6%)	56 (48.3%)	80 (46.8%)
	Non-aggressive histology	18 (32.7%)	37 (31.9%)	55 (32.2%)
mBCC	Total	13 (23.6%)	23 (19.8%)	36 (21.1%)

Sixteen of the pivotal study participants (15 laBCC and 1 mBCC) had a diagnosis of Gorlin syndrome.

The sponsor presented an initial interim pivotal study analysis which was supplemented by a 12 month and 18 month follow-up analysis presented at the second round of evaluation. The overall median duration of follow-up was 26.3 months. Overall exposure to sonidegib increased from patient-years (for the primary analysis) to 207.2 patient-years (for the 18 month analysis).

At the time of the 18 month analysis:

- 54 patients (68.4%), 34 patients (43.0%), and 17 patients (21.5%), respectively, were exposed to treatment with sonidegib 200 mg for cumulative periods of ≥ 8 months, ≥ 12 months, and ≥ 20 months.
- 65 patients (43.4%), 45 patients (30.0%) and 21 patients (14.0%) were exposed to sonidegib 800 mg for ≥ 8 months, ≥ 12 months, and ≥ 20 months, respectively.

The primary objective of the study, ORR assessed by central review according to mRECIST in patients with laBCC, and RECIST version 1.1 in patients with mBCC, was met.

Table 28: Objective response rates per central review for laBCC and mBCC cohorts combined (pEAS and FAS, 18 month analysis)

	Primary analysis: 28-Jun-2013 data cut-off		18-month analysis: 11-Jul-2014 data cut-off	
	Sonidegib 200 mg	Sonidegib 800 mg	Sonidegib 200 mg	Sonidegib 800 mg
Primary efficacy analysis set (pEAS)				
Objective response rate, %	36.4	33.6	43.6	41.4
95% confidence interval	(23.8, 50.4)	(25.1, 43.0)	(30.3, 57.7)	(32.3, 50.9)
Full analysis set (FAS)				
Objective response rate, %	41.8	32.5	48.1	41.1
95% confidence interval	(30.8, 53.4)	(25.1, 40.5)	(36.7, 59.6)	(33.1, 49.3)

Secondary end-points observed at the 18 month follow-up time-point for the 200 mg cohort (proposed dose) are shown below.

Table 29: Secondary end points observed at the 18 month follow-up time point for the 200 mg cohort (proposed dose)

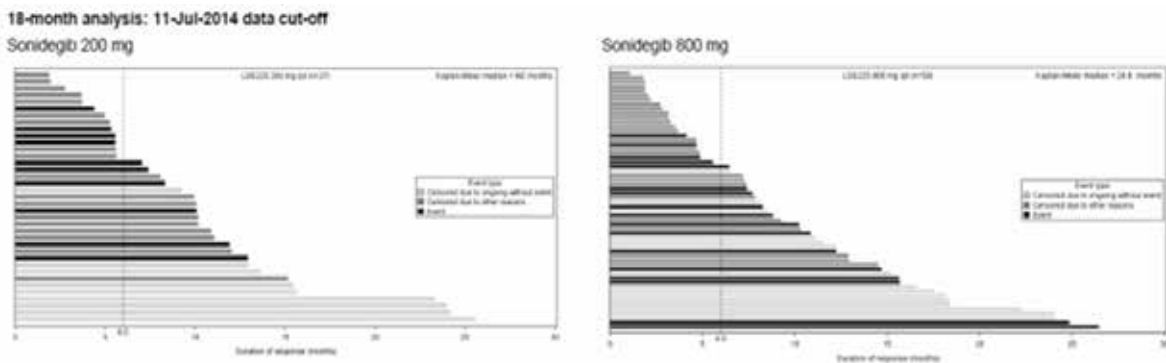
	6 month			18 month		
	laBCC N=66	mBCC N=13	combined N=79	laBCC N=66	mBCC N=13	combined N=79
Objective response rate, n (%)	31 (47.0)	2 (15.4)	33 (41.8)	37 (56.1)	1 (7.7)	38 (48.1)
95% CI	(34.6, 59.7)	(1.9, 45.4)	(30.8, 53.4)	(43.3, 68.3)	(0.2, 36.0)	(36.7, 59.6)
Best overall response, n (%)						
Complete response	2 (3.0)	0	2 (2.5)	3 (4.5)	0	3 (3.8)
Partial response	29 (43.9)	2 (15.4)	31 (39.2)	34 (51.5)	1 (7.7)	35 (44.3)
Disease stabilization	29 (43.9)	10 (76.9)	39 (49.4)	23 (34.8)	11 (84.6)	34 (43.0)
Disease progression	1 (1.5)	0	1 (1.3)	1 (1.5)	0	1 (1.3)
Unknown	5 (7.6)	1 (7.7)	6 (7.6)	5 (7.6)	1 (7.7)	6 (7.6)
Duration of response						
No. of events*	4	0	4	10	0	10
No. censored	27	2	29	27	1	28
Median (95% CI) (mo)	NE	NE	NE	NE	NE	NE
Event-free probability (%), (95% CI)						
12 months	65.9 (25.7, 88.0)	NE	66.7 (26.1, 88.6)	65.6 (43.2, 81.0)	100.0 (NE)	67.0 (45.2, 81.8)
Progression-free survival						
No. of events*	7	4	11	15	6	21
No. censored	59	9	68	51	7	58
Median (95% CI) (mo)	NE	13.1 (5.6, 13.1)	NE	22.1 (NE)	13.1 (NE)	22.1 (NE)
Progression-free survival probability (%), (95% CI)						
12 months	83.5 (64.6, 92.9)	64.9 (24.9, 87.4)	80.2 (63.5, 89.8)	82.2 (67.0, 90.8)	58.9 (23.4, 82.5)	78.2 (64.4, 87.1)
Time to tumor response						
Median (95% CI) (mo)	3.9 (3.6, 4.2)	4.6 (1.8, 7.4)	3.9 (3.6, 4.2)	4.0 (3.8, 5.6)	1.8 (NE)	4.0 (3.7, 5.6)
Overall Survival						
No. of patients who died, %	1 (1.5)	1 (7.7)	2 (2.5)	3 (4.5)	3 (23.1)	6 (7.6)

	6 month			18 month		
	laBCC N=66	mBCC N=13	combined N=79	laBCC N=66	mBCC N=13	combined N=79
No. censored, %	65 (98.5)	12 (92.3)	77 (97.5)	63 (95.5)	10 (76.9)	73 (92.4)
Median OS (mo)	NE	NE	NE	NE	NE	NE
OS rate, % (95% CI)						
12 months	100 (NE)	87.5 (38.7, 98.1)	97.8 (85.3, 99.7)	100 (NE)	90.9 (50.8, 98.7)	98.5 (89.7, 99.8)

*Full analysis set included all randomized patients.*Event refers to disease progression or death due to any reason. CI: confidence interval. NE: not estimable. Sources:

The waterfall plots of duration of response at the 18 month follow-up time point are shown below.

Figure 4: Waterfall plots of duration of response at the 18-month follow-up time-point



The evaluator states ‘exploratory patient-reported outcomes showed that the majority of patients treated with sonidegib 200 mg qd experienced maintenance and/or improvement in their health status, functioning, and disease-related symptoms’.

Safety

A total of 293 patients were included in the safety population, of which 229 were from the pivotal study.

In support of the proposed dose, in regard to AE categories, the clinical evaluator noted ‘the safety and tolerability profile of sonidegib 200 mg qd was notably superior to 800 mg qd, with lower AE incidences in each category’.

The commonest reported adverse events (any grade) for patients receiving 200 mg sonidegib daily were: muscle spasms (49.4%); alopecia (43.0%); dysgeusia (38.0%); nausea (32.9%); CK increased (29.1%); fatigue (29.1%); weight decreased (26.6%) and diarrhoea (24.1%). The Grade 3/4 AE profile of the two dose regimens are described below.

At the second round evaluation, the sponsor reported that 'no new safety findings were evident with longer-term follow-up'.

Table 30: Study A2201 rade 3/4 adverse events (irrespective of causality) with at least a 2% incidence in either treatment arm by Preferred Term; safety set

Preferred term	Sonidegib 200 mg	Sonidegib 800 mg
	N=79 Grade 3/4 n (%)	N=150 Grade 3/4 n (%)
Any grade 3/4 AE	24 (30.4)	84 (56.0)
Blood creatine phosphokinase increased	5 (6.3)	19 (12.7)
Lipase increased	4 (5.1)	8 (5.3)
Muscle spasms	2 (2.5)	8 (5.3)
Hypertension	2 (2.5)	4 (2.7)
Asthenia	2 (2.5)	0
Weight decreased	1 (1.3)	8 (5.3)
Rhabdomyolysis	1 (1.3)	5 (3.3)
Alanine aminotransferase increased	1 (1.3)	4 (2.7)
Aspartate aminotransferase increased	1 (1.3)	4 (2.7)
Nausea	1 (1.3)	4 (2.7)
Syncope	1 (1.3)	3 (2.0)
Decreased appetite	0	6 (4.0)
Anaemia	0	3 (2.0)
Fatigue	0	3 (2.0)
Dehydration	0	3 (2.0)
Hyperkalaemia	0	3 (2.0)
Myalgia	0	3 (2.0)

Deaths and serious adverse events

A total of 2 patients died in the 200 mg arm at the primary analysis point, with one further death occurring during the follow-up period. None of the deaths were directly attributable to sonidegib exposure, with the majority being associated with the underlying malignancy or co-existent morbidity.

SAEs were reported in 11 patients in the 200 mg cohort, three patients (3.8%) of the 200 mg cohort experienced CK increase, rhabdomyolysis and syncope which were considered related to sonidegib.

Adverse events of special interest

Among the AEs of special interest of myopathy/myositis, alopecia, nausea/vomiting, decreased weight/appetite, dysgeusia, fatigue and diarrhoea, all were observed less commonly in the 200 mg cohort than the 800 mg cohort. Grade 1 to 2 events occurred more commonly than Grade 3 to 4 events for each category, with the incidence of Grade 3 to 4 AEs being less than 5% in the 200 mg cohort for all categories.

Clinical chemistry

Elevations of CK were reported in 45 patients (57.0%), including 5 patients (6.3%) with Grade 3 or 4 increases, in the 200 mg cohort.

Other clinical chemistry abnormalities observed (at primary analysis) among the 200 mg cohort were: hypercholesterolaemia (56 patients (70.9%), all Grade 1/2 events), hyperglycaemia (37 patients (46.8%), including 3 patients (3.8%) with Grade 3/4 increases), and increased lipase (31 patients (39.2%), including 9 patients (11.4%) with

Grade 3 or 4 increases). In the 18 month update, Grade 3 to 4 lipase elevations were reported in 6.3% of the 200 mg cohort.

Hypersensitivity

In the 18 month update hypersensitivity events occurred in 21.5% of the 200 mg group, the most commonly occurring events were pruritis, rash, asthma and photosensitivity reaction.

Cardiovascular safety

At the primary analysis, no events of QT prolongation were reported from the pivotal study. However, at the 18-month safety update, 10 out of 72 patients (13.9%) were reported to have had new events of QTcF prolongation > 450 ms. This observed risk was not reported in the PI presented at the sponsor's response.

Risk of second malignancy

The 18 month update documented 2 out of 79 patients in the 200 mg cohort and 8 out of 150 in the 800 mg cohort having Grade 3 to 4 AEs in the neoplasm benign, malignant and unspecified category.

In the absence of a placebo-controlled arm for comparison, the background risk of malignancy in the trial participants cannot be specifically elucidated from the currently available data.

Risk management plan

The RMP evaluation was supportive of registration. The RMP evaluator recommended that the PI for sonidegib contain the same advice as for vismodegib in regard to the use of contraception in women of child-bearing potential. Satisfactory advice is contained in the sonidegib PI under the heading 'Women of child-bearing potential and sexually active men'

The sponsors' responses to the second round RMP evaluation dated 7 July are acceptable.

Risk-benefit analysis

Delegate's considerations

With the provision of the 18 month follow-up data for the pivotal study, the sponsor has satisfactorily demonstrated the efficacy and safety of sonidegib for the treatment of local advanced or metastatic basal cell carcinoma.

The wording of the proposed indication, and selection of dose regimen, is supported by the data presented for evaluation.

In the pivotal study, there were only 13 patients with metastatic disease (5.7% of the total), as compared to 33 presented in the submission for vismodegib (as seen in the currently approved PI). The estimated ORR of this small number of sonidegib-exposed patients (6 month ORR 95% CI 1.9 to 45.4%, 18-month ORR 95% CI 0.2 to 36.0%) is comparable with those exposed to vismodegib (15.6 to 48.2%).

The median duration of PFS for mBCC patients was 13.1 months for sonidegib-exposed patients, as compared to 9.5 months for vismodegib.

The clinical development program of sonidegib occurred during that for its natural comparator vismodegib, which precluded a head-to-head comparison of both agents. The sponsor has stated that no comparative study is planned. The reported ORR outcome of

the sonidegib pivotal study is consistent with that seen in the currently approved PI for vismodegib.

For patients with basal cell carcinoma that is locally advanced and not amenable to curative treatment or those with metastatic disease, treatment options remain limited. The efficacy and safety of sonidegib are similar, but not identical to those reported for vismodegib and it is plausible that patients who are intolerant of vismodegib may receive a benefit from sonidegib, and vice versa, in the event of sonidegib being registered.

Appropriate advice is contained in the PI/CMI in order to prevent inadvertent exposure of sonidegib to pregnant women or those planning on becoming pregnant. Sonidegib has been classified as Pregnancy Category X;¹² given the risk of severe fetal malformation and teratogenicity, consistent with that for vismodegib. A warning to not become pregnant following at least 20 months following last sonidegib exposure is based upon the population PK modelling.

The amended PI should be presented for review before registration can proceed.

Proposed action

Sonidegib should be approved for entry onto the ARTG for the following indications:

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.*

Request for ACM advice²³

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Odomzo hard capsule containing sonidegib diphosphate 200 mg for the following indications:

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.*

²³ The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines. The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Specific conditions of registration applying to these goods

The sonidegib Risk Management Plan (RMP), Plan Version 2.2 (dated 16 June 2015, DLP 1 June 2014) and Australian Specific Annex Version 3.0 (dated 14 July 2015) and any future updates as agreed with the TGA will be implemented in Australia.

The sponsor should:

- commit to include the procedure for handling reports of pregnancy exposure (as detailed in the response dated 8 April 2015) in the next update of the ASA
- submit the final versions of the educational materials to the TGA once they are available and attach them to the ASA.

Attachment 1. Product Information

The PI for Odomzo approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia

Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605

<https://www.tga.gov.au>