Risk Management Plan

Sonidegib

LDE225

16-September-2025

EU Risk Management Plan for Sonidegib

RMP version to be assessed as part of this application:

RMP Version number:	**8.3**
Data lock point for this RMP:	**12-Sep-2025**
Date of final sign off:	**16-Sep-2025**

Rationale for submitting an updated RMP:	To add the results of carcinogenicity studies performed in mice and rats with Sonidegib.
Summary of significant changes in this RMP:	Following changes have been performed: - added carcinogenicity results in Part II: Module SII-Non-clinical part of the safety specification and in Part VI IIB Summary of important risks. -Part II: Module SV-Post-authorization experience has been updated -minor changes in PART I: Product Overview in line with SmPC and Guidance on the format of the risk management plan (RMP) in the EU – in integrated format Rev2 (30 March 2017) by changing adverse event with adverse reactions, adding information for pharmaceutical form and deleting special population from posology. Table II 1-2 Key Safety findings (from pre-clinical studies) has been updated to include the results of carcinogenicity studies.
Other RMP versions under evaluation: *RMP Version number:* *Submitted on:* *Procedure number:*	Not applicable.
Details of the currently approved RMP: **Version number:** **Approved with procedure:** **Date of approval (opinion date):**	 7.5 EMEA/H/C/002839 05-Jul-2021
QPPV name:	Dr. Victoria Bodea
QPPV signature:	[redacted]

TABLE OF CONTENTS

List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AUC	Area under the blood concentration-time curve
AUCinf	Area under the plasma concentration-time curve from time zero extrapolated to infinity
BCC	Basal cell carcinoma
BCRP	Breast cancer resistance protein
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CK	Creatine kinase
CL/F	Apparent systemic clearance from plasma
Cmax	Peak blood concentration
CNS	Central nervous system
CR	Complete response
CSR	Clinical study report
Ctrough	Trough concentration
cuSCC	Cutaneous squamous cell carcinoma
DHCP	Dear health care providers
ECR	Eindhoven cancer registry
EMA	European Medicines Agency
EU	European Union
FPFV	First patient first visit
GI	Gastrointestinal
HCP	Health care provider(s)
Hh	Hedgehog
HIV	Human immunodeficiency virus
HLT	High level term
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
HR	Hazard ratio
IC50	Median inhibition concentration
IRR	Incidence rate ratio
laBCC	Locally advanced basal cell carcinoma
LPLV	Last patient last visit
mBCC	Metastatic basal cell carcinoma
MedDRA	Medical dictionary for regulatory activities
MRP2	Multi-drug resistant protein 2
NMSC	non-melanoma skin cancer
NOEL	No observed effect level
OAT	Organic anion-transporter
OATP	Organic anion-transporting polypeptide
OCT	Organic cation-transporter
OR	Odds ratio
ORR	Objective response rate

PAES	Post-authorization efficacy study
PASS	Post-authorization safety study
PK	Pharmacokinetics
PSUR	Periodic safety update report
PT	Preferred term
PhV	Pharmacovigilance
RMP	Risk management plan
SAEs	Serious adverse events
SCC	Squamous cell carcinoma
SCP	Summary of clinical pharmacology
SCD	Sudden cardiac death
SIR	Standardized incidence ratio
Smo	Smoothened
SmPC	Summary of product characteristics
SMQ	Standardized MedDRA query
WCBP	women of child bearing potential
ULN	Upper limit of normal
UK	United Kingdom
US	United States
UV	Ultraviolet

PART I: Product Overview

Table Part I.1– Product(s) Overview

Active substance(s) (INN or common name)	Sonidegib Odomzo®
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic agents, other antineoplastic agents, ATC code: L01XJ02
Marketing Authorisation Applicant:	Sun Pharmaceutical Industries Europe B.V (Marketing Authorisation has been transferred from Novartis to Sun Pharmaceutical Industries Europe B.V)
Medicinal products to which this RMP refers	Sonidegib 200 mg hard capsules
Invented name(s) in the European Economic Area (EEA)	Odomzo® 200 mg hard capsules
Marketing authorisation procedure	Centralized procedure EMEA/H/C/002839
Brief description of the product	**Chemical class:** Sonidegib is an antineoplastic agent (new chemical entitiy)
	Summary of mode of action: Sonidegib is an orally bioavailable inhibitor of the Hh signalling pathway. It binds to Smoothened (Smo), a G protein-coupled receptor-like molecule that positively regulates the Hh pathway and eventually activates and releases glioma-associated oncogene (GLI) transcription factors, which induces the transcription of Hh target genes involved in proliferation, differentiation and survival. Aberrant Hh signalling has been linked to the pathogenesis of several types of cancer, including basal cell carcinoma (BCC). Sonidegib binding to Smo will inhibit Hh signalling and consequently block signal transduction.
	Important information about its composition: Product obtained through chemical synthesis.
Hyperlink to the Product Information	Please refer to the enclosed section 1.3.1.
Indication(s) in the EEA	*Current:* 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.
	Proposed: Not applicable
Dosage in the EEA	*Current:* Posology: The recommended dose is 200 mg sonidegib taken orally. Treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity develops.

Dose modifications for creatine phosphokinase (CK) elevations and muscle-related adverse reactions:
Temporary dose interruption and/or dose reduction of Odomzo therapy may be required for CK elevations and muscle-related adverse reactions.

Table 1 summarises recommendations for dose interruption and/or dose reduction of Odomzo therapy in the management of symptomatic CK elevations and muscle-related adverse reactions (such as myalgia, myopathy, and/or spasm).

Table 1 Recommended dose modifications and management for symptomatic CK elevations and muscle-related adverse reactions

Severity of CK elevation	**Dose modifications* and management recommendations**
Grade 1 [CK elevation >ULN - 2.5 x ULN]	• Continue treatment at the same dose and monitor CK levels weekly until resolution to baseline level and then monthly thereafter. Monitor muscle symptoms for changes until resolution to baseline. • Check renal function (serum creatinine) regularly and ensure that patient is adequately hydrated.
Grade 2 **without** renal impairment (serum Cr ≤ ULN) [CK elevation >2.5 x ULN - 5 x ULN]	• Interrupt treatment and monitor CK levels weekly until resolution to baseline level. • Monitor muscle symptoms for changes until resolution to baseline. Upon resolution, resume treatment at the same dose level and measure CK monthly thereafter. • Check renal function (serum creatinine) regularly and ensure that patient is adequately hydrated. • If symptoms re-occur, interrupt treatment until resolution to baseline. Re-introduce sonidegib at 200 mg every other day and follow the same monitoring recommendations. If symptoms persist despite alternate-day dosing, consider discontinuing treatment.
Grade 3 or 4 **without** renal impairment (serum Cr ≤ ULN) [Grade 3 (CK elevation >5 x ULN - 10 x ULN)] [Grade 4 (CK elevation >10 x ULN)]	• Interrupt treatment and monitor CK levels weekly until resolution to baseline. Monitor muscle symptoms for changes until resolution to baseline. • Check renal function (serum creatinine) regularly and ensure that patient is adequately hydrated. • If renal function is **not impaired** and CK resolves to baseline, consider resuming treatment at 200 mg every other day. CK levels should be

	measured weekly for 2 months after re-administration of sonidegib and monthly thereafter.
Grade 2, 3 or 4 **with** renal impairment (serum Cr > ULN)	• If renal function **is impaired**, interrupt treatment and ensure that the patient is adequately hydrated and evaluate other secondary causes of renal impairment. • Monitor CK and serum creatinine levels weekly until resolution to baseline. Monitor muscle symptoms for changes until resolution to baseline. • If CK and serum creatinine levels return to baseline consider resuming treatment at 200 mg every other day and measure CK levels weekly for 2 months and monthly thereafter; otherwise discontinue treatment permanently.

* The above recommendations for dose modifications are based on the Common Terminology Criteria for Adverse Events (CTCAE) v4.03, developed by the National Cancer Institute (USA). The CTCAE is a standardised classification of side effects used in assessing medicinal products for cancer therapy.
Cr: creatinine; ULN: upper limit of normal

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

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

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

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

Duration of treatment:
In clinical trials, treatment with Odomzo was continued until disease progression or until unacceptable toxicity. Treatment interruptions of up to 3 weeks were allowed based on individual tolerability.

Benefit of continued treatment should be regularly assessed, with the optimal duration of therapy varying for each individual patient.

Method of administration:

Odomzo is for oral use. The capsules must be swallowed whole. They must not be chewed or crushed. The capsules must not be opened due to risk of teratogenicity.

	Odomzo must be taken at least two hours after a meal and at least one hour before the following meal to prevent increased risk of adverse events due to higher exposure of sonidegib when taken with a meal. If vomiting occurs during the course of the treatment, then no re-dosing of the patient is allowed before the next scheduled dose. If a dose is missed, it should be taken as soon as this is realised, unless more than six hours have passed since it was scheduled to be taken; in this case, the patient should wait and take the next scheduled dose.
	Proposed: Not applicable.
Pharmaceutical form(s) and strengths	*Current:* Hard capsule (capsule) Opaque pink hard capsule containing white to almost white powder with granules, with "NVR" imprinted in black ink on the cap and "SONIDEGIB 200MG" imprinted in black ink on the body. The size of the capsule is "Size #00" (dimensions 23.3 x 8.53 mm).
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the EU?	No

Part II Safety Specification

Part II: Module SI-Epidemiology of the indication(s) and target population(s)

Indication:

Basal Cell Carcinoma

Brand names of concerned products (with this indication)

Odomzo® is indicated for the treatment of adult patients with locally advanced basal cell carcinoma (laBCC) who are not amenable to curative surgery or radiation therapy.

SI.1- Epidemiology of the disease

Basal cell carcinoma:

Incidence:

Basal cell carcinoma (BCC) is the most common type of malignant skin tumor. In a systematic review, BCC incidence rates varied significantly between regions (Lomas et al 2012). Based on data from the United Kingdom (UK) Cancer Registration, standardized rates to the European population ranged between 76.2 to 90.4 cases per 100000 person-years in England and Scotland, respectively. However, relevant variations were observed within each region. In the case of England, incidence rates ranged from 0.24 cases in London to 121.29 cases per 100000 person-years in South West. In other European countries, incidence rates per 100000 person-years were as follows: Switzerland and Italy around 70 cases in 1995, Slovakia 38 cases in 1994, Denmark 91.2 cases in males and 96.6 cases in females in 2007, and Croatia 33.6 cases between 2003 to 2005 (Lomas et al 2012).

In North America, male incidence per 100000 person-years in Manitoba (Canada) was 93.9 cases in 2000, and in Alberta (Canada), it was 147.0 cases in 2006. In the United States (US), incidence rates per 100000 person-years were available for different states: Arizona 935.9 cases in 1996, and New Hampshire and Minnesota around 170 cases in 1980. In Australia, incidence rate per 100000 person-years in 2002 was 884 cases. In Nambour (Queensland, Australia), the male incidence was 1813 cases per 100000 person-years between 1997 and 2006 (Lomas et al 2012).

Basal cell carcinoma incidence rates also varied between countries in a study conducted based on data from four European cancer registries. Incidence rates for first primary BCC were highest in the Eindhoven Cancer Registry (ECR) area (the Netherlands), with a European standardized incidence rate of 158 per 100000 person-years. The incidence was lowest for Malta, with a European standardized incidence rate of 77, and Finland and Scotland had intermediate rates of 95 and 99 (de Vries et al 2012a).

A sustained rise in the incidence of BCC has been documented in different studies. In the Netherlands, incidence rate trend based on the ECR (Netherland), a population based cancer registry, yielded an annual increase of 2.3% (95% confidence interval (CI): 2.0, 2.7) in men and 3.9% (95% CI: 3.5, 4.2) in women (Flohil et al 2013). In the UK, a study based on The Health Improvement Network (THIN) database for the period 1996 to 2003, observed a significant 12% increase in incidence in 2003 as compared to 1996 (Incidence rate ratio (IRR) 1.121, 95% CI: 1.004, 1.251), which equated to a 3% annual increase (IRR 1.026, 95% CI: 1.013, 1.040) (Bath-Hextall et al 2007a). An increase of the BCC incidence rate has also been reported in Denmark

where the age-adjusted BCC incidence increased from 27.1 to 96.6 cases per 100000 person-years for women and from 34.2 to 91.2 cases for men (Birch-Johansen et al 2010).

Prevalence:

In the Netherlands, based on the ECR registry, the overall BCC prevalence in 2009 was estimated to be 1.4% (1.3% and 1.5% for men and women, respectively). In the case of the people aged 65 or older, the overall 19-year prevalence was 5.4% (6.1% for men and 4.9% women), and the 5-year prevalence for this same age group was 2.7% (3.1% and 2.3% for men and women, respectively) (Flohil et al 2011). In the US, an incidence-based mathematical model estimated that 13 million white non-Hispanics at the beginning of 2007 have had at least one non-melanoma skin cancer (Stern 2010). In a population-based cohort study performed in Sant Boi de Llobregat (Catalonia, Spain), 1000 women were examined for skin cancer. The sample was obtained from women attending a massive campaign of mammography addressing all women aged 50 to 65 years in the area, and the estimated prevalence was 0.9% (95% CI: 0.60, 1.19) (Estrada 2005).

Demographics of the target population - age, sex, race/ethnic origin

BCC occurs primarily in adults with the majority of cases in people older than 40-year. Incidence rate increases with age, although BCC is also diagnosed in the young population (Bath-Hextall et al 2007a, Christenson et al 2005, Flohil et al 2013, and Richmond-Sinclair et al 2009). On the other hand, an increase in incidence rates has been observed for both sexes in studies from different countries. Although increasing longevity may underlie some of the increasing incidence of BCC, the incidence of BCC among the younger than 40 populations also appears to be increasing. A large Danish population-based study for the period between 1978 and 2007 showed that the average percentage of change in BCC incidence was significantly higher among those younger than 40 years than in older persons, especially in women (Birch-Johansen et al 2010). In the Netherlands (period 1973 to 2009), a higher annual incidence rate increase was observed in the younger population when compared with the older population, although women aged 40 to 64 years were those who had the highest estimated annual percentage of change. The observed trend of BCC rates may be associated with an increase in ultraviolet (UV) exposure due to outdoor leisure activities and sports, sunny destinations and due to sunbeds (Flohil et al 2013).

Frequency according to sex varies across studies. In a study conducted in Denmark, BCC incidence was higher in women than in men. During the study period, the incidence of BCC was markedly higher for men than for women in all age groups above 60 years, whereas in age groups below 60 years, the incidence of BCC was at a comparable level or even a little higher for women than for men (Birch-Johansen et al 2010). A similar incidence pattern was also observed in a study conducted in the UK and in a prevalence study performed in the Netherlands (Bath-Hextall et al 2007a, Flohil et al 2011). However, in Australia, BCC incidence was more frequent in men than in women for all age groups (Richmond-Sinclair et al 2009).

Differences between race and ethnicity on BCC incidence rate have not been analyzed. However, evidence from differences in BCC risk of patients treated with psoralen plus ultraviolet A (PUVA) for dermatological conditions, could serve as a basis for inferring differences in race or ethnicity incidence rates. Sun exposure is the most important environmental cause of BCC (van Dam et al 1999). However, in a literature review of BCC frequency in psoralen and ultraviolet A-treated patients, it was concluded that there was no increased risk of non-melanoma skin cancer in Asian and Arabian-African populations (Murase et al 2005). In consequence, a higher incidence rate may be expected in Caucasian populations when compared to non-Caucasian.

Risk factors for the disease

The main environmental BCC risk factor is sun exposure, and most risk factors relate directly to a person's sun exposure habits or susceptibility to solar radiation. These risk factors include having fair skin, light-colored eyes, red hair, northern European ancestry, older age, childhood freckling, and an increased number of past sunburns (van Dam et al 1999). In addition, BCC incidence has an inverse relationship with latitude as the amount of ambient ultraviolet radiation varies greatly with geography of residence. In a study conducted in the US, the risk of multiple non-melanoma skin cancer development was higher in those people living in high-UV index state at age 30 compared with those living in low-UV states (Wei-Passanese et al 2012). The use of tanning beds has been identified as a risk factor for the development of BCC. A systematic review found that every exposure to indoor tanning was associated with a 29% higher risk for BCC. In addition, exposure to indoor tanning at a young age (<25 years) was significantly associated with an increased risk for BCC, although high dose exposure did not increase risk (Wehner et al 2012). Regarding exposure to psoralen plus ultraviolet A treatment, a 30-year follow up study conducted in the US showed an increase of BCC risk of treated patients when compared with the US population-based incidence rates for whites (IRR = 3.09, 95% CI: 2.36, 4.06) (Stern 2012).

In a case-control study conducted in eight European countries, a potential association between BCC, and some medications taken daily for more than 3 months was observed. In this study, non-steroidal anti-inflammatory drugs (NSAID), ciprofloxacin and oral retinoids were associated with a reduced risk of BCC (odds ratio (OR): 0.72, 0.33 and 0.08, respectively), whereas thiazines were associated with an increased risk of BCC (OR: 2.04) (de Vries et al 2012b). Ever use of photosensitizing antimicrobials was associated with increased risks of BCC (OR: 1.9, 95% CI: 1.3, 2.8), specifically with the tetracycline class of antibiotics (OR: 1.8, 95% CI: 1.2, 2.8) (Robinson et al 2013). Human immunodeficiency virus (HIV) infection has also been associated to BCC. In a cohort study using Kaiser Permanent Northern California data, HIV infected patients had a higher incidence rate compared with those without infection (IRR: 2.1, 95% CI: 1.8, 2.3), although incidence was not associated with the level of immunosuppression according to cluster of differentiation four (CD4) counts (p for trend: 0.13) (Silverberg et al 2013). Ionizing radiation used to treat childhood cancers has been also observed to increase the risk for the subsequent development of BCC (Levi et al 2006).

Some lifestyles have been associated to BCC. In the case of alcohol consumption, a large Danish cohort study which included people living in the greater Copenhagen and Aarhus, and aged 50 to 64 years, observed that alcohol intake may increase the risk for BCC. However, the relation seemed to depend on beverage type such as wine (Hazard ratio (HR): 1.05, 95% CI: 1.02, 1.08) or spirits (HR: 1.11, 95% CI: 1.02, 1.21) (Jensen et al 2012). With regard to smoking, several studies have shown no relationship with BCC, whereas others have suggested that smoking may increase the risk of BCC in heavy smokers. However, a recent meta-analysis showed that smoking does not appear to modify the risk of BCC or could even be protective (OR: 0.95, 95% CI: 0.82, 1.09) (Leonardi-Bee et al 2012).

Main treatment options

The first line treatment of BCC is often surgical excision. Numerous treatment options are available including; curettage, cryosurgery (delivered by a variety of methods), laser, surgical excision with predetermined margins of clinically normal tissue, excision under frozen section control, Mohs micrographic surgery (the removal of the tumor layer by layer until it has gone as determined histologically), radiotherapy, intra-lesional therapy, photodynamic therapy (the application of a cream to induce photo damage to the tumor using varying light sources), immunomodulators (agents used to stimulate the immune system to eradicate the tumor), and the chemotherapy (Bath-Hextall et al 2007b). The risk of recurrence (tumor size, location, and pathology) influences the

treatment chosen. In the case of BCC, that lacks aggressive clinical or pathological features, excision, electrodessication, curettage, cautery, or topical imiquimod or 5-fluorouracil could be the desired option. Treatments that provide histologic confirmation of tumor removal are preferred in the management of BCC with clinical or pathological features associated with an elevated risk for recurrence. For patients with BCC at high risk for recurrence, Mohs surgery or a conventional surgical approach to completely resect the tumor, are preferred. Radiotherapy is useful for patients with inoperable lesions or for elderly patients who are unwilling to undergo surgery (Rubin et al 2005, Telfer et al 2008, Goldenberg and Hamid 2013). Vismodegib is the only currently approved systemic treatment option for advanced or metastatic BCC. In a multicenter, international, two-cohort, non-randomized study, treatment with vismodegib resulted in objective response rates (ORRs) of 43% and 30%, respectively, for patients with laBCC and mBCC, with complete response rates (CRRs) of 21% and 0%, and a median duration of objective response (DoR) of 7.6 months (Sekulic et al 2012).

Mortality and morbidity (natural history)

Locally advanced BCC may represent between 1% and 10% of all BCC. Basal cell carcinoma is rarely fatal but localized tissue invasion may induce considerable functional and cosmetic morbidity, especially because the majority of the lesions are located on the face (Mohan and Chang 2014).

A small proportion of BCCs may progress to an advanced state that is no longer amenable to available treatments. In these cases, progressive disease results in considerable morbidity from local tissue invasion and destruction particularly on the face, head, and neck, causing severe disfigurement (Wong et al 2003). These lesions includes both laBCCs, that are either inoperable or in patients who have medical contraindications to surgery and for whom radiotherapy was unsuccessful or contraindicated, or very rarely, and mBCC, for patients whose BCC has spread to distant sites (von Domarus and Stevens 1984, Lo et al 1991, Wadhera et al 2006, Dreier et al 2014). The aggressive phenotype of BCC with deep local invasion and/or resistance to standard treatment has been associated with different factors such as large size, facial location, neglect or longstanding tumor, incomplete excision, histologic variants or perineural or perivascular invasion (Walling et al 2004). Aggressive BCC subtypes have higher rates of recurrence and excision margin involvement (Pyne et al 2012). Infiltrative BCC has the highest representation in perineural invasion and its estimated incidence is approximately 3% (Brown and Perry 2000). Squamous differentiation, which represents between 1.2% and 2.7% of BCC, indicates a nonexclusive increased risk for the quite rare event of metastasis in BCC. The published recurrence rates are 12% to 51% for surgical excision and 4% for Mohs micrographic surgery (Garcia et al 2009).

The metastatic rate ranges from 0.0028% to 0.5%. Tumors that metastasize tend to be large, locally aggressive, neglected lesions that have recurred despite repeated treatment (Wong et al 2003). In the case of the BCC subtype, basosquamous carcinoma the incidence of metastasis is at least 5% (Garcia et al 2009). The prognosis of metastatic BCC patients is poor with a median survival of 8-10 months and a 5-year survival rate of approximately 10% (Wong et al 2003, Wysong et al 2013). About overall BCC patient's mortality, according to data from the Finnish Cancer Registry, the age- and sex-adjusted mortality rates per 100000 person-years for BCC were 0.08 cases in men and 0.05 in women, and deaths occurred mostly in the age groups of 65 years and older (Hannuksela-Svahn et al 1999). On the other hand, a study using data from the Danish Cancer Registry found a slightly reduced total mortality among patients with BCC compared with that of the general population (standardized mortality ratio (SMR): 0.97, 95% CI: 0.96, 0.98) (Jensen et al 2008).

Important co-morbidities found in the target population

Information on comorbidities in BCC patients was obtained from three studies. The study by the Italian Group for Epidemiological Research in Dermatology (GISED) included patients with a BCC diagnosis from total 16 centers (Pelucchi et al 2008). The other two studies used information from the Danish Cancer Registry (Jensen et al 2008, Jensen et al 2010). The comorbidities reported in these three studies are presented in the following table. No relevant differences were observed between BCC patients and the general population with regards to frequency of specific comorbidities (Jensen et al 2010). Patients receiving sonidegib may also receive pharmacological agents directed to conditions that are prevalent in the general elderly population like hypertension, diabetes, dyslipidemia, and chronic respiratory diseases.

Table 0-1 Frequency of comorbidities in BCC population

Comorbidity	Prevalence (%) Pelucchi et al 2008	Prevalence (%) Jensen et al 2010	Standardized mortality ratio*(95% CI) Jensen et al 2008
History of cancer			
Cancer, overall		6.7	1.15 (1.13-1.18)
Benign tumors	3.8		
Leukemia		0.3	
Lymphoma		0.6	
Malignant tumors	6.6		
Malignant melanoma		1.0	
Metastatic solid tumor		0.6	
Cardiovascular			
Cardiovascular disease	8.7		
Cerebrovascular disease		5.7	0.93 (0.90-0.97)
Congestive heart failure		3.0	
Hypertension	25.0		
Ischaemic heart disease			0.93 (0.91-0.95)
Myocardial infarction		4.0	
No ischaemic heart disease			0.94 (0.90-0.99)
Peripheral vascular disease		2.7	0.94 (0.89-1.00)
Digestive			
Diseases of the digestive tract			0.91 (0.83-1.00)
Hepatitis	3.2		
Mild liver disease		0.6	

Moderate to severe liver disease		0.1	
Ulcer disease		3.4	
Endocrine			
Diabetes mellitus	7.4	2.7	0.78 (0.70-0.86)
Diabetes with end organ disease		1.0	
Thyroid conditions	2.7		
Respiratory			
Asthma	3.8		
Chronic obstructive pulmonary disease		4.7	0.87 (0.83-0.92)
Pneumonia			0.97 (0.91-1.04)
Others			
Connective tissue disease		2.7	
Dementia		0.7	
Hemiplegia		0.2	
Herpetic infections	5.1		
HIV/Acquired immune deficiency syndrome		0.03	
Moderate to severe renal disease		1.1	
Organ transplantation		0.2	
Severe skin disease		1.7	
Suicide			1.16 (1.02-1.31)

*The standardized mortality ratio was calculated as the ratio between the observed cause-specific deaths in BCC patients, and the expected cause-specific deaths according to the Danish general population

Part II: Module SII-Non-clinical part of the safety specification

Table II 1-2 Key Safety findings (from Pre-clinical studies)

Key Safety findings (from Pre-clinical studies)	**Relevance to human usage**
Toxicity including:	
Single dose toxicity Single oral doses in rats up to 2000 mg/kg (0970683)	The effects observed in rats are not deemed clinically meaningful.
Repeat-dose toxicity	

The safety of sonidegib was evaluated on an oral daily dosing schedule for up to 6 months in rats (0770732, 0870704, and 1070056) and dogs (0770733, 0870705, and 1070055). The majority of adverse effects of sonidegib observed in toxicity studies in rats, dogs can be attributed to its pharmacologic mechanism of action on developmental pathways, and effects in rats and dogs were similar. **Bone toxicity/fractures/post-natal developmental defects** The most striking effects were on growing bone and consisted of thinning or closure of growth plates in the sternum, and femur and decreasing proliferating chondrocytes in the costochondral junction of ribs. These effects are not likely to occur in the adult cancer patient due to the maturity of their skeletal system. Likewise, effects on growing teeth in rats including dentine dysplasia of the incisors and loss of incisors is not expected to occur in adult cancer patients. Other drug-related effects, likely associated with the pharmacology of sonidegib, included effects on the male and female reproductive tract. Effects included delayed or arrested maturation as well as atrophy of testes, seminal vesicles prostate, ovary, and uterus. Atrophy of the hair follicles and hair thinning is also a pharmacologic effect of sonidegib. Gastrointestinal (GI) toxicity with body weight loss was dose limiting in rats and dogs. In rats, distention of stomach and duodenum, hemorrhage in the stomach wall, loss of mucosa with inflammation, and ulcerations of the non-glandular mucosa occurred. Emesis and diarrhea with single cell necrosis of intestinal epithelium and thinning of the epithelium with erosion were also seen in dogs. Lymphoid depletion in thymus and spleen and lymphocytolysis/lymphophagocytes in lymph nodes and gut-associated lymphoid tissue (GALT) were also seen in both rats and dogs. Hepatotoxicity was not seen in any studies in rats or dogs.	The pre-clinical effects seen in bone and on growing teeth are not likely to occur in adult humans due to the maturity of their skeletal system. However, since the effect of sonidegib on mature bones is unknown, as the toxicology studies were conducted in growing animals, it is possible that treatment with sonidegib could have effects on bone metabolism in addition to its effect on the growth plate. Some of the gastrointestinal effects of sonidegib at very high oral doses given to animals in short term studies may be related to the low solubility of the compound and incomplete absorption from the gastrointestinal (GI) tract, resulting in direct irritation of the mucosa. At lower doses, effects on the mucosa may be related to the effects of pathway inhibitors on the maintenance and proliferation of stem cells. In on-going clinical studies, nausea, vomiting, and diarrhea have been reported as adverse event (AEs). Most GI events reported in clinical studies were nausea, vomiting and diarrhea of grade 1 or 2 and clinically manageable, thus it does not constitute a major safety concern. Lymphopenia or infections reported mostly were grade 1 or grade 2, thus it does not constitute a major safety concern.

Nephrotoxicity An additional target organ was the kidney with acute tubular necrosis and mineralization of tubular epithelium seen in rats.	Renal failure/renal insufficiency have been observed in patients treated with sonidegib. However, the effects are not deemed to be clinically meaningful given 90% creatinine elevations were grade 1 or grade 2 and the paucity of grade 3 and 4 renal toxicity or elevated creatinine. In the registration study, the reports of renal failure/insufficiency appear to be pre-renal in nature possibly related to dehydration rather than a direct intrinsic nephrotoxic effect.
Reproductive toxicity Sonidegib was shown to be foetotoxic as evidenced by abortion and/or complete resorption of foetuses (0970151) and teratogenic at all doses tested in rabbits at very low exposure (0970151 and 0970631). Teratogenic effects included vertebral, distal limb and digit malformations, severe craniofacial malformations and other severe midline defects. Foetotoxicity in rabbits was also seen at very low maternal exposure. In a fertility study in rats (0970632), sonidegib administered to female rats at 20 mg/kg resulted in a complete lack of fertility even though estrous cycling was within normal ranges and the pre-coital interval was comparable to concurrent controls. The no observed effect level (NOEL) for female fertility was 0.2 mg/kg. For sonidegib-treated males, the 20 mg/kg/day (high) dose did not impact the ability of the male rat to impregnate the untreated females and therefore, the 20 mg/kg/day dose is considered the NOEL for fertility and reproduction in the male rat. There was also reduced fertility at low exposure.	Sonidegib was shown to be teratogenic in laboratory animals and based on its mechanism of action, Sonidegib is suspected to cause congenital malformations when administered during pregnancy. Thus, sonidegib is potentially teratogenic in humans. Given the potential teratogenic effects, sonidegib must not be used during pregnancy and women of childbearing potential should be advised of reproductive risk; and use effective contraceptives.

	Women of childbearing potential should be advised to use a highly effective method of contraception while receiving sonidegib, and for 20 months after ending treatment. This is to ensure more than 95% of the female patients of childbearing potential have plasma sonidegib levels below the safety threshold of 3 pg/mL when they conceive. Sexually active males using sonidegib should not father a child while receiving sonidegib and for at least 6 months after ending treatment. They must use a condom during intercourse during this period. The 6-month duration of condom use after ending treatment is to minimize any risk of sonidegib being transmitted to female partners via the seminal fluid of male patients. The safety threshold of 3 pg/mL is 1/10th of the predicted trough concentration (Ctrough) at 0.1 mg/kg/day, a dose level that caused minimal fetal toxicity in the embryo-fetal development toxicity study in rabbits (097631). Patients should be informed that treatment with sonidegib carries the potential risk of causing infertility.
Developmental toxicity In a juvenile rat, study (0770903) effects were seen in bone, teeth, reproductive tissues, GI tract, and lymphoid tissues similar to the effects in adult rats. In addition, a minimal to slight degeneration of nerve fibers was found in the sciatic nerve and, less commonly, in the thoracic spinal cord, but not in the cervical or lumbar spinal cord or optic nerve. Effects on nerves were not seen in any of the toxicity studies on more mature rats or dogs.	The effects are not deemed clinically meaningful in adult humans as BCC occurs primarily in adults. However, there is a potential risk of postnatal developmental defects in children (e.g. off label use in medulloblastoma).
Genotoxicity Sonidegib was not genotoxic in studies conducted in vitro (0770725 and 0770727) and in vivo (1070158).	There is no human risk for genotoxicity.
Carcinogenicity Sonidegib was not considered oncogenic in a 2-year carcinogenicity study in Wistar rats up to 3 mg/kg/day and in a 26-week carcinogenicity study in transgenic mice up to 10 mg/kg/day.	The clinical data on carcinogenicity is limited and therefore the potential risk for humans is yet to be determined. However, the preclinical studies performed

However, exposure levels were far below clinical exposure levels in rats, and around clinical exposure levels in mice. No pre-neoplastic or neoplastic lesions were observed in rat and dog studies up to 6-months in duration. Cell proliferation was assessed on a subset of relevant tissues from the 6 month repeat dose rat toxicology study using Ki-67 immunohistochemistry with quantification using image analysis when appropriate. No differences in Ki 67 stained cells were observed in IHC sections of the liver, duodenum and inguinal skin between rats given 10 mg/kg/day sonidegib for 26 weeks and concurrent vehicle control rats. There was an expected decrease in the number of Ki 67 stained cells in the uterus which correlated with the uterine atrophy observed during histological examination of H&E stained slides.	concluded that sonidegib was not genotoxic, did not cause increases in pre-neoplastic/hyperplastic findings or in cell proliferation in 6 month toxicology studies, and did not promote growth in pharmacologic human tumor models. Sonidegib was not oncogenic in rat and mice carcinogenicity studies. However, exposure levels in rats were far below clinical exposure levels and around clinical exposure levels in mice. Further, a review of genetic mutations/modifications in the Smo gene did not indicate a theoretical risk of SMO inhibition contributing to tumorigenesis. Thus, these results are not suggestive of a carcinogenic potential for sonidegib in human.
Hepatotoxicity There was no hepatotoxicity in rat and dog studies up to 6-months in duration.	The effects observed in humans are not deemed clinically meaningful.
Phototoxicity Sonidegib showed no potential risk for phototoxicity (0770120).	Sonidegib is not phototoxic in humans.
General safety pharmacology	
Cardiovascular (including potential for QT interval prolongation) Data from dogs dosed at 1000 mg/kg do not indicate a clinical risk for QTc prolongation, (0770734), and no changes in heart rate, blood pressures, electrocardiogram interval durations, or electrocardiogram rhythm and morphology were observed.	Therapeutic doses of sonidegib are unlikely to have a clinically relevant effect on the QTc interval given up to 25-fold exposure margins relative to animal exposure.
Central nervous system (CNS) and Respiratory System A rat CNS and respiratory safety pharmacology study indicated that sonidegib was unlikely to interfere with vital functions of the respiratory and central nervous systems (0770728).	Effects on the CNS and respiratory systems are not expected to be clinically meaningful. In Study A2201, the total plasma steady state maximum concentration (Cmax) in humans at 200 mg once daily was 2.1 µM, and the free fraction in human plasma was 2.5% so the free Cmax is 0.053 µM, making it unlikely that any of these off target related effects would be seen in patients.

Sonidegib was assessed for its off-target activity in a panel of 150 GPCRs, transporters, ion channels, nuclear receptors, and enzymes performed in house and at MDS Pharma (RD-2007-50628). Activities of ≥ 50% inhibition at 10 µM were found in four assays: melatonin MT1 (Ki=0.55 µM; EC50=1.75 µM), CB2 (Ki=6.5 µM), rat brain sodium channel type II (Ki = 0.75 µM) and monoamine transporter VMAT2 (median inhibition concentration [IC50] =~10 µM). No significant binding to any of the remaining targets was found up to a free drug concentration of 10 µM. These assays are run in the absence of protein and thus the values should be compared to unbound or free drug fraction in human plasma. In general, toxicology studies there were no specific functional effects that would be attributable to any of the low potency off target interactions. Safety pharmacology data do not show effects on the cardiovascular, respiratory and central nervous systems.	
Mechanisms for drug interactions Sonidegib is primarily metabolized by CYP3A. Sonidegib is an inhibitor CYP2C9 and CYP2B6, and therefore, it is possible to increase exposure of a co-medication that is a sensitive substrate of these enzymes. A high-fat meal was shown to increase Cmax and area under curve (AUC) of 800 mg sonidegib capsules to 7.8-fold and 7.4-fold, respectively, compared with the fasting conditions. Longer duration of concomitant use of CYP3A4 strong inhibitors/inducers (e.g. more than 14 days) will lead to a larger fold change in sonidegib exposure based on simulation. The uptake of sonidegib into human hepatocytes in vitro was investigated to determine if there was an active carrier-mediated uptake into the liver. The data indicated that human hepatocyte uptake of sonidegib occurs, most likely, by a high passive permeation process without modulation by a solute-carrier system. Further, in vitro data suggest that sonidegib is not a substrate of P-gp (P-glycoprotein), MRP2 (multidrug-resistant protein 2), or BCRP (breast cancer resistance protein).	Sonidegib should be taken at least one hour before, or two hours after a meal. A clinical drug interaction study (LDE225A2112) was conducted to evaluate the effect of repeated doses of sonidegib on the pharmacokinetics (PK) of warfarin and bupropion. The results of study demonstrated that co-administration of sonidegib did not have any effect on systemic exposures of warfarin and had no influence on the pharmacodynamics profiles of warfarin. In addition, co-administration of sonidegib did not affect systemic exposure of bupropion. These results indicate that sonidegib is not a perpetrator of drug interaction with CYP2C9 and CYP2B6 substrates. Inhibitors or inducers of CYP3A may change the systemic exposure of sonidegib. It is expected that concurrent administration of strong CYP3A4 inhibitors to patients could increase the incidence and severity of the sonidegib toxicities.

Based on in vitro data, sonidegib is not a substrate of P-gp, BCRP, or multi-resistance protein 2 (MRP2). Sonidegib did not inhibit apical efflux transporters, P-gp or MRP2, hepatic uptake transporters OATP1B1 or OATP1B3, renal organic anion uptake transporters OAT1 and OAT3, or the organic cation uptake transporters OCT1 or OCT2 at clinically relevant concentrationsThe potential of sonidegib to inhibit human efflux transporters, P-gp, MRP2 and BCRP, OATP (organic anion-transporting polypeptide) uptake transporters, OAT transporters (organic anion transporter), and OCT transporters (organic cation transporter) was evaluated. Sonidegib is not an inhibitor of P-gp, MRP2, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, or OCT2. In vitro results showed inhibition of BCRP by sonidegib with an IC50 of 1.54 µM. The Cmax/IC50 (2.1 µM /1.54 µM) value was calculated to be approximately 1.4 for 200 mg once daily. Consequently, there is a possibility for interactions with BCRP substrates, most of which are chemotherapeutic agents, which are not expected to be concomitantly used with sonidegib, and statins, the use of which should be closely monitored because of a potential increase in the risk of developing muscle toxicity. Sonidegib was administered with and without a dose of simvastatin known to produce muscle toxicity in rats (1170580). The presence of sonidegib exacerbated the simvastatin induced muscle toxicity, therefore protocols only allowed pravastatin to be used with extra caution if it was essential for the patients to continue treatment with a statin to control the hyperlipidemia.	Similarly, it is anticipated that concurrent administration of strong CYP3A4 inducers to patients could reduce the effectiveness of sonidegib. In addition, concomitant use of statins with sonidegib may increase the incidence of muscle-related symptoms or creatine kinase (CK) elevation. However, in Study A2201, acknowledging the small number of patients taking statins in conjunction with sonidegib, muscle related symptoms (68.9% on statins vs 74.0% not on statins) and grade 3 or grade 4 CK elevation (6.9% on statins vs.14.5% not on statins) appear to occur less frequently compared to those not on statins (Table 5-4).

Interaction with proton-pump inhibitors Sonidegib has shown pH-dependent solubility in vitro.	In clinical trial (Study LDE225A2118), the plasma exposure (AUC0-14d, AUC0-7d and Cmax) of a 200 mg oral dose of sonidegib was decreased by 32-38% when sonidegib was co-administered with esomeprazole compared to sonidegib alone in healthy subjects. This change in exposure was not determined to be clinically relevant. No new safety concerns were identified in this study. The safety profile observed was consistent with the known safety profile of sonidegib. No dose adjustment is necessary when sonidegib is used concomitantly with esomeprazole or other proton pump inhibitors.
Source: Non-clinical overview addendum, Non clinical overview, Summary of clinical pharmacology, Pharmacology written summary	

No additional non-clinical studies are required at this stage.

Table II 1-2 Safety concerns from non-clinical data

Safety concerns
Important identified risks (confirmed by clinical data)
Drug-interactions with CYP3A inducers or inhibitors
Reproductive toxicity (teratogenicity)
Food interactions
Important potential risks (not refuted by clinical data or which are of unknown significance)
Impaired fertility
Post-natal developmental defects
Fractures
Drug-interaction with sensitive BCRP substrates with low therapeutic index
Missing information
None

Part II: Module SIII - Clinical trial exposure

Approximately 1,361 subjects (495 healthy volunteers and 866 patients) received sonidegib treatment in MAH sponsored investigational clinical trials cumulatively since the Development IBD (DIBD; 17 Dec 2008).

Tb SIII.1 Cumulative subject exposure to sonidegib from completed clinical trials by gender and age (healthy volunteer studies)

Age group	Male	Female	Total
< 65 years	**434**	**59**	**493**
≥ 65 years	**2**	**0**	**2**
≥65 to <75 years	**2**	**0**	**2**
Total	**436**	**59**	**495**

Tb SIII.2 Cumulative subject exposure to sonidegib from completed clinical trials by racial group (healthy volunteer studies)

Caucasian	Asian	Black	Other[i]	Total
304	43	141	7	495

Source: Data from completed studies as of 29 December 2018;
'Other' category includes all other reported or missing racial groups.

TB SIII.3 Cumulative subject exposure to sonidegib from completed clinical trials by gender and age (patient studies)

	Age group	Male	Female	Total
Number of subjects exposure to sonidegib monotherapy	< 65 years	225	159	384
	≥ 65 years	155	115	270
	≥65 to <75 years	93	71	164
	≥75 to <85 years	49	35	84
	≥85 years	13	9	22
	Total	**380**	**274**	**654**
Number of subjects exposure to sonidegib combination therapy	< 65 years	63	63	126
	≥ 65 years	46	27	73
	≥65 to <75 years	38	22	60
	≥75 to <85 years	7	5	12

	Age group	Male	Female	Total
	≥85 years	1	0	1
	Total	**109**	**90**	**199**
Total number of subjects exposure to sonidegib	< 65 years	290	223	513
	≥ 65 years	201	142	343
	≥65 to <75 years	131	93	224
	≥75 to <85 years	56	40	96
	≥85 years	14	9	23
	Total	**491[ii]**	**365[iii]**	**856[iv]**

Source: Data from completed studies as of 29 December 2018. For CLDE225C2301, subject who exposed to sonidegib in arm1 (N=18) all goes to the monotherapy arm. The total number of patients exposed to sonidegib is the patients in arm1 + 3 patients from Temozolomide who switched over to sonidegib after crossover; [i]Excluding CLDE225XUS20; [ii]Includes two patient from study CLDE225C2301 who crossed over from TMZ to sonidegib after protocol amendment 2 (who are not included in either the monotherapy or combination therapy group); [iii]Includes one patient from study CLDE225C2301 who crossed over from TMZ to sonidegib after protocol amendment 2 (who are not included in either the monotherapy or combination therapy group); [iv]The total number of subjects exposed to sonidegib is the subjects in arm1 plus three subjects from TMZ who switched over to sonidegib after protocol amendment 2.

TB SIII.4 Cumulative subject exposure to sonidegib from completed clinical trials by racial group (patient studies)

	Caucasian	Asian	Black	Other[ii]	Total
Number of subjects exposure to sonidegib monotherapy	552	51	17	34	654
Number of subjects exposure to sonidegib combination therapy	183	7	3	6	199
Total	**737[iii]**	**58**	**20**	**41[iv]**	**856[v]**

Source: Data from completed studies as of 29 December 2018.

For CLDE225C2301, subject who exposed to sonidegib in arm1 (N=18) all goes to the monotherapy arm. The total number of patients exposed to sonidegib is the patients in arm1 + 3 patients from Temozolomide who switched over to sonidegib after crossover; [i]Excluding CLDE225XUS20;

[ii]'Other' category: All other reported or missing racial groups; [iii]Includes two patients from study CLDE225C2301 who crossed over from TMZ to sonidegib after protocol amendment 2 (not included in either the monotherapy or combination therapy group); [iv]Includes one patient from study CLDE225C2301 who crossed over

from TMZ to sonidegib after protocol amendment 2 (not included in either the monotherapy or combination therapy group), [v]Total number of subjects includes subjects in arm1 plus three subjects who switched from TMZ to sonidegib.

TB SIII.5 Cumulative subject exposure to sonidegib from study **CLDE225XUS20** by age (patient study)

Age group	Total
< 65 years	4
≥65 to <75 years	6
≥75 years	0
Total	**10**

Source: CLDE225XUS20 Clinical Study Report

TB SIII.6 Cumulative subject exposure to sonidegib from study **CLDE225XUS20** by gender (patient study)

Gender group	Total
Female	6
Able to bear children	0
Premenarche	0
Postmenopausal	5
Sterile of child bearing age	1
Male	4
Total	**10**

Source: CLDE225XUS20 Clinical Study Report

TB SIII.7 Cumulative subject exposure to sonidegib from study **CLDE225XUS20** by racial group (patient study)

	Caucasian	Asian	Black	Other[i]	Total
Number of subjects exposure to sonidegib monotherapy	6	0	2	2	10

Source: CLDE225XUS20 Clinical Study Report

Efficacy and safety data from the pivotal registration Study LDE225A2201 (hereafter referred as Study A2201) provide robust clinical data to support the approved indication; 230 patients with advanced BCC were randomized to treatment with sonidegib 200 mg/day (n=79) or sonidegib 800 mg/day (n=151).

This study forms the foundation of the efficacy analysis and is central to the safety analysis as this study was specifically conducted in the approved indication. Based on the 42 months dataset, exposure to sonidegib has increased from 155.3 patient-years in the primary analysis to 241.2 patient-years in patients with laBCC or mBCC with 98.2 patient-years for sonidegib 200 mg and 143.0 patient-years for sonidegib 800 mg. The exposure data is considered to be adequate to allow for an informed assessment of the safety profile of sonidegib and a judgment of the overall benefit-risk for this indication.

In a separate study, sonidegib was evaluated for the treatment of medulloblastoma in adult and pediatric patients. This is another disease with mutations in hedgehog pathway.

Overall, clinical trial exposure to sonidegib in patients with BCC by duration of treatment, by dose level, age, gender, and race are summarized in below tables. Until the cut-off date of 08-Jul-2016 for the registration Study A2201, a total 229 patients were exposed to sonidegib; 79 patients in 200 mg group and 150 patients in 800 mg group. The median duration of exposure remained identical to that for the 30-month analysis (i.e. 11.0 months for sonidegib 200 mg and 6.6 months for sonidegib 800 mg), while the mean (standard deviation) duration of exposure increased from 14.0 months (9.63) to 14.9 months (11.89) for sonidegib 200 mg and from 10.8 months (10.66) to 11.4 months (12.47) for sonidegib 800 mg (LDE225A2201 CSR).

TB SIII.8 CUMULATIVE SUBJECT EXPOSURE TO SONIDEGIB FROM STUDY A2201 (SAFETY SET) BY DURATION

Duration of exposure (at least)	**Persons**	**Person-time (month)**
1 day	229	2894.7
1 m	222	2890.1
4 m	177	2775.3
8 m	119	2432.0
12 m	80	2037.5
16 m	61	1779.6
20 m	42	1441.6

Person-time is defined as sum of duration of exposure for all patients.
Person-time (months) = sum (last dose of study drug – first dose of study drug + 1) for all patients / 30.4375.
Source: A2201 Clinical Study Report

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

- **Pregnancy and breast-feeding women**

Reason for exclusion:

Since sonidegib has teratogenic potential, pregnant and breast-feeding women must avoid exposure to sonidegib.

Is it considered to be included as missing information?

No

Rationale:
Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.3, SmPC Section 4.4, SmPC Section 4.6

- **Women of childbearing potential who do not comply with the Sonidegib Pregnancy Prevention Programme**

Reason for exclusion:

Since sonidegib has teratogenic potential, woman of childbearing potential must comply with sonidegib Pregnancy Prevention Program to avoid exposure to sonidegib

Is it considered to be included as missing information?

No

Rationale:
Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.3, SmPC Section 4.4, SmPC Section 4.6

Table SIV.1.2 Exclusion criteria which are NOT proposed to remain as contraindications

Criteria	Reason for being an exclusion criterion	Justification for not being a contraindication
Patients who have neuromuscular disorders (e.g. inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis and spinal muscular atrophy) or are on concomitant treatment with drugs that are recognized to cause rhabdomyolysis, such as HMG CoA inhibitors (statins), clofibrate and gemfibrozil, and that cannot be discontinued at least 2 weeks prior to starting sonidegib treatment. If it is essential that the patient stay on a statin to control hyperlipidemia, only pravastatin may be used with extra caution.	In first-in-human Study X2101, grade 3 or 4 CK elevation was the dose limiting toxicity. Therefore, in the subsequent clinical studies, patients who were at increased risk of myopathy were excluded.	This is appropriately addressed in current labeling with details on the cautionary use (or discontinuation) of sonidegib in patients with pre-existing neuromuscular disorders or medications that may increase the risk for myopathy (or CK elevation). However, in Study A2201, acknowledging the small number of patients taking statins in conjunction with sonidegib 200 mg and 800 mg, muscle related symptoms (68.9% on statins vs 74.0% not on statins) and grade 3 or 4 CK elevation (6.9% on statins vs.14.5% not on statins) appear to occur less frequently compared to those not on statins
Patients who are receiving treatment with medications known to be moderate and strong inhibitors or inducers of CYP3A4/5 or drugs metabolized by CYP2B6 or CYP2C9 that have narrow therapeutic index, and that cannot be discontinued before starting treatment with sonidegib. Medications that are strong CYP3A4/5 inhibitors should be discontinued at least 7 days and strong CYP3A/5 inducers for at least 2 weeks prior to starting treatment with sonidegib.	Sonidegib is primarily metabolized by CYP3A4. It is a competitive inhibitor of CYP2B6 and CYP2C9 in vitro, potentially increasing the concentrations of drugs metabolized by these enzymes. Sonidegib is a BCRP inhibitor. Therefore, substrates of these enzymes or transporter, especially those with a narrow therapeutic range, should be used with caution.	This is appropriately addressed in current labeling with details on the need for discontinuation of medications that may interfere with sonidegib metabolism. The results of Study A2112 indicated that sonidegib is not a perpetrator of drug interaction with CYP2C9 and CYP2B6 substrates
Women of child-bearing potential who are not using highly effective contraception	Sonidegib was shown to be teratogenic in laboratory animals and is thus potentially teratogenic in humans.	This is appropriately addressed in current labeling with details on the need to use a highly effective method of contraception while receiving sonidegib, and for up to 20 months after ending treatment.

Criteria	Reason for being an exclusion criterion	Justification for not being a contraindication
Sexually active males who are not using a condom.	In animal studies, sonidegib has been found to be teratogenic and fetotoxic. Whether sonidegib passes through seminal fluid remains unknown, and potential risk may exist.	This is appropriately addressed in current labeling with details on the need to use a condom during intercourse and for 6 months after stopping drug treatment. They should not father a child during this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
Serum creatinine <1.5 x upper limit of normal (ULN) or 24-hour clearance <50ml/min	An additional target organ was the kidney with acute tubular necrosis and mineralization of tubular epithelium seen in rats.	Since sonidegib is not renally excreted, no change in systemic exposure is anticipated in patients with renal impairment. Additionally, as per the labeling, a population pharmacokinetic analysis in patients with mild and moderate renal impairment did not find significant influence of renal function on the apparent clearance (CL/F) of sonidegib suggesting that dose adjustment is not necessary in patients with renal impairment. Patients with severe renal impairment were not studied so it is not known if the pharmacokinetics (and therefore safety) of sonidegib is altered in this group of patients. Therefore, patients with severe renal impairment are included as missing information.
Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) >2.5 x ULN or >5 x ULN if liver metastases are present	The exclusion criteria were established as a precautionary measure, as at initiation of pharmacokinetic studies in special populations (hepatic insufficiency) was not completed.	A formal clinical study and analysis of patients with mild, moderate, or severe hepatic impairment did not find clinically relevant influence of hepatic function on the PK of sonidegib suggesting that dose adjustment is not necessary in patients with mild, moderate, or severe impairment (Study LDE225A2113)
Patients with hemoglobin of <9 g/dL	In animal studies, decreased bone marrow cellularity and decreased reticulocyte counts were present	This is appropriately addressed in current labeling with the inclusion of hemoglobin decrease in the ADR table. In addition, patients with anemia (hemoglobin of <9 g/dL) is included as missing information.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Table SIV.21 Limitations of ADR detection common to clinical trial development programs

Ability to detect adverse drug reactions (ADR)	Limitation of trial Program	Discussion of implications for target population
Which are rare/uncommon	Cumulatively, as of 16-May-2016, a total 1359 subjects (495 healthy volunteers and 864 patients) have received sonidegib treatment in Novartis-sponsored investigational clinical trials since the Development IBD (DIBD)-17-Dec-2008 in US and 06-Mar-2009 in EU. As of the cut-off date of 08-Jul-2016 a total 229 BCC patients had received sonidegib in the registration Study A2201.	As per the "rule of threes" if no events of a particular type are observed in a study of X individuals, then one can be 95% certain that the event occurs no more often than 3/X. According to this guide, any event that is not observed in this population occurs less often than 3 in 1359 exposed individuals, or has an incidence of less than 0.0022 (2.2 per 1000). In patients with BCC (based on the total 229 patients who received sonidegib in the registration study) the incidence is less than 0.013.
Due to prolonged exposure	There is limited information from prolonged exposure of patients treated with sonidegib from clinical studies. Overall, the median duration of exposure in Study A2201 was 8.4 months (range: 0.3 to 53.9 months). The median duration of exposure with sonidegib 200 mg was 11.0 months (range: 1.3 to 53.2 months), compared to 6.6 months (range: 0.3 to 53.9 months) for the 800 mg group.	The types and frequencies of ADRs are anticipated to be similar in the target population from that of the clinical study population. Long-term safety in patients is included as missing information in the RMP.

Ability to detect adverse drug reactions (ADR)	Limitation of trial Program	Discussion of implications for target population
Due to cumulative effects	In the Phase I Study CLDE225X2101 (here after referred as X2101) in patients with advanced solid tumors, 34 of 103 patients achieved steady state before undergoing dose modifications or interruptions. The median accumulation ratio based on Ctrough was 16-fold for once-daily dosing (range 6 to 90-fold). In the BCC Phase II Study A2201, most patients (91.1% in the 200 mg group and 70% in the 800 mg group) had drug exposure for 4 months or longer when steady state was reached and therefore, cumulative effects would have been identified in the study.	Given the patient exposure to sonidegib at steady state in Study A2201, and in particular patient exposure in the 800 mg group (twice the number of patients to the 200 mg, and 4-fold the treatment dose); ADRs due to cumulative effects are expected to be within the range of those identified in Study A2201.
Which have a long latency	The median duration of exposure in Study A2201 was 8.4 months (range: 0.3 to 53.9 months). With inherent limitations of clinical studies, ADRs with a long latency period (longer than 6 months) are unlikely to be detected.	Long latency ADRs are defined as ADRs that occur six months or more after initial exposure (Fletcher and Griffin 1991). Based on the review of the safety profile for patients with more than six months of exposure there is no evidence for sonidegib-induced long latency adverse drug reactions so far. Long-term safety in patients is included as missing information in the RMP.

Source: Fletcher and Griffin 1991, LDE225X2101, Study LDE225A2201 CSR

SIV.3. Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.3: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program**.** There has been one report of a pregnancy in a female partner of a male subject in non-pivotal study CLDE225A2114. The outcome of the pregnancy is not available despite multiple follow-up attempts.
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities:	
Patients with hepatic impairment	The pharmacokinetics of sonidegib were examined in subjects with mild (Child-Pugh A; N=8), moderate (Child-Pugh B; N=8), and severe (Child-Pugh C; N=9) hepatic impairment and healthy subjects with normal hepatic function (N=8). After a single 800 mg dose, sonidegib pharmacokinetics was modestly affected by hepatic impairment
Patients with renal impairment	Sonidegib has not been studied in a dedicated PK study in patients with renal impairment. Based on the available data, sonidegib elimination via the kidney is negligible. A population pharmacokinetic analysis found that mild or moderate renal impairment did not have a significant effect on the apparent clearance (CL/F) of sonidegib suggesting that dose adjustment is not necessary in patients with renal impairment. No efficacy and safety data are available in patients with severe renal impairment (SmPC).
Patients with cardiovascular impairment	In Study A2201, patients with recent myocardial ischemia or cardiac failure were underrepresented. Therefore, clinical experience in these patients is limited.
Immunocompromised patients	Not included in the clinical development program
Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable since there were no patients with disease severity different from the patient population included in the BCC

Type of special population	Exposure
	registration Study A2201, which represents the target population.
Patients with relevant different ethnic origin	Safety data in patients of different racial and/or ethnic origin are limited. In Study A2201, 94% of patients treated with sonidegib were Caucasian, and 6% were non-Caucasian patients (CSR LDE225A2201). Separately, Japanese healthy volunteers given a single dose of sonidegib 200 mg seemed to have a higher exposure in terms of Cmax and AUC compared to Western healthy volunteers (PK EI report). Population PK analysis did not identify Japanese ethnicity as a significant covariate after accounting for differences in the distribution of other covariates. Nor did it indicate clinically relevant difference in sonidegib exposure between Japanese patients versus patients from western countries (SCP).
Subpopulations carrying relevant genetic polymorphisms	Not applicable as patients were not screened based on polymorphisms, as there was no concern about the possible effects
Other	Patients who have neuromuscular disorders (e.g. inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis and spinal muscular atrophy) or are on concomitant treatment with drugs that may increase the risk of muscle toxicity. This is appropriately addressed in current labeling with details on the cautionary use (or discontinuation) of sonidegib in patients with pre-existing neuromuscular disorders or medications that may increase the risk for myopathy (or CK elevation).
Pediatric patients	The safety of sonidegib in pediatric patients has not been evaluated in BCC program. However, pediatric patients were studied within the development program for medulloblastoma.
Elderly (patients>=65 years)	The median age of the population in Study A2201 was 66 years (range: 24 to 93 years), and more than half of the population were 65 years or older; 54.3% patients were ≥ 65 years old and 27.5% patients were ≥ 75 years old with oldest patient receiving sonidegib being 93 years old (Clinical study report (CSR) LDE225A2201).

Type of special population	Exposure
	Based on a population PK analysis of patients with 20 to 93 years of age, no clinically significant difference in the predicted steady-state area under the concentration-time curve from time zero to 24 hours (AUC0-24h) of sonidegib was observed between patients aged ≥ 65 years and aged <65 years. Hence, no dose adjustment is required based on age (SCP).

Part II: Module SV-Post-authorization experience

Sonidegib was first authorized in Switzerland on 30 June 2015 for Novartis under the brand name Odomzo®, which was later transferred to Sun Pharma from Novartis. Currently, sonidegib is approved for Sun Pharma in 36 countries, under the brand name Odomzo® for advanced basal cell carcinoma (BCC) at the approved dose of 200 mg once daily. In addition, Taro is the marketing authorization holder for sonidegib in Israel. SPIL's sonidegib is available as 200 mg hard gelatin capsules.

SV.1. Post authorization exposure

The cumulative *(all available sales data till 29 June 2024)* worldwide post authorization patient exposure to SPIL's Sonidegib in terms of Patient Treatment Years (PTY) is estimated to be 5,980**.** (**Table SV.1.2)**

The cumulative patient exposure has been estimated on the basis of the all available global sales data for Sonidegib capsule for Novartis, Sun Pharmaceutical Industries Ltd. (SPIL) and Taro and is presented below.

SV.1.1 Method used to calculate exposure

The methodology used for calculating an estimate of patient exposure for Sonidegib is:

$$\frac{Patient\ Exposure}{(Patient\ Treatment\ Years)} = \frac{Sales\ figure\ in\ mg}{DDD\ \times 365}$$

As per RSI, recommended daily dose of sonidegib is 200 mg taken orally once daily on an empty stomach, at the same time each day. Sonidegib is usually prescribed for longer duration; therefore the patient exposure has been calculated in terms of Patient Treatment Years (PTY).

SV.1.2 Exposure

TABLE SV.1.2: CUMULATIVE SALES & ESTIMATED PATIENT EXPOSURE TO SONIDEGIB CAPSULE

Molecule	Dosage Form (Units)	Formulation strength	DDD*	Sales figure (units)		Sales figure in mg		Patient Exposure (PTY)		Patient Exposure (PTY)
				EU	Non EU#	EU	Non EU	EU	Non EU	
Sonidegib	Capsule	200 mg	200 mg	1,220,420	952,034	244,084,000	190,406,720	3,344	2,608	5,952
Total										**5,980$**

DDD = Define Daily Dose
$In addition to the above presented patient exposure, one patient each in Israel and Ireland was exposed to Sonidegib under compassionate use. . In Canada, 26 patients were exposed to sonidegib.
#This includes the quantity given under patient familiarization program and compassionate use in Australia.

Part II: Module SVI-Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

A possible risk of misuse for illegal purposes or dependence on sonidegib is not anticipated based on its mechanism of action and lack of psychopharmacologic effects. While no clinical studies have been carried out to specifically investigate abuse potential, no evidence has emerged that would suggest a potential for abuse or dependence with sonidegib. Given the pattern of side effects, and given the absence of effects that could lead to dependence, there is no known potential for abuse of sonidegib.

Potential for harm from overdose

In dose-escalation studies, sonidegib was administered at doses of up to 3000 mg once daily, and extensively studied at the 800 mg oral once-daily dose with acceptable acute tolerability.

There is no known antidote for sonidegib overdose. In cases of overdose, patients should be monitored closely for adverse events (AEs) and receive appropriate supportive measures.

Potential for transmission of infectious agents

There is low potential for transmission of infectious agents, as the components of the sonidegib drug products are derived from non-animal products with the following exceptions.

Based on the oral route of administration of sonidegib, a potential transmission of infectious agents is unlikely.

Potential for medication errors

SPIL has received seven cases of medication error with the use of products containing sonidegib during the reporting interval. Out of seven cases, 03 cases were spontaneous (1 serious and 02 non-serious), 03 from post marketing surveillance sources (all non-serious) and 01 from literature (Non-serious).

In one serious case of product dose omission, no adverse reaction was reported. In three non-serious cases of 'product dose omission', patient ran out of the medication for a few days (3 - 10 days) and no adverse reaction was reported.

Accidental exposure to product, circumstance or information capable of leading to medication error and product storage error was reported in one case each.

A review of reports of medication errors did not reveal any patterns or other safety information relevant to the benefit-risk assessment for sonidegib***.***

Prevention of error due to wrong medication

Name confusion

Sonidegib is marketed under the trade name Odomzo. The name is considered unlikely to cause confusion with other marketed product names.

The US FDA reviewed the proposed proprietary name Odomzo, and concluded in August 2013 that it is acceptable.

The presented name for sonidegib (Odomzo) was reviewed by all National Competent Authorities in the European Member States, and did not identify potential for similarity with existing trade names. Following national review, and following subsequent

discussion at the Name Review Group (NRG), the Committee for Medical Product for Human use (CHMP) communicated that it had no objections to the proposed invented name on 22-Feb-2013.

Each sonidegib capsule will bear the following imprint: 'NVR' for Novartis; 'SONIDEGIB' for the containing drug substance; and '200MG' for the dose strength. This will allow for clear product identification even outside the secondary and primary packaging. Sonidegib capsules are available only as single strength, so mix-up with other dose strengths is not possible. Therefore, the likelihood of medication errors due to its presentation is considered to be low.

Part II: Module SVII-Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Not applicable.

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

There are no new safety concerns or reclassification of safety concerns since the last approved RMP for sonidegib, vs.7.5.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Muscle related events:

The MedDRA terms used for Pharmacovigilance are Rhabdomyolysis/myopathy (SMQ Broad) and Muscle spasms (preferred term [PT]).

Potential mechanism:

Muscle toxicity with CK elevation is a notable clinical toxicity with sonidegib and is believed to be a class effect for all inhibitors of the Hh signaling pathway. To date, the underlying mechanism(s) of the treatment emergent CK elevations are unknown. In an attempt to learn more about the mechanism of muscle toxicity, Novartis has conducted in vitro experiments that suggest that the effects of sonidegib on skeletal muscle cells can dissociate inhibition of the Smoothened pathway, from CK release, a sign of muscle pathology.

However, due to the complex interplay between involved pathways no clear hypothesis on the mechanism of muscle toxicity has emerged from those cellular experiments.

Therefore, one potential hypothesis is that although sonidegib is not directly myotoxic, which is consistent with the fact that many patients do not get CK elevation despite high drug exposures, blockade of the Hedgehog pathway, which is required for tissue regeneration/repair mechanism, could result in CK elevation in the event that an injury occurs.

Evidence source(s) and strength of evidence:

The pre-clinical studies in normal healthy rats and dogs, including juvenile rats does not show any evidence of CK elevation, or muscle toxicity. However, muscle toxicity with CK elevation is a notable clinical toxicity with sonidegib, and is believed to be a class effect for all inhibitors of the Hh signaling pathway.

Overall, in the 200 mg dose group, 54 patients (68.4%) reported muscle-related events and in 50 patients (63.3%), these events were suspected to be related to sonidegib treatment by the Investigator. The most frequently reported events were muscle spasms (54.4%), blood CK elevation (30.4%), and myalgia (19.0%). Myopathy, defined as muscular weakness, was reported in four patients (5.1%) and rhabdomyolysis was reported in one patient (1.3%).

In the 200 mg group, grade 3 or grade 4 events were reported in seven patients (8.9%). The most frequently reported grade 3 or grade 4 muscle-related events in ≥1% of patients were: blood CK increased (6.3%), muscle spasm (2.5%), and rhabdomyolysis (1.3%). Most of these grade 3 or grade 4 events were clinically manageable by sonidegib dose adjustment/interruptions (Study A2201).

In the 200 mg group, three patients (3.8%) reported muscle-related events categorized as serious adverse events (SAEs), one as rhabdomyolysis, one as acute kidney injury and one as blood CK increased. The patient with blood CK increased had a normal CK at baseline and a history of muscular weakness (Study A2201). The patient with rhabdomyolysis had muscular weakness with a peak CK ≤10 x ULN and did not require IV hydration. There were 2 other patients in the 200 mg group who had CK>10 x ULN with muscle symptoms; one of whom required IV hydration. There were no patients in the 200 mg group with CK>10 x ULN, muscle symptoms, and renal impairment (1.5-fold increase in serum creatinine from baseline). Overall in the pivotal study, there was one patient taking 200 mg sonidegib and 6 patients taking 800 mg sonidegib who had CK >10x ULN associated with muscle symptoms who also required IV hydration (Safety Adjudication Report-Section 6.2).

There were no deaths reported due to muscle-related events in the 200 mg group (Study A2201).

Creatine phosphokinase (CK) elevations remained unchanged from those reported in the 30 month analysis. There were no new shifts from baseline to grade 3 and grade 4 from those reported in the 12-month , 18-month and 30 month analyses in either the sonidegib 200-mg group or the sonidegib 800-mg group

In the 200 mg group, 4 patients (5.1%) had worst post-baseline grade 3 CK elevation (all 4 patients had baseline grade 0) and 2 (2.5%) patients had worst post-baseline grade 4 CK elevation (of these 2 patients: 1 patient had baseline grade 0 and 1 patient had missing baseline value). In addition, concomitant use of statins with sonidegib may increase the incidence of muscle-related symptoms or creatine kinase (CK) elevation. However, in Study A2201, acknowledging the small number of patients taking statins in conjunction with sonidegib 200 mg and 800 mg, muscle related symptoms (68.9% on statins vs 74.0% not on statins) and grade 3 or 4 CK elevation (6.9% on statins vs.14.5% not on statins) appear to occur less frequently compared to those not on statins.

Muscle-related symptoms or signs were preceded by the onset of CK elevation in most patients, who developed grade 2 or higher CK elevation post-baseline (Study A2201). For patients with grade 2 and higher CK elevation, the median time to onset was 12.9 weeks (range: 2 to 39 weeks) in the 200 mg group and the median time to resolution (to grade ≤ 1) was 12 days (95% CI: 8 to 14 days) (Study A2201).

Overall, muscle-related AEs or CK elevations were reported with higher frequency, and more severity in the 800 mg group compared to the 200 mg group. The data suggests a shorter time to onset (6.7 weeks vs.12.9 weeks) and longer time to resolution (to grade ≤ 1) (15 days vs. 12 days) of grade 2 CK and higher elevation for 800 mg group compared to the 200 mg group (Study A2201-Table 12-34 Table 14.3-2.6b and Table 14.3-2.7b). Sonidegib demonstrated a better safety and tolerability with 200 mg dose compared to that of the 800 mg dose.

A search in the Safety Database was conducted using MedDRA.

The following cases were considered noteworthy:

- All serious medically confirmed cases of muscle-related events supported by grade 3 and above increase in creatine phosphokinase (CPK) without any of the following confounders:
  - Underlying history of concomitant use of statins.
  - Recent history of alcohol use and resultant unresponsiveness.
  - Heatstroke, metabolic disorders, inflammatory myopathies or other history of muscle disorders, trauma, or infections.
- All well documented serious medically confirmed (health-care professional; HCP) cases of rhabdomyolysis.
- All serious HCP cases of muscle-related events or worsening of muscle-related events within plausible temporal relationship with sonidegib treatment.
- All well documented fatal cases where cause of death was due to muscle-related event.

Due to a wide range of muscle-related events involved with different severity, the noteworthy cases will be discussed by the severity category as defined below as appropriate (from less severe to more severe):

- CPK elevation without muscle-related events reported.
- Spasms without CPK reported.
- Myalgia without CPK more than 5x LLN.
- Myopathy (muscular weakness) with or without CPK up to 5x ULN.
- Rhabdomyolysis with or without acute renal injury reported.

Cumulative data analysis

A total of 105 cases were retrieved cumulatively from clinical trials and literature. However, cumulatively one case reported acute kidney injury due to underlying metastatic endometrial cancer with no associated muscle-related event. Therefore, this case has been excluded from further analysis.

Report type and seriousness of the remaining 104 cases is presented in the below table except for four spontaneous reports (SRs), all other cases were medically confirmed.

Tabel. SVII.3.1 -1

Report type	Cumulative		
	Serious[i]	Non-serious	Total
Clinical trial	87	1	**88**
Post-marketing solicited sources	1	2	**3**
Spontaneous incl. literature	4	9	**13**
Total	**93**	**12**	**104**

Excluding one case reporting acute kidney injury due to underlying metastatic endometrial cancer: 2016RR-167381; [i]A case is considered serious only if the most relevant event retrieved by the search is serious.

Characterisation of the risk:

The impact on individual patient is often limited to muscle symptoms such as myalgia or muscle weakness and is often reversible after sonidegib dose adjustment and interruptions, or discontinuation of the treatment with sonidegib. Creatine kinase elevation is often reversible with no apparent impact on the safety of the individual patient. Rhabdomyolysis is a very rare and life-threatening condition. Rhabdomyolysis may be preventable if prompt action is taken.

Risks factors and risk groups:

There are various factors which can impact serum CK levels non-specifically such as physiological factors (physical exercises etc.), alcohol, surgery or trauma, concurrent medical conditions or drugs (statins etc.). The development of rhabdomyolysis is associated with a variety of diseases, injuries, medications and toxins, or by metabolic inequalities between energy consumption and production (Bagley et al 2007). In the pivotal study, no particular related risk factors have been identified in terms of risk groups, or demographics neither for CK elevation and muscle-related findings, nor for those subjects reported with 'rhabdomyolysis'. Rhabdomyolysis, is a severe myopathy with an acute onset and rapidly progressing course resulting from extensive necrosis of skeletal muscle with release of muscle contents into the systemic circulation, particularly myoglobin, CK and muscle enzymes (aminotransferases and lactic dehydrogenase), and elevation of creatinine, potassium, uric acid, calcium, and phosphorus. In general, rhabdomyolysis can be possibly life threatening as renal failure sometimes complicates the outcome; however, no life-threatening muscle-related events requiring hemodialysis have been reported with sonidegib in the Study A2201.

Preventability:

CK levels should be checked prior to starting sonidegib treatment, and thereafter as clinically indicated, for instance, if muscle-related symptoms are reported. If muscle-related symptoms are detected, patients should be monitored for CK elevation and impaired renal function. Dose modification or interruption guidelines should be followed as detailed in the label. Management using supportive therapy including proper hydration should be considered according to local standards of medical practice and treatment guidelines.
Patients should be closely monitored for muscle-related symptoms if sonidegib is used in combination with certain medications that may increase the potential risk of developing muscle toxicity (e.g. CYP3A4 inhibitors, chloroquine, hydroxychloroquine, fibric acid derivatives, Penicillamine, zidovudine, niacin, HMG-CoA reductase inhibitors) as these medications may increase one's risk for CK elevation and/or myopathy.

Impact on the risk-benefit balance of the product:

Taking into consideration the severity of Sonidegib's indication (BCC), and the fact that muscle related events are preventable and the public health concern is low, the risk-benefit balance is considered favorable.

Public health impact:

Drug-induced myopathy is often reversible after cessation of treatment. For most of the patients, complete recovery of grade 3 or 4 CK elevations often occurred within approximately 2 weeks. CK elevations have been used as a laboratory biomarker for confirming clinical diagnoses of myopathy.

In the sonidegib clinical development program, muscle-related events were identified through monitoring of CK level, muscle symptoms, and signs, and manageable through dose modification, interruption, and proper hydration as necessary. The public health impact depends on the prompt recognition, treatment and the clinical consequences. Drug-induced myopathy can be preventable as described above and with prompt treatment; the public health concern is low.

Reproductive toxicity (teratogenicity)

MedDRA terms used:

The MedDRA term used for Pharmacovigilance is Pregnancy and neonatal topics (SMQ broad).

Potential mechanism:

The effects of sonidegib on the male and female reproductive tract of young rats and dogs included delayed or arrested maturation of the testes, prostate, ovary, and uterus in young dogs and uterine atrophy in rats.
As with other Smo inhibitors, sonidegib was shown to be teratogenic in laboratory animals and is thus potentially teratogenic in humans. A dose finding study conducted by oral gavage on pregnant rabbit showed that doses of sonidegib ≥ 35.65→ 10 mg/kg/day were not tolerated and was fetotoxic as evidenced by abortion and/or morbidity and complete resorption of fetuses. The 17.8→5 mg/kg/day dose was not overtly toxic to the maternal animal, but resulted in resorption and severely malformed fetuses. The spectrum of external and skeletal anomalies observed is not completely unexpected, as it is known that disruption of the sonic hedgehog pathway (Smo antagonism), which is an essential regulator of embryonic development, is known to produce developmental abnormalities, including cranio-facial malformations, in sheep, rats, mice, hamsters, rabbits and chicks.

Evidence source(s)and strength of evidence:

Sonidegib was shown to be fetotoxic in rabbits as evidenced by abortion and/or complete resorption of fetuses and teratogenic resulting in severe malformations at ≥ 5 mg/kg/day at plasma exposure lower than the steady-state exposure at the recommended human dose. Teratogenic effects included vertebral, distal limb and digit malformations, severe craniofacial malformations and other severe midline defects. Fetotoxicity in rabbits was seen at low maternal doses (0.01 mg/kg/day) where maternal exposure was below the limit of detection (0.05 ng/mL) (Non-clinical overview).

None reported within the SMQ search were relevant to the reproductive toxicity at risk population given that all events (one case of hydrocele in the 200 mg group and one case each of hydrocele, cryptorchism and failure to thrive in the 800 mg group) were reported in adult patients.

There was no case of pregnancy reported in pivotal registration Study A2201.

There has been one report of a pregnancy in a female partner of a male patient in a non-pivotal Study A2114.

PHHO2012US006612: A report of a pregnancy in a partner of a male subject in Study A2114, a randomized, open label study to evaluate the relative bioavailability of three final market image (FMI) formulations of sonidegib compared with the CSF capsule formulation and the effect of food in healthy subjects.

The subject's medical history and concomitant medications were not reported. On 01-Feb-2012, the subject received one single dose of study medication. The subject reported that sometimes he was not practicing contraception. During his D85 visit, the subject reported that his girlfriend was 10 to 11 weeks pregnant. The subject's partners last menstrual period date was reported as 11-Feb-2012. She was suspecting pregnancy because of morning sickness. The subject's partner saw an obstetrician/gynecologist because she was having abdominal pain, and had a history of irregular menses. The outcome of pregnancy was not reported. The event of paternal drug exposure was considered as non-serious by the Investigator. The Investigator did not suspect any relationship between the event of paternal drug exposure and the study medication.
The investigational site had tried to contact the subject at least 3 times but there was no response and the certified letter that had been sent by the site failed to be delivered to the subject.

A search in the Safety Database was conducted using MedDRA version 21.1. Search definitions are provided in Appendix 7.

The following cases were considered noteworthy:

- All cases of pregnancy with congenital anomaly, abortions or any complications during the pregnancy.
- All cases with reported anomaly confirmed by quadruple test, amniocentesis and/or ultrasonography.

Cumulative data analysis

Ten cases were retrieved cumulatively. Report type and seriousness of these cases is presented in below table. All cases were medically confirmed.

Tabel. SVII.3.1 -2

Report type	Cumulative		
	Serious[i]	Non-serious	Total
Clinical trial	8	3	**11**
Post-marketing solicited sources	0	0	**0**
Spontaneous incl. literature	0	0	**0**
Total	**8**	**3[ii]**	**11**

[i]A case is considered serious only if the most relevant event retrieved by the search is serious; [ii]All three non-serious cases reported 'exposure via father' with no other events or outcomes reported.

Of the 11 cases retrieved cumulatively, six subjects were male, five were female and the age range was from 28 to 67 years (nine adults, three elderly [≥ 65 years], and two subjects of unknown age). The TTO was reported in seven cases ranging from 20 to 1109 days. Outcome of the most relevant event of interest was reported in six

cases: condition deteriorated (one case), condition unchanged (one case), complete recovery (one case) and condition improving (four cases).

Three cases reported 'exposure via father' and no other AEs were reported. Five cases reported the event 'failure to thrive'; one case reported 'pyloric stenosis' one case reported 'uterine dehiscence' and the remaining case reported 'encephalocele'. None of the 11 cases reported events relevant to reproductive toxicity (teratogenicity) and were considered as non-noteworthy.

Characterisation of the risk:

The impact on individual patients is high given the likelihood of reproductive toxicity and the effect this would have on a pregnant female.

Risks factors and risk groups:

Women of childbearing age becoming pregnant and/or requiring treatment with sonidegib through pregnancy or female partners of male patients.

Preventability:

Given the teratogenic effects, it is recommended that sonidegib should not be used during pregnancy. Patients must be informed of the potential risk to the fetus. In addition, women of childbearing potential should be advised to use a highly effective method of contraception while receiving sonidegib, and for up to 20 months after ending treatment. This is to ensure more than 95% of the female patients of childbearing potential have plasma sonidegib levels below the safety threshold of 3 pg/mL when they conceive. Men should not father a child or donate semen while taking sonidegib and for at least 6 months after ending treatment. Male patients, even those who have had a vasectomy, must always use a condom when having sex with a female partner during treatment and for 6 months after ending treatment to prevent exposure of female partners to the active substance via seminal fluid. They must use a condom during intercourse during this period. The 6-month duration of condom use after ending treatment is to minimize any risk of sonidegib being transmitted to female partners via the seminal fluid of male patients. The safety threshold of 3 pg/mL is $1/10^{th}$ of the predicted Ctrough at 0.1 mg/kg/day, a dose level that caused minimal fetal toxicity in the embryo-fetal development toxicity study in rabbits (Non-clinical overview, Toxicology written summary).

Impact on the risk-benefit balance of the product:

Since the risk can be adequately managed by appropriate risk minimization activities through the Odomzo Pregnancy Prevention Programme, the risk-benefit impact is acceptable.

Public health impact:

Sun Pharma is sponsoring a pregnancy prevention program to reduce the likelihood that women of childbearing potential become pregnant while taking sonidegib. This will consist of the following:

1) educational materials for both health care providers (HCPs) and patients
2) a verification of counseling form
3) dear health care providers (DHCP) letter

4) verification of pregnancy by a test supervised by a health care professional within 7 days prior to initiation of sonidegib as well as monthly medically supervised pregnancy tests

5) prescription duration limited to one Month

6) background information on the teratogenic risks associated with sonidegib,

7) the need for highly effective contraception in combination with a barrier method and

8) information to be followed in the event of a pregnancy.

In addition, SunPharma is planning to evaluate pregnancy and infant outcomes following direct (maternal) and indirect exposure (through the seminal fluid of a male partner) to sonidegib during pregnancy, through a centralized safety database (ARGUS) in which sonidegib pregnancy exposure status will be captured. In addition, the outcome of each sonidegib pregnancy will be documented, including abnormal fetal outcomes.

Food interaction

MedDRA terms used:

The MedDRA term used for Pharmacovigilance is Food interaction (preferred term [PT]).

Potential mechanism:

Food can enhance bioavailability of sonidegib, a poorly soluble drug in aqueous fluid.

Evidence source(s) and strength of evidence:

Study LDE225A2114

A search in the Safety Database was conducted using MedDRA version 21.1. Search definitions are provided in Appendix 7.

The following cases were considered noteworthy:

- All cases reporting an interaction within 4 hours between sonidegib and food intake, followed by an SAE.

The above mentioned search retrieved no cases cumulatively.

Characterisation of the risk:

A high-fat meal was shown to increase Cmax and AUC of 800 mg sonidegib capsules to 7.8-fold and 7.4-fold, respectively, compared with the fasting conditions. Therefore, sonidegib should be taken at least one hour before or two hours after a meal.

Risks factors and risk groups:

Patients with endocrine disorders, diabetes

Preventability:

The risk can be easy prevented by informing patients and HCPs through the PIL and SmPC

Impact on the risk-benefit balance of the product:

Risk-benefit balance remains favorable, considering the severity of the indication (BCC)

Public health impact:

The public health impact is expected to be minor, since the risk is easy preventable

Interactions with strong CYP3A4 inhibitors and CYP3A4 inducers

MedDRA terms used:

The MedDRA term used for Pharmacovigilance is Drug interaction (preferred term [PT]).

Potential mechanism:

CYP3A4 is the primary hepatic enzyme for sonidegib turnover, and therefore, co-medications that inhibit or induce CYP3A4 have a potential to reduce or enhance sonidegib metabolism and increase or reduce sonidegib exposure.

Evidence source(s)and strength of evidence:

Study LDE225A2108

A search in the Safety Database was conducted using MedDRA.

The following cases were considered noteworthy:

- All cases reporting a decrease or increase in pharmacological effect of sonidegib temporally related to concomitant use of sonidegib and a CYP3A4 inducer or inhibitor.

The above mentioned search retrieved no cases during the reporting interval.

Cumulative data analysis

One case was retrieved cumulatively. Report type and seriousness of this cases is presented in the below Tabel SVII.3.1 -3. This case was medically confirmed.

Tabel SVII.3.1 -3

Report type	Cumulative		
	Serious[i]	Non-serious	Total
Clinical trial	0	0	**0**
Post-marketing solicited sources	0	0	**0**
Spontaneous incl. literature	0	1	**1**
Total	**0**	**1**	**1**

Characterisation of the risk:

Strong CYP3A4 inhibitors increase sonidegib Cmax and AUC and
strong CYP3A4 inducers decrease sonidegib Cmax and AUC

CYP3A4 inhibitors:

Pre- and co-treatment of healthy subjects with multiple-dose ketoconazole (200 mg twice daily for 14 days) followed by a single 800 mg dose of sonidegib increased sonidegib Cmax and AUC0-10d 1.49-fold and 2.25-fold, respectively. Based on these findings, it is expected that concurrent administration of strong CYP3A4 inhibitors to patients could increase the incidence and severity of the sonidegib toxicities.

CYP34A inducers:

Pre- and co-treatment of healthy subjects with multiple-dose rifampicin (600 mg once daily for 14 days) followed by a single 800 mg dose of sonidegib decreased sonidegib Cmax and AUC0-10d to by 54% and 72%, respectively. Based on these findings, it is expected that concurrent administration of strong CYP3A4 inducers to patients could reduce the effectiveness of sonidegib. If co-administration of potent CYP3A4 inducers is necessary, an increase in the sonidegib dose from 200 mg to 800 mg daily should be considered, using 200-mg increments. The 800-mg once daily dose is predicted to adjust the AUC to the approximate range observed in the absence of the inducer based on PK data. If the potent inducer is subsequently discontinued, the sonidegib dose should be reduced to that used prior to inducer initiation.

Risks factors and risk groups:

Patient with multiple co-morbidities

Preventability:

The risk can be prevented by informing patients and HCPs through the PIL and SmPC

Impact on the risk-benefit balance of the product:

Risk-benefit balance remains favorable, since the risk can be prevented

Public health impact:

CYP3A4 inhibitors: Moderate
CYP3A4 inducers: Low

Impaired fertility

MedDRA terms used:

The MedDRA term used for Pharmacovigilance is Fertility disorders (SMQ broad),

Potential mechanism:

The potential for sonidegib to cause infertility in male and female patients is unknown. Based on findings from animal studies, male and female fertility may be compromised with sonidegib

Evidence source(s)and strength of evidence:

Study A2201

Letourneau et al 2012, van der Kaaij et al 2010, Mancini et al 2008

In a fertility study in rats, sonidegib administered to female rats at ≥ 20 mg/kg resulted in a complete lack of fertility even though estrous cycling was within normal ranges and the pre-coital interval was comparable to concurrent controls. There was also a reduction of the number of pregnant females and a decrease in the number of viable fetuses at 2 mg/kg/day. The NOEL for female fertility was 0.2 mg/kg. For sonidegib-treated males, the 20 mg/kg/day (high) dose did not impact the ability of the male rat to impregnate the untreated females and therefore, the 20 mg/kg/day dose is considered the NOEL for fertility and reproduction in the male rat. The plasma sonidegib exposure for 20 mg/kg/day in rats corresponds to approximately 3-times the steady-state AUC at the recommended human dose (Non-clinical overview).

In the 200 mg group, only one patient had grade 3 amenorrhea that was suspected to be related to sonidegib treatment by the Investigator. No action taken with the study medication and the event was ongoing at the time of cut-off for this analysis (10-Jul-2015) (Study A2201).

A search in the Safety Database was conducted using MedDRA

The following cases were considered noteworthy:

- All cases related to male infertility (spermatogenesis, sperm count decreased, abnormal sperms and similar) reported within plausible temporal relationship with sonidegib intake and not confounded by underlying history and concomitant medications.
- All cases related to female infertility that were reported within plausible temporal relationship with sonidegib intake and not confounded by underlying history and concomitant medications.

Cumulative data analysis

One non-serious case (2016RR-167529; SR, HCP) was retrieved cumulatively and is considered as noteworthy and this case concerns a 45-year-old female subject who experienced non-serious **amenorrhea** while on treatment with sonidegib for about a year for BCC. Limited information regarding medical history was reported. Outcome of the event was unknown.

A causal relationship between amenorrhea and sonidegib cannot be excluded; however, menopause cannot be excluded due to the subject's age. The impact on fertility is therefore difficult to assess.

A review of the one noteworthy case received cumulatively does not suggest an affirmative causal relationship to sonidegib.

Characterisation of the risk:

The impact on individual patients is moderate.

Risks factors and risk groups:

Women of childbearing age becoming pregnant and/or requiring treatment with sonidegib through pregnancy or female partners of male patients.

Preventability:

Patients should be informed that treatment with sonidegib carries the potential risk of causing infertility. Fertility preservation options should be discussed prior to starting treatment with sonidegib.

Impact on the risk-benefit balance of the product:

Since the risk can be adequately managed by appropriate risk minimization activities, the risk-benefit impact is acceptable.

Public health impact:

The public health impact is moderate considering that there may be difficulties with fertility in females. In addition, women of childbearing potential treated with sonidegib may be at a risk of amenorrhea compared to the general population. However, there is expected to be limited exposure in woman of child bearing potential (median age of patients who received sonidegib was 66 years) compared to the general population.

Second primary malignancies

MedDRA terms used:

The MedDRA terms used for Pharmacovigilance are Neoplasms benign, malignant, and unspecified (incl. cysts and polyps) (SOC): all PTs within this SOC (Primary Path).

Potential mechanism:

Genotoxicity studies are negative for sonidegib. Sonidegib is non-mutagenic, and there is no known mechanism by which inhibition of Hedgehog pathway signaling would be expected to initiate or promote cancer. A pre-clinical 6-month rat study did not show evidence of any benign cutaneous tumors.

Evidence source(s) and strength of evidence:

Study A2201--
Study A2201--
CSR LDE225A2201

Non-clinical overview, Marcil and Stern 2000, Levi et al 1998, Nugent et al 2005, Youlden and Baade 2011, Travis et al 2006, Mariotto et al 2007, Chen et al 2008, Wheless et al 2010

Sonidegib was not genotoxic in studies conducted in vitro and in vivo.

Carcinogenicity studies were performed with sonidegib in mice and rats;
-26-Week Oral Gavage Carcinogenicity Study with LDE225 in Transgenic Mice (RasH2 [001178-T(hemizigous), CByB6F1-Tg(HRAS)2Jic]), study number: 8371102
-104-Week cecinogenicity Study of LDE225 (Sonidegib) in Wistar Rats by Oral Route, study number: BRT_17_037G_TN

In a 26-week oral gavage carcinogenicity study in transgenic mice, sonidegib was considered not oncogenic at a dose up to 10 mg/kg/day when administered to mice daily for 26 weeks. The second carcinogenicity study was performed in Wistar Rats. Based on these observations, sonidegib was not considered oncogenic up to 3 mg/kg/day when administered orally to Wistar rats daily for minimum 104 weeks.

No carcinogenic potential was identified in either species.

Overall, 36 patients (15.7%) had reported AEs in the neoplasm SOC (as per the search criteria below), including second primary malignancies; 12 patients (15.2%) while receiving 200 mg dose and 26 patients (17.3%) receiving the 800 mg dose. The most frequently reported secondary neoplasms in both 200 mg and 800 mg arms were; squamous cell carcinoma (4.4%), malignant melanoma 1.3%), basal cell carcinoma (1.7%)', Seborrhoeic keratosis (1.3%)', dysplastic naevus (0.9%)', tumour pain (0.9%), squamous cell carcinoma of skin (0.9%), prostate cancer (0.9%), and lipoma (0.9%).

The events of squamous cell carcinoma of the skin were reported as either 'squamous cell carcinoma' or 'squamous cell carcinoma of the skin'.

Squamous cell carcinoma (SCC) was reported in four patients (5.1%) in the 200 mg and six patients (4.0%) in the 800 mg group. In addition, squamous cell carcinoma of the skin was reported in one patient each in the 200 mg (1.3%) and in the 800 mg group (0.7%).

Of the 12 patients reporting second primary malignancy, 8 patients had lesions at the specific sites; one patient each had lesion on left neck (BCC site unspecified), left forehead (BCC site; preauricular), left retroauricular (BCC site; unspecified) and left temple (primary site of BCC on scalp), 2 patients each had lesion on right eyebrow (primary site of BCC on scalp), and scalp (primary site of BCC on ears, and other). The remaining 4 patients had lesions at unspecified locations (primary site of BCC on chin for one patient and unspecified for others).

Malignant melanoma was reported in 3 patients (1.3%), with two patients (2.5%) in the 200 mg group, and one patient in the 800 mg group (0.7%) (lesions were on right forehead, unspecified site, left cheek with unspecified primary site of BCC).

Bowen's disease was reported in a single patient (0.7%) in the 800 mg group (lesion was on left back and primary site of BCC preauricular). Other secondary malignancies occurring as single cases were B-cell lymphoma, lung neoplasm, and vulval cancer (Study A2201).
Of the 15 patients (6.6%) who reported cutaneous skin cancers while on sonidegib, a review of patients' medical histories demonstrates that: 2 patients had prior history of either Bowen's disease (one patient who reported squamous cell cancer of the skin in the 800 mg group) or history of malignant melanoma (one patient who reported malignant melanoma in the 800 mg group) (CSR LDE225A2201).

A search in the Safety Database was conducted using MedDRA.

The following cases were considered noteworthy:

- All cases without similar pre-existing malignant condition or progression of underlying malignancy* where the subject develops a new malignancy confirmed by histopathology.
- All cases of second primary malignancy without a confounder that provides an alternative etiology for second primary malignancy.

*Considering the difficulty in assessing causality of the product in the development of pre- existing malignancy, such events are therefore excluded from further discussion.

Cumulative data analysis

A total of 174 cases were retrieved cumulatively. Of these 174 cases, 164 cases are not discussed further as these cases either reported progression of underlying malignancy; relapse or metastases of underlying malignancy; complications of underlying malignancy; and prior history of the reported malignancy.

The remaining 10 cases, reported second primary malignancy. Distribution of cases by report type and seriousness is presented in the Tabel SVII.3.1 -4 below. All cases were medically confirmed.

Tabel SVII.3.1 -4

Report type	Cumulative		
	Serious[i]	Non-serious	Total
Clinical trial	10	0	**10**
Post-marketing solicited sources	0	0	**0**
Spontaneous incl. literature	0	0	**0**
Total	**10**	**0**	**10**

Source: Safety Database as of 29 December 2018; [i]A case is considered serious only if the most relevant event retrieved by the search is serious.

Of the 10 cases, three cases were considered as noteworthy, but the review of these three cases did not suggest an affirmative causal relationship to sonidegib.

Characterisation of the risk:

The impact on individual patients is low given the low likelihood of second primary malignancies, namely squamous cell cancers, and the ability to detect at an early stage through careful monitoring.

Risks factors and risk groups:

The excess risk of developing a second malignancy among cancer survivors can likely be attributed to factors including similar etiologies (e.g. lifestyle factors, environmental exposures), genetics, and the effects of treatment (Travis et al 2006, Mariotto et al 2007, Youlden and Baade 2011). Associations between specific sites of primary and secondary cancers have been noted.
Among BCC patients, significantly increased risk was observed of lung, melanoma, non-Hodgkin lymphoma and mouth and pharynx cancers. As noted above, having a personal history of non-melanoma skin cancer, including BCC or SCC, is an independent risk factor for the development of secondary cancers (Chen et al 2008, Wheless et al 2010). Evidence from the literature also suggests that earlier age of non-melanoma skin cancer is associated with a higher risk of developing a secondary cancer (Chen et al 2008).

Preventability:

Currently, there are no known methods for prevention of these events.

Impact on the risk-benefit balance of the product:

The impact on the risk benefit balance of the product is considered low in the post-marketing setting as adequate risk minimization activities are included in the product information.

Public health impact

Second primary malignancies in the BCC population, especially lung, melanoma, non-Hodgkin's lymphoma and mouth and pharynx cancers, have been observed in the literature. These events may be serious and can be fatal. A safety review of serious second primary cancer events taking into consideration risk factors indicated that at the present time, there is a low incidence of second primary cancer events reported in sonidegib studies and no evidence of a positive association to sonidegib. Regarding squamous cell carcinoma of the skin, no clear signal has arisen from the analysis of safety information available to date and no clear association with sonidegib has been made. Most cases of SCC of the skin are in most cases is curable by surgical resection. The population of laBCC and mBCC is at a substantial increased risk of SCC when compared with the general population.

Post-natal developmental defects

MedDRA terms used:

The MedDRA terms used for Pharmacovigilance are Epiphyseal disorders (HLT) exclude PT Epiphyses delayed fusion; search to run in Pediatric population <18, Dental developmental disorders and anomalies (HLT), Dental disorders NEC (HLT), Dental pulp disorders (HLT), Dental surface disorders (HLT), Tooth missing (HLT), Body height below normal (PT), Body height abnormal (PT), Body height decreased (PT), Bone formation decreased (PT), Bone development abnormal (PT), and Bone disorder (PT).

Potential mechanism:

The Hh pathway remains active during postnatal development in the root of growing teeth and in the epiphyseal plate of growing long bones. Inhibition of the Hh pathway by sonidegib disrupts normal proliferation and differentiation at these sites, resulting in abnormal tooth development and premature closure of the epiphyseal plate.

Evidence source(s) and strength of evidence:

Borato Viana and Oliveira Pinto Vilela 2008, Katz et al 1993, Lehmann et al 2012, Peck 2010, LDE225X2104

The pre-clinical effects seen in bone and on growing teeth are not likely to occur in adult humans due to the maturity of their skeletal system. However, since the effect of sonidegib on mature bones is unknown, as the toxicology studies were conducted in growing animals, it is possible that treatment with sonidegib could have effects on bone metabolism in addition to its effect on the growth plate.
There were no cases of post-natal developmental defects reported during the registration trial of sonidegib since the population studied was adult patients (aged >18 years).

However, in Study X2104, three pediatric patients reported epiphyseal disorder, bone disorder, and chondropathy. The two pediatric patients with epiphyseal disorder and chondropathy were discontinued from the study due to the events. While data is still limited, this study provides early clinical evidence to what was observed in preclinical studies regarding this potential risk.

A search in the Safety Database was conducted using MedDRA.

The following cases were considered noteworthy:

- All cases from subjects less than 18 years old reporting any SAE related to growing bone or teeth formation that cannot be explained by any acquired disease and is more likely congenital in origin.

Cumulative data analysis

The above mentioned search retrieved one case (CT, serious, HCP) which is presented above in reporting interval data analysis.Distribution of cases by report type and seriousness is presented in the Table SVII.3.1 -5 below. This case was medically confirmed.

Table SVII.3.1 -5

Report type	Cumulative		
	Serious[i]	Non-serious	Total
Clinical trial	0	0	**0**
Post-marketing solicited sources	1	0	**1**
Spontaneous incl. literature	0	0	**0**
Total	**1**	**0**	**1**

Source: Safety Database as of 29 December 2018; [i]A case is considered serious only if the most relevant event retrieved by the search is serious

The review of this case did not suggest an affirmative causal relationship to sonidegib.

Characterisation of the risk:

The impact on individual patients is moderate.

Risks factors and risk groups:

Infants being breastfed by mothers receiving sonidegib and/or paediatric patients being treated in clinical studies with sonidegib for indications in oncology for which there are no other therapeutic alternatives.

Preventability:

The extent to which sonidegib or any of its metabolites are excreted in breast milk is not known. Due to its potential to cause developmental defects, sonidegib is contraindicated in breastfeeding and women are warned to not breast-feed while taking sonidegib or for 20 months after the final dose.
The safety of sonidegib in paediatric patients has not been established. It is unknown whether post-developmental defects can be caused by the use of sonidegib in this population. Clinical studies in pediatric patients are ongoing. Sonidegib is not recommended for use in paediatric patients, as safety and efficacy have not been established. Due to safety concerns, sonidegib should only be used in adult patients.

Impact on the risk-benefit balance of the product:

The risk benefit-balance is considered favorable.

Public health impact:

Advanced BCC has not been reported and is unlikely to be seen in children. Safety and efficacy have not been established for sonidegib in any paediatric indications, so treatment with sonidegib in the paediatric population should be limited to clinical trial participation.

Odomzo is contraindicated in breastfeeding women, and women must not breastfeed for 20 months after the final dose. Therefore, the risk of lactational exposure is expected to be zero or minimal.
It is possible that off-label use in pediatric cancer populations may be seen in the post-marketing environment.

Fractures

MedDRA terms used:

The MedDRA term used for Pharmacovigilance is Fractures (HLGT).

Potential mechanism:

Epiphyseal disorder can be attributed to sonidegib's pharmacologic mechanism of action on developmental pathways as seen in rats and dogs. The most striking effects were on growing bone and consisted of thinning or closure of growth plates in the sternum and femur and decreasing proliferating chondrocytes in the costochondral junction of ribs. These effects are not likely to occur in the adult cancer patient due to the maturity of their skeletal system. Likewise, effects on growing teeth in rats including dentine dysplasia of the incisors and loss of incisors is not expected to occur in adult cancer patients.

Evidence source(s)and strength of evidence:

Srikanth et al 2007, Lamberg et al 2011, Anderson et al 2014, Bassgen et al 2013, CDC 1996, Wade et al 2012

Overall, 11 patients (4.8%) reported events of fractures; 5 patients (6.3%) in the 200 mg group and 6 patients (4.0%) in the 800 mg group. In the 200 mg group most frequently reported events in at least one patient were; spinal compression, upper limb, femoral neck, and lumbar vertebral fracture.

Six patients (2.6%) had grade 3/4 events; 3 patients (3.8%) in the 200 mg and 3 patients (2.0%) in the 800 mg dose group. In the 200 mg group, one patient (1.3%) had lumbar fracture that led to discontinuation of sonidegib treatment, and two patients (2.5%) had a fracture (femoral and spinal) that resulted in sonidegib dose interruption. None of these events were considered to be related to sonidegib treatment.

No dose adjustments due to fracture-related events occurred for both the sonidegib 200-mg and sonidegib 800-mg groups.

Discontinuation from study drug occurred in one patient in each of the sonidegib 200-mg and sonidegib 800-mg groups (1.3% and 0.7%, respectively).[SCS addendum 3-Appendix 1-Table 14.3.1-1.14]
Eleven patients (4.4%) reporting fractures were aged between 42 to 86-years; six patients were female and 5 were male. Of these, six patients were receiving sonidegib 800 mg dose and 5 patients were on 200 mg. Ten of the 11 patients suffered trauma prior to the fracture, including nine patients who fell and 1 patient with a history of osteoporosis and low back pain who suffered lifting trauma resulting in a an osteoporotic lumbar vertebral fracture. All these events were considered not to be related to sonidegib by the Investigator.

A search in the Safety Database was conducted using MedDRA.

The following cases were considered noteworthy:

- All serious and medically confirmed cases of fractures with confirmed radiologic diagnosis reported within plausible temporal relationship with drug intake without any of the following confounders.
- Trauma.
- Bone tumors, bone cysts, or malignancies metastasizing to bones (breast, prostate, lung, thyroid, renal etc.).
- Osteoporosis or osteogenesis imperfecta.
- Rickets.
- Osteomyelitis.
- Concomitant medications such as hormone replacement therapy, corticosteroids, aromatase inhibitors, bisphosphonates, CYP450 inducers leading to increased Vitamin D metabolism etc.
- All cases related to female infertility that were reported within plausible temporal relationship with sonidegib intake and not confounded by underlying history and concomitant medications.

Cumulative data analysis
A total of twelve cases were retrieved cumulatively. Report type and seriousness are presented in the Table SVII.3.1 -6 below. All cases were medically confirmed.

Table SVII.3.1 -6

Report type	Cumulative		
	Serious[i]	Non-serious	Total
Clinical trial	12	0	**12**
Post-marketing solicited sources	0	0	**0**
Spontaneous incl. literature	0	0	**0**
Total	**12**	**0**	**12**

Source: Safety Database as of 29 Dec 2018; [i]A case is considered serious only if the most relevant event retrieved by the search is serious.

None of the twelve cases met the noteworthy criteria as either an alternative explanation (fall, ankle twist) or contributory factors (extensive sacral tumor, deep vein thrombosis, hip prosthesis and crutch user) were provided

Characterisation of the risk:

The impact on individual patients is moderate. The overall risk of fractures is considered low with an uncertain correlation with sonidegib.

Risks factors and risk groups:

Given sonidegib's effect on growing bone, pediatric patients are at highest risk. The effect of sonidegib on mature bones is not known, since the toxicology studies were conducted in growing animals, however, these effects are not likely to occur in the adult cancer patient due to the maturity of their skeletal system.

Preventability:

Not applicable.

Impact on the risk-benefit balance of the product:

The risk-benefit balance is considered favorable.

Public health impact:

No definitive signal has risen from the analysis of safety information available to date and no clear association with sonidegib has been made.

Interaction with sensitive BCRP substrates with low therapeutic index

MedDRA terms used:

The MedDRA term used for Pharmacovigilance is Drug interaction (Low Level Term).

Potential mechanism:

Sonidegib was shown to inhibit BCRP-mediated efflux of a known BCRP substrate in a BCRP-overexpressing cell line and has a potential to inhibit BCRP in vivo.
BCRP inhibition by sonidegib has a potential to increase the exposure of BCRP substrates.

Evidence source(s) and strength of evidence:

Study DMPK R0800323-01

A search in the Safety Database was conducted using MedDRA.

The following cases were considered noteworthy:

- All cases reporting a decrease or increase in pharmacological effect of sonidegib temporally related to concomitant use of sonidegib and BCRP substrates, followed by an SAE.

The above-mentioned search retrieved no cases during the reporting interval and cumulatively.

Characterisation of the risk:

Sonidegib inhibited BCRP-mediated efflux of Bodipy FL prazosin (BCRP substrate) with an estimated EC50 value of 1.54 µM. The inhibition of BCRP by 2.5 µM sonidegib was less than 50% of a potent BCRP inhibitor, 10 µM of Fumitremorgin C. The vast majority of the known BCRP substrates (methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan) excluding statins are anti-cancer agents that are not expected to be used for advanced basal cell carcinoma.

Risks factors and risk groups:

Patients with malignancies, patients with co-morbidities

Preventability:

The proposed label will contain a caution to closely monitor patients taking statins due to a potential for overlapping muscle toxicity.

Impact on the risk-benefit balance of the product:

The risk-benefit balance is considered favorable.

Public health impact: low

Interaction with drugs with a known risk of myopathy

MedDRA terms used:

The MedDRA term used for Pharmacovigilance is Drug interaction (Low Level Term).

Potential mechanism:

Interaction mechanisms have not been identified.

Evidence source(s)and strength of evidence:

Rat study number 1170580

Study LDE225A2201
Sonidegib was dosed with and without a dose of simvastatin known to produce muscle toxicity in rats. The presence of sonidegib exacerbated the simvastatin induced muscle toxicity.

A search in the Safety Database was conducted using MedDRA.

The following cases were considered noteworthy:

- All serious cases where the subject develops events related to myopathy within a plausible temporal relationship of administration of sonidegib in conjunction with medications known to cause myopathy without confounding factors as mentioned in the definition of muscle- related events.

The above mentioned search retrieved no cases during the reporting interval and cumulatively

Characterisation of the risk:

Patients who are taking medications that may increase CK levels (e.g. statins) may be at increased risk of developing grade 3 or grade 4 CK elevations and therefore the concomitant use of these medications and sonidegib should be closely monitored. In Study A2201, acknowledging the small number of patients taking statins in conjunction with sonidegib 200 mg and 800 mg, muscle related symptoms (68.9% on statins vs 74.0% not on statins) and grade 3 or 4 CK elevation (6.9% on statins vs.14.5% not on statins) appear to occur less frequently compared to those not on statins

Risks factors and risk groups:

Muscle toxicity is worsened by co-administration of two drugs with a known risk of myopathy, therefore Patients who are taking medications that may increase CK levels (e.g. statins) may be at increased risk of developing grade 3 or grade 4 CK elevations

Preventability:

Warning stated in the Product Information

Impact on the risk-benefit balance of the product:

The risk-benefit balance is considered favorable.

Public health impact:

Moderate

Cardiac events (myocardial ischemia, cardiac failure and cardiac death)

MedDRA terms used:

The MedDRA terms used for Pharmacovigilance are cardiac disorder (SOC), cardiac and vascular investigations (excluding enzyme tests) (HLGT), sudden death (PT), Sudden cardiac death (PT) cardiac death (PT).

Potential mechanism:

Review of published non-clinical data indicate that the inhibition of Hh-signalling results in myocardial ischemia, cardiac failure and cardiac death and that Hh signaling is protective against acute myocardial infarction (Paulis L et al 2015). Therefore, there, potential for sonidegib to cause cardiac events cannot be excluded; particularly in patients with recent ischaemic injury, (a group of patients in which exposure to sonidegib is limited). However, there is no available information on the potential mechanism specifically between sonidegib and cardiac events based on preclinical data which extensively evaluated cardiovascular data.

Evidence source(s)and strength of evidence:

Koch et al 2015, Davies et al 2007, Go et al 2014, Smolina et al 2012, Seferovic et al 2013, Johansson et al 2001, Koek et al 2007, Stecker et al 2014, Adabag et al 2010, Paulis et al 2015

Overall, 74 patients (32.3%) reported cardiac events, of these 22 patients (27.8%) were treated with 200 mg and 52 patients (34.7%) were treated with 800 mg.

There was one event of cardiac death reported in an 80-year old male patient in the 800 mg group who had underlying cardiac risk factors and active cardiovascular disease. The event was considered not suspected to sonidegib.

There was one event of cardiac arrest reported in an 88-year old female patient in the 800 mg group who had multiple cardiac risk factors and experienced recurrent infections, which eventually led to a cardiac arrest and death. The event was considered not suspected to sonidegib.

There was one event of cardiac failure congestive in an 83-year old male patient in the 800 mg group who had multiple risk factors including advanced age and diabetes who experienced congestive heart failure leading to death. No echocardiogram or EKG was done at the time of the event and therefore it is uncertain if there was cardiac dysfunction or cardiac ischemia. Congestive heart failure was only diagnosed based on clinical assessment. The event was considered not suspected to sonidegib.

In the 200 mg group, the most frequently reported events were dizziness (seven patients; 8.9%), peripheral edema (three patients; 3.8%), dyspnoea (three patients; 3.8%), atrial fibrillation and syncope (each in two patients 2.5%).

In the 200 mg group, three patients (3.8%) reported grade 3/4 cardiac events (syncope, atrial fibrillation, dizziness, dyspnoea and endocarditis). Of the 22 patients reporting AEs, in eight patients (10.1%) the following suspected events were reported by Investigator: dizziness (three patients; 3.8%), edema peripheral, chest discomfort, dyspnea exertional, electrocardiogram T wave inversion, dyspnoea, sinus arrhythmia and supraventricular extra systoles (each in one patient; 1.3%). Of the seven patients, four patients; did not have any medical history or current medical condition related to cardiac events. One patient had a current medical condition related to vascular disorder, one patient had atrial fibrillation and heartburn as current medical condition and one patient had hypertension as current medical condition.
Four patients (5.1%) reported cardiac events categorized as SAEs; syncope, angina pectoris, dyspnoea, endocarditis. Four patients (5.1%) had cardiac events (dizziness, edema peripheral, angina pectoris, atrial fibrillation) that resulted in sonidegib dose adjustment/interruption and one patient (1.3%) had chest discomfort and dyspnea exertional that led to discontinuation of sonidegib treatment.

A search in the Safety Database was conducted using MedDRA.

The following cases were considered noteworthy:

- All serious and medically confirmed cases of myocardial ischemia, cardiac failure and cardiac death with confirmed diagnosis supported by ECG, troponin T test or echocardiogram findings within a plausible temporal relationship of administration of sonidegib without a history of cardiac disease (e.g. ischemic heart disease, chronic heart failure) or at least two risk factors for cardiac disease (e.g. hypertension, uncontrolled diabetes, smoking, obesity, hypercholesterolemia).

Cumulative data analysis

A total of 84 cases were retrieved cumulatively. In three cases, the cardiac events (fatal cardiac arrest, atrial fibrillation and fluid overload) occurred prior to sonidegib treatment. These cases were therefore excluded from further analysis. Distribution of the remaining 81 cases (79 HCP and 2 non-HCP) by report type and seriousness is presented in Table SVII.3.1 -7 below.

Table SVII.3.1 -7

Report type	Cumulative		
	Serious[i]	Non-serious	Total
Clinical trial	75	2	**77**
Post-marketing solicited sources	1	2	**3**
Spontaneous incl. literature	0	1	**1**
Total	**76**	**5**	**81**

Source: Safety Database as of 29 Dec 2018 excluding three cases with onset prior to sonidegib treatment: 2013RR-166217, 2013RR-165977 and 2014RR-167071; **i**A case is considered serious only if the most relevant event retrieved by the search is serious.

A review of the noteworthy cases received during the cumulative period did not suggest an affirmative causal relationship to sonidegib.

Characterisation of the risk:

The impact on individual patients is moderate. The overall risk of cardiac events is considered low with an unlikely correlation with sonidegib.

Risks factors and risk groups:

There are various factors which can impact the risk for cardiac events in general such as the presence of the following history: diabetes, hypercholesterolemia, hypertension, previous myocardial ischemia and smoking history. In the pivotal study, no particular related risk factors have been identified in terms of risk groups or demographics for those subjects with related cardiac events.

Preventability:

Not applicable.

Impact on the risk-benefit balance of the product:

The impact on the risk-benefit balance of the product is considered low and is expected to remain low in the post marketing setting.

Public health impact:

No definitive signal has risen from the analysis of safety information available to date and no clear association with sonidegib has been made.

Syncope

MedDRA terms used:

The MedDRA terms used for Pharmacovigilance are syncope (PT) and loss of consciousness (PT)

Potential mechanism:

There is no available information on the potential mechanism between sonidegib and syncope. Although few events of syncope have been observed in patients treated with sonidegib, these events were generally associated with underlying factors such as vasovagal episodes, hypertension, medulloblastoma/craniotomy.

Evidence source(s)and strength of evidence:

Soteriades et al 2002, Olde Nordkamp et al 2009, Malasana et al 2011

Overall, eight patients (3.9%) reported syncope related events; three patients (3.8%) in 200 mg group and five patients (3.3%) in 800 mg group. Syncope was the most frequently reported preferred term within this risk across both the groups (two patients; 2.5% in 200 mg group and all seven patients 3.1% in 800 mg group).
In the 200 mg group, one patient reported grade 3/4 syncope, which was categorized as an SAE. In one patient (1.3%), the event, loss of consciousness was deemed related to sonidegib treatment by Investigator. None of the patients in the 200 mg group discontinued sonidegib treatment due to syncope related events.

A search in the Safety Database was conducted using MedDRA.

The following cases were considered noteworthy:

- All serious and medically confirmed cases of syncope within a plausible temporal relationship of administration of sonidegib without major confounders of hypovolemia or orthostatic hypotension, history of neural syncope, or cardiac syncope.

Cumulative data analysis

A total of ten cases were retrieved cumulatively. Distribution of cases by report type and seriousness is presented in the Table SVII.3.1 -8 below. All ten cases were medically confirmed.

Table SVII.3.1 -8

Report type	Cumulative		
	Serious[i]	Non-serious	Total
Clinical trial	10	0	**10**
Post-marketing solicited sources	0	0	**0**
Spontaneous incl. literature	0	0	**0**
Total	**10**	**0**	**10**

Source: Safety Database as of 29 December 2018; **i**A case is considered serious only if the most relevant event retrieved by the search is serious.

Only one case met the noteworthy case definition and its review does not suggest an affirmative causal relationship to sonidegib.

Characterisation of the risk:

The impact on individual patients is moderate. The overall risk of syncope is considered low with an unlikely correlation with sonidegib.

Risks factors and risk groups:

Several etiologic factors have been noted to contribute to syncope in cancer patients, the most common being orthostatic hypotension, with cardiac causes assuming a secondary role. Other causes are drugs, vasovagal reactions, and cerebrovascular disease. Patients with head and neck tumors, thyroid tumors, and cervical lymphadenopathy can develop recurrent syncope related to carotid sinus hypersensitivity. Syncope in patients with head and neck tumors can occur through several mechanisms: glossopharyngeal, neuralgia– asystole syndrome, carotid sinus syndrome, and glossopharyngeal-related reflex cardiogenic syncope without neuralgic pain. In these patients, syncope does not respond to medical management or in some cases to pacemaker insertion. Syncope may resolve after treatment of the tumor or may require intracranial intervention to resect the glossopharyngeal nerve.

Preventability:

Not applicable.

Impact on the risk-benefit balance of the product:

The risk-benefit balance is considered favorable.

Public health impact:

No definitive signal has risen from the analysis of safety information available to date and no clear association with sonidegib has been made. In the general population, syncope is common in patients with co-morbidities or concurrent medications affecting the heart rate. These events are infrequent in patients taking Odomzo.

Corneal disorders

MedDRA terms used:

The MedDRA term used for Pharmacovigilance is corneal disorders (SMQ Narrow).

Potential mechanism:

There is no available information on the potential mechanism between sonidegib and corneal disorders. Although few keratopathies have been observed in patients treated with sonidegib, these corneal-related adverse events are frequently associated with underlying factors such as pre-existing medical conditions or concomitant medications.

Evidence source(s)and strength of evidence:

Jeng et al 2010, Kuruvilla et al 2015

Overall, four patients (1.7%) reported corneal disorders, one patient (1.3%) (corneal abrasion) in the 200 mg and three patients (2.0%) (corneal abrasion, corneal perforation, keratitis and keratopathy) in the 800 mg group. No grade 3/4 events, SAEs, dose adjustment/interruption, and discontinuation due to these events were reported in the 200 mg group.

A search in the Safety Database was conducted using MedDRA.

The following cases were considered noteworthy:

- All serious and medically confirmed cases of corneal disorder within a plausible temporal relationship of administration of sonidegib confirmed with slit lamp examination without any confounders such as past history of eye trauma, diabetes or corneal disorders etc.

Cumulative data analysis

A total of three cases were retrieved cumulatively. Distribution by report type and seriousness is presented in the Table SVII.3.1 -9 below table. All three cases were medically confirmed.

Table SVII.3.1 -9

Report type	Cumulative		Total
	Serious[i]	Non-serious	
Clinical trial	0	1	**1**
Post-marketing solicited sources	0	0	**0**
Spontaneous incl. literature	0	2	**2**
Total	**0**	**3**	**3**

Source: Safety Database as of 29 Aug 2018; [i]A case is considered serious only if the most relevant event retrieved by the search is serious.

None of the cases were noteworthy, as defined above, or reported a fatal outcome. All three cases had limited information (unknown age, no medical history, concomitant medications, TTO, etc.). Furthermore, one case did not provide a new event but rather provided worsening of the concurrent conditions corneal irritation and red eye.

Characterisation of the risk:

The impact on individual patients is moderate. The overall risk of corneal disorders is considered low with an unlikely correlation with sonidegib.

Risks factors and risk groups:

Contact lens wearers are at greatest risk of developing ulcerative keratitis. Other risk factors for ulcerative keratitis include previous eye disease (except myopia), nonsurgical ocular trauma and HIV infection.

Preventability:

Routine medical screening could be used to detect keratitis/ulcerative keratitis in patients at risk.

Impact on the risk-benefit balance of the product:

The risk-benefit balance is considered favorable.

Public health impact:

No definitive signal has risen from the analysis of safety information available to date and no clear association with sonidegib has been made.

SVII.3.2. Presentation of the missing information

Use in patients with severe renal impairment

Evidence source:

Patients with serum creatinine <1.5 x upper limit of normal (ULN) or 24-hour clearance <50ml/min were excluded from clinical trials, since animal studies have shown that exposure to sonidegib could lead to acute tubular necrosis and mineralization of tubular epithelium (as seen in rats).

A search in the Safety Database was conducted using MedDRA.

The following cases were considered noteworthy:

- All cases with development of an SAE or worsening of renal function after a plausible temporal relationship with either of the following prior to receiving sonidegib:
  - Serum creatinine levels ≥ 1.5 x ULN or creatinine clearance <60 ml.
  - Moderate/severe renal failure.

The focus of the analysis of the cases was to evaluate any new trends/differences in the safety profile in subjects with severe renal impairment receiving sonidegib.

Cumulative data analysis

A total of 47 cases were retrieved cumulatively. Of these 47 cases, 24 cases did not report renal impairment prior to study treatment and thus, excluded from further analysis. Distribution of the remaining 23 cases by report type and seriousness is presented in the Table SVII.3.2 -1 . All cases were medically confirmed.

Table SVII.3.2 -1

Report type	Cumulative		
	Serious	Non-serious	Total
Clinical trial	23	0	**23**
Post-marketing solicited sources	0	0	**0**
Spontaneous incl. literature	0	0	**0**
Total	**23**	**0**	**23**

Source: Safety Database as of 29 Aug 2018.

None of the 23 cases met the noteworthy criteria. Seventeen cases had no creatinine values or details to assess the severity of renal disease. In the remaining six cases

with specific history of renal impairment, the reported event could be explained by either concomitant medications or underlying diseases.

Cumulative distribution of 'patients with severe renal impairment' by seriousness compared to 'all cases' is presented in the below Table SVII.3.2 -2 :

Table SVII.3.2 -2

Seriousness criteria	Cumulative	
	Patients with severe renal impairment[i]	All cases[ii]
Fatal	14 (60.9%)	181 (23.3%)
Life-threatening	0 (0%)	32 (4.1%)
Other serious	9 (39.1%)	466 (62.2%)
Non-serious	0 (0%)	80 (10.3%)
Total	**23 (100%)**	**776 (100%)**

Source: Safety Database as of 29 December 2018; [i]Excluding 24 cases with no renal impairment prior to study treatment (case IDs available upon request); [ii]This includes all cases regardless of pre-existing conditions.

Cumulatively, the fatality appears to be higher among the subjects with renal impairment of various severities. However, due to the limited information regarding the reporting pattern for this population as well as the substantially lower number of cases with known renal function status at baseline, it is yet to determine whether the observed difference in the reporting frequency of fatality between subjects with severe renal impairment vs other subjects is valid. Of note, severe renal dysfunction by itself may increase the risk of death that is often multifactorial and may not be necessarily related to the sonidegib treatment. Therefore, the limited information does not provide substantiated evidence for increased risk in this population.

Population in need of further characterization:

Since sonidegib is not renally excreted, no change in systemic exposure is anticipated in patients with renal impairment. Additionally, as per the labeling, a population pharmacokinetic analysis in patients with mild and moderate renal impairment did not find significant influence of renal function on the apparent clearance (CL/F) of sonidegib suggesting that dose adjustment is not necessary in patients with renal impairment. Patients with severe renal impairment were not studied so it is not known if the pharmacokinetics (and therefore safety) of sonidegib is altered in this group of patients. Therefore, patients with severe renal impairment are included as missing information

Use in races other than Caucasians

Evidence source:

In Study A2201, 94% of patients treated with sonidegib were Caucasian, and 6% were non-Caucasian patients (CSR LDE225A2201). Separately, Japanese healthy volunteers given a single dose of sonidegib 200 mg seemed to have a higher exposure in terms of Cmax and AUC compared to Western healthy volunteers.

A search in the Safety Database was conducted for subjects who had information on ethnic origin ('ethnicity' field).

The following cases were considered noteworthy:

- All cases of races or ethnicity other than Caucasians receiving sonidegib and after plausible temporal relationship develop an SAE.

The focus of the analysis of the cases was to evaluate any new trends/differences in the safety profile in these non-Caucasian subjects

Cumulative data analysis

A total of 75 cases were retrieved cumulatively. Distribution by report type and seriousness is presented in the below Table SVII.3.2 -3 . All cases were medically confirmed.

Table SVII.3.2 -3

Report type	Cumulative		Total
	Serious	Non-serious	
Clinical trial	74	0	**74**
Post-marketing solicited sources	1	0	**1**
Spontaneous incl. literature	0	0	**0**
Total	**75**	**0**	**75**

Source: Safety Database as of 29 Dec 2018.

Distribution of cases by race/ethnicity is presented in the Table SVII.3.2 -4:

Table SVII.3.2 -4

Race/Ethnicity	Number of cases
Asian	28
Black	15
Hispanic	15
Other	17

Race/Ethnicity	Number of cases
Total	**75**

Source: Safety Database as of 29 December 2018

Twenty-three cases reported a fatal outcome in the non-Caucasian population. The cause of death in these cases was reported as neoplasm progression (16 cases), and in one case each for malignant pleural effusion, lung infection, embolism, sepsis, multi-organ failure, pneumonia, pneumonia aspiration and dysphagia. These events (except dysphagia) were also among the fatal events often reported for the Caucasian and were more likely related to or, complications of, the underlying disease and unlikely related to sonidegib therapy.

Population in need of further characterization:

Population PK analysis did not identify Japanese ethnicity as a significant covariate after accounting for differences in the distribution of other covariates. Nor did it indicate clinically relevant difference in sonidegib exposure between Japanese patients versus patients from western countries. However, since the safety data in patients of different racial and/or ethnic origin are limited, long-term safety will be further characterized by Pharmacovigilance activities.

Use in female patients of childbearing potential taking concomitant oral contraceptives

Evidence source:

A search in the Safety Database was conducted using MedDRA.

The following cases were considered noteworthy:

- All cases from female subjects of childbearing potential taking concomitant oral contraceptives who receive sonidegib and subsequently become pregnant.

The above mentioned search retrieved no cases cumulatively.

Population in need of further characterization:

Use of sonidegib in female patients of childbearing potential taking concomitant oral contraceptives is considered as missing information and will be further characterized by Pharmacovigilance activities.

Long term safety in laBCC patients

Evidence source:

A search in the Safety Database was conducted for subjects with treatment > 18 months (540 days; conservatively considering 30 days per month) for the indication of BCC (laBCC or mBCC).

The following cases were considered noteworthy:

- All cases of BCC where the subject has been taking sonidegib for a period of > 18 months and develops an SAE or progression of the underlying disease.

Cumulative data analysis: A total of 11 cases were retrieved cumulatively using aforementioned search criteria. Of the 11 cases retrieved cumulatively, the reported events had onset within less than 540 days of sonidegib treatment in two cases (2014RR-166238, 2015RR-166244) and thus, the cases are excluded from further analysis. Distribution of cases by report type and seriousness is presented in the Table SVII.3.2 -5. All the cases retrieved were medically confirmed.

Table SVII.3.2 -5

Report type	Cumulative		
	Serious	Non-serious	Total
Clinical trial	8	1	**9**
Post-marketing solicited sources	0	0	**0**
Spontaneous incl. literature	0	0	**0**
Total	**8**	**1**	**9**

Source: Safety Database as of 29 Aug 2018. Excluding two cases with onset of reported events within less than 540 days sonidegib treatment (2014RR-166238 and 2015RR-166244).

All nine cases are noteworthy and the review of these cases does not reveal any particular pattern of AEs in subjects with long-term treatment of sonidegib.

The percentage of fatal and life-threatening cases was slightly higher in all laBCC patients regardless of treatment duration. However, due to the substantially less number of cases with long term use, it is yet to determine whether the observed difference is valid.

Population in need of further characterization:

Long-term safety is considered as missing information requiring further characterization as there is currently limited data on long-term safety profile available. Long-term safety will be further characterized by routine Pharmacovigilance activities and through a non-interventional post-authorization safety study (PASS).

Off-label use in patients with medulloblastoma, BCC appropriate for surgery or radiotherapy, and other cancers

Evidence source:

A review of post-marketing reports in the Safety Database was conducted to identify cases with off-label use in patients with medulloblastoma, BCC appropriate for surgery or radiotherapy, and other cancers in post-marketing setting.

The following cases were considered noteworthy:

- All cases of medulloblastoma or other non-BCC cancers where subjects receive sonidegib and after plausible temporal relationship develop an SAE or there is progression of disease leading to discontinuation of therapy.

The focus of the analysis of the cases was to evaluate any new trends/differences in the safety profile in these subjects with non-BCC cancers.

Cumulative data analysis

Twelve cases were identified cumulatively. Distribution of cases by report type and seriousness is presented in the Table SVII.3.2 -6.

Table SVII.3.2 -6

Report type	Cumulative		
	Serious	Non-serious	Total
Clinical trial	0	0	**0**
Post-marketing solicited sources	0	0	**0**
Spontaneous incl. literature	10	2	**12**
Total	**10**	**2**	**12**

Source: Safety Database as of 29 Dec 2018.
There were no cases with a fatal outcome.

Population in need of further characterization:
Off-label use in patients with medulloblastoma, BCC appropriate for surgery or radiotherapy and other cancers is considered as missing information requiring further characterization as there is currently limited data on long-term safety profile available. Long-term safety will be further characterized by routine Pharmacovigilance activities.

Use in patients with anemia (haemoglobin of <9 g/dL)

Evidence source:

A search in the Safety Database was conducted using MedDRA.

The following cases were considered noteworthy:

- All cases with a history of anemia (hemoglobin <9 g/dL) where subject received sonidegib and after plausible temporal relationship develops an SAE or decrease in hemoglobin.

Cumulative data analysis

A total of 50 cases were retrieved cumulatively. Of these 50 cases, 13 cases reported anemia as incidental finding and one case reported family history of anemia (grandparents). These 14 cases are excluded from the further discussion. Distribution of remaining 36 cases is presented by report type and seriousness in the Table SVII.3.2 -7. All cases were medically confirmed.

Table SVII.3.2 -7

Report type	Cumulative		
	Serious	Non-serious	Total
Clinical trial	36	0	**36**
Post-marketing solicited sources	0	0	**0**

Spontaneous incl. literature	0	0	**0**
Total	**36**	**0**	**36**

Source: Safety Database as of 29 Dec 2018; Excluding 13 cases reporting anemia as incidental findings and one case reported family history of anemia.

Twenty-six subjects were male, 10 were female, and the age range was from 35 to 91 years (seven adults, 27 elderly [≥ 65 years]). Seven cases reported a fatal outcome. None of these cases met the noteworthy criteria as the severity (common terminology criteria for adverse events grade) of anemia or the hemoglobin levels were not reported in subjects' medical history among these cases. Seven subjects developed aggravation of anemia, however, five of them were confounded by bleeding events and another case was confounded by co- suspect drugs (hydroxyzine and warfarin). In the last case, the information was limited for a meaningful assessment.

Cumulatively, seven cases reported a fatal outcome. In four cases, the subject died due to progression of the underlying malignancy. In one case, the subject died due to sepsis confounded by the underlying malignancy, in one case the subject died due to pneumonia which was also confounded by the underlying malignancy and in one case the patient had pre-existing cardiac disease (atrial fibrillation and right bundle branch block) along with chronic renal insufficiency which may have lead to the death of the patient. The fatality appears to be slightly higher among all the subjects. However, due to the limited information regarding the reporting pattern for this population as well as the substantially less number of cases with anemia(hemoglobin of <9 g/dL) at baseline, it is yet to determine whether the observed difference in the reporting frequency of fatality between subjects with anemia compared to other subjects is valid.

Population in need of further characterization:

Use of sonidegib in this population is considered as missing information and will be further characterized by Pharmacovigilance activities.

Use in patients with recent myocardial ischemia or cardiac failure

Evidence source:

A search in the Safety Database was conducted using MedDRA.

Cases where the reported event of interest did not have onset prior to sonidegib treatment were excluded from the analysis.

The following cases were considered noteworthy:

- All cases with recent myocardial ischemia or cardiac failure (within three months prior to initiating sonidegib) confirmed by ECG, troponin test, echocardiography and after plausible temporal relationship develop an SAE or aggravation of the underlying cardiac disease.

The focus of the analysis of the cases was to evaluate any new trends/differences in the safety profile in these subjects with a recent (within three months prior to initiating sonidegib) history of heart failure or ischemic heart disease.

A total of 38 cases were retrieved cumulatively. Four cases did not report myocardial ischemia or cardiac failure prior to study treatment and were therefore excluded from further analysis. Distribution of remaining 34 cases by report type and seriousness is presented in the Table SVII.3.2 -8. All the cases are medically confirmed.

Table SVII.3.2 -8

Report type	Cumulative		
	Serious	Non-serious	Total
Clinical trial	33	1	**34**
Post-marketing solicited sources	0	0	**0**
Spontaneous incl. literature	0	0	**0**
Total	**33**	**1**	**34**

Source: Safety Database as of 29 Aug 2018; Excluding four cases with no myocardial ischemia or cardiac failure prior to study treatment: 2013RR-167063, 2016RR-167374, 2016RR-167377 and 2012RR-166977.

No cases met the noteworthy case definition. Thirty-four cases, did not mention if the medical history/concurrent condition of myocardial ischemia or cardiac failure was within three months prior to initiating sonidegib, or the events were not confirmed by ECG, troponin test, echocardiography. The remaining case presented with medical history of myocardial ischemia but was not associated with SAEs or aggravation of the underlying cardiac disease as only non- serious AEs of hematuria and platelet count decreased were reported for this case.

Cumulatively, the fatality appears to be higher among the subjects with medical history of cardiac disorders. However, due to the limited information regarding this population as well as the substantially less number of cases, it is yet to determine whether the observed difference in the reporting frequency of fatality between subjects with medical history of cardiac disorders vs other subjects is valid.

Population in need of further characterization:

Use of sonidegib in this population is considered missing information, and will be further characterized by Pharmacovigilance activities.

Part II: Module SVIII - Summary of the safety concerns

The summary of safety concerns for Odomzo 200 mg hard capsules is based on the last version of Odomzo RMP, EU Risk Management Plan LDE225/Sonidegib version 7.0 signed off on 21 Jul 2017.

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• **Muscle related events** • **Reproductive toxicity (teratogenicity)** • **Food interactions** • **Interactions with strong CYP3A4 inhibitors and CYP3A4 inducers**
Important potential risks	• **Impaired fertility** • **Second primary malignancies** • **Post-natal developmental defects** • **Fractures** • **Interaction with sensitive BCRP substrates with low therapeutic index** • **Interactions with drugs with a known risk of myopathy** • **Cardiac events (myocardial ischemia, cardiac failure and cardiac death)** • **Syncope** • **Corneal disorders**
Missing information	• **Use in patients with severe renal impairment** • **Use in races other than Caucasians** • **Use in female patients of childbearing potential taking concomitant oral contraceptives** • **Long-termsafety on laBCC patients** • **Off-label use in patients with medulloblastoma, BCC appropriate for surgery or radiotherapy and other cancers** • **Use in patients with anemia(hemoglobin of<9 g/dl)** • **Use in patients with recent myocardial ischemia or cardiac failure**

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1. Routine Pharmacovigilance activities

Sun Pharma has implemented and continuously maintains a pharmacovigilance system described in details in Pharmacovigilance System Master File.

The routine pharmacovigilance practices conducted by Sun Pharma comply with the pharmacovigilance practices covered in the "Guideline on good pharmacovigilance practices (GVP)".

The objective of Sun Pharma's pharmacovigilance strategy is to systematically collect ADRs from multiple sources and to conduct real time and periodic medical assessments of single and aggregate cases. The applicant has in place a process to ensure regular signal detection analysis of post-marketing data. Signal detection reports are thoroughly reviewed to identify any possible arising risk in order to take appropriate actions.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- **Specific adverse reaction follow-up questionnaires:**

Targeted follow up of Muscle-related events following Sonidegib exposure will be used in order to collect structured data (Annex 4)

- **Other forms of routine pharmacovigilance activities:**

None proposed.

III.2 Additional pharmacovigilance activities

As part of additional Pharmacovigilance activities, Sun Pharmaceutical Industries is conducting:

- **a post-authorisation safety study (PASS)** EUPAS28453 in order to assess the long-term safety and tolerability of Odomzo^{R} (Sonidegib) on patients with locally advanced basal cell carcinoma (laBCC).

Study name and title:

CLDE225A2404

"A non-interventional, multi-national, multi-center post-authorization safety study (PASS) to assess the long-term safety and tolerability of Odomzo^{R} (Sonidegib) administered in patients with locally advanced basal cell carcinoma (laBCC)."

Rationale and study objectives:

The approval of sonidegib was based on a Phase II, multicenter, double-blind, and multiple cohort clinical trial conducted in patients with locally advanced BCC or mBCC ([CLDE225A2201]). Patients were followed for at least 18 months unless discontinued earlier. Although the safety results demonstrated that sonidegib is associated with an acceptable and manageable safety profile in the intended target population characterized by predictable, primarily low-grade events, which are generally reversible and noncumulative, safety data from patients with long-term exposure to sonidegib are limited. Consequently, this long-term PASS is to further characterize the long term safety and tolerability profile of sonidegib under real-world (routine clinical practice) conditions.

Identified risks for sonidegib are muscle-related events and reproductive toxicity. Potential risks are impaired fertility, second primary malignancy, post-natal developmental defects, fractures, cardiac events (myocardial ischemia, cardiac failure, and cardiac death), syncope and corneal disorders. Of the above identified and potential risks, the AEs of special interest for this study are second primary malignancy, post-natal developmental defects, fractures and cardiac events [(myocardial ischemia, cardiac failure, and cardiac death).
In order to further characterize the safety profile of under real-world conditions this Post Authorization Safety Study (PASS) will collect data from patients prescribed sonidegib according to the EU prescribing information.

The objectives of this study are:

Primary objective
To assess the long-term safety and tolerability profile of sonidegib in the treatment of laBCC as determined by the occurrence of AEs, SAEs, deaths and discontinuation in a real world setting according to the approved EU prescribing information, over a 3 year observation period.

Secondary objectives

- To assess the occurrence and characteristics (such as type, time to onset, severity, duration, outcome measures taken) of adverse events of special interest (AESI):
  - muscle related events,
  - second primary malignancies,
  - lipase and amylase elevations,
  - fractures,
  - cardiac disorders,
  - asthenia, fatigue, lethargy, dysgeusia,
  - alopecia,
  - diarrhea and their complications,
  - nausea and/or vomiting and their complications,
  - Torsade de points/QT prolongation,
  - decreased appetite and/or weight loss, and
  - hypersensitivity.

- The proportions of patients with AEs of special interest will be summarized descriptively.

- To assess the occurrence and characteristics (such as type, time to onset, severity, duration) of AEs and SAEs of special populations:
  - Patients carrying known and relevant polymorphism
  - Elderly patients: ≥65 yrs.
  - Patients with hepatic impairment
  - Patients with renal impairment
  - Female patients with child bearing potential taking concomitant oral contraceptives
  - Patients with anemia (hemoglobin <9 g/dL)
  - Patients with recent myocardial ischemia or cardiac failure
  - Patients taking concomitant medications with known risk of creatine kinase elevation.

Study design:
This is a non-interventional, multinational, multi-center post-authorization safety study, to further assess the safety of sonidegib administered in routine clinical practice in patients with laBCC who are not amendable to curative surgery or radiation therapy. This study is observational in nature and does not impose a therapy protocol, diagnostic/therapeutic interventions or a specific visit schedule.
For this study, each enrolled patient will be observed for 3 years after enrollment. A 3 year observation period is considered to be appropriate to further characterize the safety of sonidegib with long term exposure. Given the limitations and difficulties of a direct control group within this PASS, and the resulting lack of a comparator arm, results of this PASS will be provided with a critical discussion of the data, taking into consideration available public information on the background rates of these AESI and on safety data of other alternative treatments for this condition.

Study population:
The patient population will consist of male and female patients aged 18 years or older with a diagnosis of laBCC who are not amenable to curative surgery or radiation therapy and who are treated with sonidegib 200 mg taken orally once daily.

Milestones:
Study milestones are given in the following table:

Milestone	Planned date
Start of data collection	1 November 2018*
End of data collection	1 November 2024**
Registration in the EU-PAS register	25 February 2019
Final report of study results	1 November 2025

* Tentative, depending on local commercial availability of sonidegib

**Anticipates 3 year recruitment period

***Status updates and safety data review report will be provided through the PSUR.

- **Study EUPAS35766: "Physicians' knowledge on the risks associated with Odomzo®** exposure after the implementation of a risk minimization program ***CLDE225A2405:***

Primary objective:
-To assess HCPs' knowledge on the risk of teratogenicity associated with sonidegib exposure during pregnancy and impaired fertility after the delivery of the HCP educational materials including the DHCP letter.

Secondary objective:
To evaluate the delivery of educational materials to HCPs consisting of DCHP letter and HCP educational brochure.

Safety concerns addressed:

-reproductive toxicity

-impaired fertility

Interim results:
- interim reports may be generated e.g. after the end of local data collection in a country as some countries might launch only many years after approval

Milestones
Dates when data collection starts and ends, and also final study reports dates will vary between the countries where the study is conducted and will depend on Odomzo®'s National Competent Authorities approval.

Start of data collection: approximately one year after the drug is locally approved and available for prescription
End of data collection: six months of local data collection. This may be extended to 12 months, if relevant data collection is not possible within 6 months, e.g. if more followup/reminders are needed in case of a low response rate
Final report of study results: one year after the end of data collection in all countries which participate in this survey.

Date of final study report submission

Final study report:
- one year after the end of data collection in all countries which participate in this survey

III.3. Summary Table of additional Pharmacovigilance Activities

Table III.1: On-going and planned additional Pharmacovigilance activities

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1-Imposed mandatory additional Pharmacovigilance activities which are conditions of the marketing authorization authorization Not applicable				
Category 2-Imposed mandatory additional Pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances Not applicable				
Category 3-Required additional Pharmacovigilance activities				
Measuring effectiveness of Pregnancy Prevention Programs	Measuring the effectiveness of the Odomzo Pregnancy Prevention Programs on a country-specific level, in agreement with National Competent Authorities	Reproductive toxicity (teratogenicity) and Impaired fertility	"regular updates"	Regularly, as part of PSURs
A non-interventional, multi-national, multi-center post-authorization safety study (PASS) to assess the long-term safety and tolerability	Assessing the long-term safety and tolerability of Odomzo® (sonidegib) administered in patients with locally	To assess the occurrence and characteristics of adverse events of special interest (AESI): muscle related events, second primary malignancies, lipase and amylase elevations, fractures,	Start of data collection End of data collection	1 November 2018* 01 November 2024** 25 February 2019

of Odomzo® (sonidegib) administered in patients with locally advanced basal cell carcinoma (laBCC) CLDE225A2404, EUPAS28453	advanced basal cell carcinoma (laBCC)	cardiac disorders, asthenia, fatigue, lethargy, dysgeusia, alopecia, diarrhea and their complications, nausea and/or vomiting and their complications, Torsade de points/QT prolongation, decreased appetite and/or weight loss, and hypersensitivity. To assess the occurrence and characteristics (such as type, time to onset, severity, duration, outcome, measures taken) of AEs and SAEs of special populations (patients carrying known and relevant polymorphism, elderly patients: ≥65 yrs, patients with hepatic or renal impairment, female patients with child bearing potential taking concomitant oral contraceptives, patients with anemia, patients with recent myocardial ischemia or cardiac failure, patients taking	Registration in the EU-PAS register Final report of study results	01 November 2025

		concomitant medications with known risk of creatine kinase elevation)		

* Tentative, depending on local commercial availability of sonidegib
**Anticipates 3 year recruitment period

CLDE225X2116

This was a Phase Ib/II, open-label, multi-center, dose-finding study to assess the safety and efficacy of the oral combination of LDE225 (Sonidegib) and INC424 (Ruxolitinib) in subjects with Myelofibrosis (MF).

There was an early termination (10-Apr-2018) as the benefit/risk assessment of the combination treatment based on interim analysis data was not supportive to pursue further development in MF subjects. While this lack of observed supportive data contributed to the decision to terminate the study, the divestment of one of the combination agents, LDE225, eventually led to early termination.

The study enrolled 50 subjects (23 in the Phase Ib part of dose escalation, 27 in the Phase Ib dose expansion phase and Phase II Stage 1), and three DLTs were observed (one at the MTD dose level). All three subjects had elevated levels of blood creatine phosphokinase (grade 4 severity in 2 subjects and grade 3 severity in 1 subject). All these events were suspected to be related to the study drug and led to temporary interruption of study drug dosage. The MTD and RPIID was determined and confirmed to be LDE225 400 mg qd + INC424 20 mg bid.

Summary of safety results:

- -The median exposure time to LDE225 and INC424 was 411.50 days (range: 30 to 1505) and 424 days (range: 30 to 1505), respectively.
- -For LDE225, the median relative dose intensity was 100%, and 64% of subjects had a relative dose intensity of greater than 90%.
- -For INC424, the median relative dose intensity was 99.92%, and 74% of subjects had a relative dose intensity of greater than 90%.
- -Two subjects (4%) and one subject (2%) experienced DLTs (elevated levels of blood creatine phosphokinase in all three subjects) at the LDE225 400 mg qd + INC424 15 mg bid dose level and LDE225 400 mg qd + INC424 20 mg bid dose level from Phase I dose expansion phase, respectively.
- -All subjects experienced at least one AE, and majority of the subjects (78%) experienced grade 3 or 4 AEs.
- -The most frequently reported AEs (one AE, and majorityere muscle spasms (62%), anemia (60%), alopecia (50%), diarrhea (44%), dysgeusia (38%), blood creatine phosphokinase increased (36%), fatigue (34%), thrombocytopenia (30%), pyrexia (30%), myalgia (28%), vomiting (24%), nausea (24%), constipation (22%), and cough (22%).
- -Four subjects (8%) died during the study. Of these, one subject died on treatment (or up to 30 days after the end of treatment).
- -SAEs occurred in 26 subjects (52%). Most frequent SAEs (≥ 5% subjects) were pyrexia
- (10%), and blood creatine phosphokinase increased (10%).
- -Adverse events leading to study drug discontinuation were reported in 29 subjects (58%). The most frequently reported (y drug discontinuation were reporbjects) were pyreuation were blood creatine phosphokinase increased (8%), thrombocytopenia (6%), muscle spasms (6%), acute myeloid leukemia (6%), and alopecia (6%).
- Adverse events requiring dose adjustment or interruption were reported in 36 subjects (72%). The most frequently reported AEs (or interruption were reported in 36 subject interruption were blood creatine phosphokinase increased (18%), thrombocytopenia (14%), anemia (12%), muscle spasms (10%), myalgia (10%), alopecia (10%), platelet
- count decreased (8%), and diarrhea (6%).
- -Newly occurring or worsening from Baseline to grade 3 hematological abnormalities (lymphocytes, platelets, and partial thromboplastin time) were infrequently reported.
- -Newly occurring or worsening from Baseline to grade 3 or 4 clinical chemistry abnormalities (alkaline phosphatase, creatine kinase, glucose, potassium, ALT, AST, bilirubin, and urate) were infrequently reported.
- -Post Baseline notable ECG changes in QTcF of > 450 - 480 ms was noted in seven subjects (all subjects had hanges in QTcF of > 450 - 480 ms was noted in seven00 ms (> 450 - 480 ms at Baseline).

Discussion and overall conclusions

Modest efficacy with the combination treatment was observed with spleen volume reduction of ≥ 35% in 44.4% of subjects and 50% reduction in spleen length in 26% of subjects by Week 24.
The descriptive analysis of PK parameters did not reveal any impact of LDE225 on the PK of INC424.
A total of four deaths were reported in the study, of which one subject died on treatment (or up to 30 days after the end of treatment).
The benefit/risk assessment of the combined treatment based on a lack of sufficient efficacy was not supportive to pursue further development of this combination in MF subjects.

CLDE225A2201

This was a phase II, randomized double-blind study of efficacy and safety of two dose levels of LDE225 in patients with locally advanced or metastatic basal cell carcinoma.

Objectives: The primary objective was to evaluate the efficacy of sonidegib as measured by the objective response rate (ORR). The key secondary objectives were to determine the duration ofresponse (DoR) and the rate of complete response (CRR). Other secondary objectives included evaluations of time to tumor response (TTR), progression-free survival (PFS), and overall survival
(OS), and further characterization of the safety and pharmacokinetics (PK) of sonidegib therapy.

Methodology: This was a randomized, non-comparative, parallel-cohort, international, multicenter Phase-II study designed to evaluate the safety and antitumor activity of two doses of sonidegib in patients with locally advanced basal cell carcinoma (laBCC) or metastatic basal cell carcinoma (mBCC). Eligible patients were randomly assigned (1:2) to treatment with either sonidegib 200 mg orally once-daily or sonidegib 800 mg orally once-daily. Randomization was stratified by: stage of disease (laBCC vs. mBCC), disease histology for patients with laBCC (aggressive vs. nonaggressive);geographic region of enrollment.

Diagnosis and main criteria for inclusion: To be eligible for this study, patients were required to be ≥ 18 years of age and have a histologically-confirmed diagnosis of either laBCC that was not amenable to surgery or radiation therapy or of mBCC. Eligible patients included: patients who had experienced recurrence following prior surgery and/or radiation therapy and were not deemed to be candidates for further curative treatment; patients with BCCs in anatomically challenging locations,
such as the eye, inner canthus of the nose and ears, for which surgery and/or radiation therapy might result in severe disfigurement or dysfunction; patients with laBCC who were considered to be poor risk for surgery due to comorbidities or for whom radiation therapy was contraindicated.

Criteria for evaluation

Efficacy: Primary endpoint of ORR was defined as the proportion of patients with a confirmed best overall response (determined on repeat assessments ≥ 4 weeks apart) of complete response (CR) or partial response (PR), per central review. Objective response was assessed in accordance with the following:
- Patients with laBCC: protocol-specified modified Response Evaluation Criteria in Solid Tumors (mRECIST), using an integrated composite response based on all radiographic (MRI),photographic (digital clinical photography), and histological (histopathology) data
- Patients with mBCC: RECIST 1.1

Key secondary endpoints were DoR and CRR; both were determined per central review, according to mRECIST for patients with laBCC and RECIST 1.1 for patients with mBCC. Other secondary endpoints included: DoR and CRR per investigator review; PFS and time to tumor response (TTR) per central and investigator review; and OS.

Safety: Safety was evaluated on the basis of the: frequency, type, severity, and causal relationship of AEs to study treatment; frequency of deaths, serious adverse events (SAEs), and clinically significant AEs (including AEs leading to discontinuation and AEs requiring dose reduction and/or interruption); changes in laboratory parameters, with particular attention to grade 3/4 abnormalities; electrocardiogram (ECG) changes.

Summary – Conclusions

The safety and tolerability profile of sonidegib remains consistent with prior experience with other Hedgehog (Hh) signaling pathway inhibitors and with that of the primary, 12 month, 18 month, 30 months and 42 month analyses.

Muscle spasms, alopecia, and dysgeusia were reported in ≥ 40% of patients receiving sonidegib 200 mg whereas muscle spasms, dysgeusia, alopecia, nausea, and decreased weight were reported in ≥ 40% of patients receiving sonidegib 800 mg.

Grade 3 to 4 events were reported in 43.0% of patients receiving sonidegib 200 mg group vs. 64.7% in the 800 mg group.

SAEs were reported less frequently in patients receiving treatment with sonidegib 200 mg (20.3% vs. 38.7%) than for sonidegib 800 mg.

As expected, slight increases in percentages were observed in most AE categories with longer exposure to sonidegib. Sonidegib 200 mg continues to be more favorable than that for sonidegib 800 mg with lower overall incidences in each AE category.

Overall, the final safety data of sonidegib do not reveal any new or late onset safety signals that affect the safety profile of sonidegib in the advanced BCC. AEs were generally manageable with dose interruptions/reductions. No new or unexpected safety signals have been observed. Sonidegib continues to demonstrate an acceptable and well-characterized safety profile for patients with advanced BCC.

The study had previously met its primary endpoint of independently-assessed objective response (with point estimates ≥ 30% for both treatment arms). Response rates for all patients (laBCC and mBCC cohorts combined) for the 42-month analysis was numerically higher than those for the primary (6 month) analysis and nearly identical to those for the 30-month and 18-month analyses.

In summary, the long-term follow-up results presented herein confirm the benefit-risk profile that led to the approval of sonidegib.

Part IV: Plans for post-authorisation efficacy studies

Not applicable

PART V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities) Risk minimization plan

All the safety concerns (the risks, interactions, and the missing information) are appropriately communicated through either the current or the proposed labeling. In addition, additional risk minimization measures are proposed for reproductive toxicity (teratogenicity) as identified risksand impaired fertility as potential risk.

V.1. Risk Minimisation Measures

Table V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation measures
Muscle-related events	***Routine risk communication*:** **-SmPC Section 4.2, 4.4 and 4.8** **Section 4.2 Posology and method of administration** under *Dose modifications for creatine phosphokinase (CK) elevations and muscle-related adverse events* **Section 4.4 Special warnings and precautions for use** **Section 4.8 Undesirable effects** under Musculoskeletal and connective tissue disorders **Other routine risk minimization measures beyond the Product Information:** ***Legal status*:** prescription only medicine, to be used by experienced physicians in the approved indications.
Reproductive Toxicity (teratogenicity)	***Routine risk communication:*** **-SmPC Section 4.3 4.4 and 4.6** **Section 4.3 Contraindications** **Section 4.4 Special warnings and precautions for use under** Embryofoetal death or severe birth defects, Counselling and Contraception **Section 4.6 Fertility, pregnancy and lactation** under - *Women of childbearing potential* - *In case of pregnancy or missed menstrual periods* - *Contraception in males and females* **Other routine risk minimization measures beyond the Product Information:** ***Legal status*:** prescription only medicine, to be used by experienced physicians in the approved indications.

	Prescriptions of Odomzo should be limited to 30 days of treatment, with continuation of treatment requiring a new prescription.
Food interactions	**Routine risk communication**: -**SmPC Section 4.2 4.3, 4.4, 4.5, 5.2** Section 4.2 Posology and method of administration: - Odomzo must be taken at least two hours after a meal and at least one hour before the following meal Section 4.3 Contraindications Section 4.4 Special warnings and precautions for use in Excipients Section 4.5 Interaction with other medicinal products and other forms of interaction under Food interaction Section 5.2 Pharmacokinetic properties **Other routine risk minimization measures beyond the Product Information:** ***Legal status*:** prescription only medicine, to be used by experienced physicians in the approved indications
Interactions with strong CYP3A4 inhibitors/ CYP3A4 inducers	**Routine risk communication**: -**SmPC Section 4.4 and 4.5** SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction **Other routine risk minimization measures beyond the Product Information:** ***Legal status*:** prescription only medicine, to be used by experienced physicians in the approved indications
Impaired fertility	**Routine risk communication**: **-SmPC Section 4.6, SmPC Section 4.8** SmPC Section 4.6 Fertility, pregnancy and lactation SmPC Section 4.8 Undesirable effects **Other routine risk minimization measures beyond the Product Information:** ***Legal status*:** prescription only medicine, to be used by experienced physicians in the approved indications. Prescriptions of Odomzo should be limited to 30 days of treatment, with continuation of treatment requiring a new prescription.
Second primary malignancies	**Routine risk communication**: -SmPC Section 4.6 **Fertility, pregnancy and lactation** and SmPC Section 4.8 Undesirable effects

	Routine risk minimisation activities recommending specific clinical measures to address the risk: -Since patients with advanced BCC have an increased risk of developing cuSCC all patients should be monitored routinely while taking Odomzo, and cuSCC should be treated according to the standard of care **Other routine risk minimization measures beyond the Product Information:** ***Legal status*:** prescription only medicine, to be used by experienced physicians in the approved indications
Post natal developmental defects	**Routine risk communication**: -**SmPC Section 5.3** Preclinical safety data under General toxicology **Other routine risk minimization measures beyond the Product Information:** ***Legal status*:** prescription only medicine, to be used by experienced physicians in the approved indications
Fractures	**Routine risk communication**: -none **Routine risk minimisation activities recommending specific clinical measures to address the risk:** - Currently available data do not support the need for risk minimization **Other routine risk minimization measures beyond the Product Information:** ***Legal status*:** prescription only medicine, to be used by experienced physicians in the approved indications
Interaction with sensitive BCRP substrates with low therapeutic index	**Routine risk communication**: -SmPC Section 4.5 Preclinical safety data under Effects of sonidegib on other medicinal products **Other routine risk minimization measures beyond the Product Information:** ***Legal status*:** prescription only medicine, to be used by experienced physicians in the approved indications
Interaction with drugs with known risk of myopathy	**Routine risk communication**:

	-SmPC Section 4.5 Preclinical safety data under Agents that may increase muscle-related events **Other routine risk minimization measures beyond the Product Information:** ***Legal status*:** prescription only medicine, to be used by experienced physicians in the approved indications
Cardiac events	**Routine risk communication**: -none **Routine risk minimisation activities recommending specific clinical measures to address the risk:** - Currently available data do not support the need for risk minimization **Other routine risk minimization measures beyond the Product Information:** ***Legal status*:** prescription only medicine, to be used by experienced physicians in the approved indications
Syncope	**Routine risk communication**: -none **Routine risk minimisation activities recommending specific clinical measures to address the risk:** - Currently available data do not support the need for risk minimization **Other routine risk minimization measures beyond the Product Information:** ***Legal status*:** prescription only medicine, to be used by experienced physicians in the approved indications
Corneal disorders	**Routine risk communication**: -none **Routine risk minimisation activities recommending specific clinical measures to address the risk:** - Currently available data do not support the need for risk minimization **Other routine risk minimization measures beyond the Product Information:** ***Legal status*:** prescription only medicine, to be used by experienced physicians in the approved indications

Use in patients with severe renal impairment	**Routine risk communication**<u>:</u> -SmPC Section 4.2 and SmPC Section 5.2 SmPC Section 4.2 **Posology and method of administration** under <u>*Special populations*</u> and SmPC Section 5.2 **Pharmacokinetic *properties*** <u>*under Patients with renal impairment*</u> **Routine risk minimisation activities recommending specific clinical measures to address the risk:** -No efficacy and safety data are available in patients with severe renal impairment **Other routine risk minimization measures beyond the Product Information:** ***Legal status*:** prescription only medicine, to be used by experienced physicians in the approved indications
Use in races others than Caucasians	**Routine risk communication**<u>:</u> -SmPC Section 5.2 **Pharmacokinetic properties** **Routine risk minimisation activities recommending specific clinical measures to address the risk:** - The C_{max} and AUC_{inf} of sonidegib in Japanese healthy subjects were 1.56 and 1.68-fold higher, respectively, than those seen in Western healthy subjects for a single dose of 200 mg **Other routine risk minimization measures beyond the Product Information:** ***Legal status*:** prescription only medicine, to be used by experienced physicians in the approved indications
Use in female patients of childbearing potential taking concomitant oral contraceptives	**Routine risk communication**<u>:</u> -none **Routine risk minimisation activities recommending specific clinical measures to address the risk:** - Currently available data do not support the need for risk minimization **Other routine risk minimization measures beyond the Product Information:** ***Legal status*:** prescription only medicine, to be used by experienced physicians in the approved indications

Long term safety in laBCC patients	**Routine risk communication**: -none **Routine risk minimisation activities recommending specific clinical measures to address the risk:** - Currently available data do not support the need for risk minimization **Other routine risk minimization measures beyond the Product Information:** ***Legal status*:** prescription only medicine, to be used by experienced physicians in the approved indications
Off-label use in patients with medulloblastoma, BCC appropriate for surgery or radiotherapy and other cancers	**Routine risk communication**: -SmPC section 4.1 Therapeutic indication **Routine risk minimisation activities recommending specific clinical measures to address the risk:** -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 **Other routine risk minimization measures beyond the Product Information:** ***Legal status*:** prescription only medicine, to be used by experienced physicians in the approved indications
Use in patients with anemia: Haemoglobin<9g/dl	**Routine risk communication**: -none **Routine risk minimisation activities recommending specific clinical measures to address the risk:** - Currently available data do not support the need for risk minimization **Other routine risk minimization measures beyond the Product Information:** ***Legal status*:** prescription only medicine, to be used by experienced physicians in the approved indications
Use in patients with recent myocardial ischemia or cardiac failure	**Routine risk communication**: -none **Routine risk minimisation activities recommending specific clinical measures to address the risk:** - Currently available data do not support the need for risk minimization

	Other routine risk minimization measures beyond the Product Information: ***Legal status*:** prescription only medicine, to be used by experienced physicians in the approved indications

V.2.Additional risk Minimisation Measures

The additional risk minimisation measures are for the following risks:

- Reproductive toxicity (teratogenicity)
- Impaired fertility:

The Odomzo (sonidegib) educational materials are supplied as a physician education information pack (see Annex6), which contains:

- DHCP letter
- Physician brochures integrated with reminder card
- Patient brochures integrated with reminder card
- Verification of counselling form

1. DHCP letter

Objective

This letter is sent in agreement with the European Medicines Agency and <local authority> to inform about the teratogenic effects of Odomzo® and the Pregnancy Prevention Programme (PPP).

Rationale for the additional risk minimisation activity:

This letter is implemented to minimize this risks.

Target audience and planned distribution path:

- For physicians in order to support the safe and effective use of sonidegib.
- Local Sun Pharma representatives are responsible to convey the key safety messages into the local versions and to distribute it in line with national requirements.

Plans to evaluate the effectiveness of the interventions and criteria for success:

- The effectiveness of the education material for HCPs will be assessed in agreement with the National Competent Authorities prior to launch
- This may include a physician survey on their knowledge of the risks associated with sonidegib.
- In addition, pregnancy exposures to sonidegib that are reported to occur in female patients or in the female partners of male patients will be actively collected and analysed
- Descriptive statistics will be the primary approach for summarizing data, including subject's age, gender, concomitant medication, medical and obstetric history, indication for and duration of sonidegib treatment, weeks of gestational age at exposure, type of delivery, pregnancy outcome by maternal/paternal exposure and by prospective/retrospective case definition, fetal outcome, infant status,

and congenital abnormalities

- It will be considered that the educational materials have been successful if more than 80% of responses to the survey are correct. The number of pregnancy reports will be considered in this evaluation as well.
- Results of assessment of the effectiveness of risk minimisation activities will be presented in the PSURs.

2. Physician brochures integrated with reminder card

Objective

The material provides information for the physicians on how to safely prescribe sonidegib. It highlights the key safety messages by describing signs and symptoms of potential adverse reactions, thereby ensuring rapid identification and treatment of these events.

Rationale for the additional risk minimisation activity:

HCP guide and reminder card is implemented to minimize this risks.

Target audience and planned distribution path:

- Health Care Professionals
- The educational material will be distributed in the EU from the first launch of this product
- Educational material will be review annually for a period of 5 years
- Further details of educational materials can be found in Annex 6

Plans to evaluate the effectiveness of the interventions and criteria for success:

- The effectiveness of the education material for HCPs will be assessed in agreement with the National Competent Authorities prior to launch
- This may include a physician survey on their knowledge of the risks associated with sonidegib.
- In addition, pregnancy exposures to sonidegib that are reported to occur in female patients or in the female partners of male patients will be actively collected and analysed
- Descriptive statistics will be the primary approach for summarizing data, including subject's age, gender, concomitant medication, medical and obstetric history, indication for and duration of sonidegib treatment, weeks of gestational age at exposure, type of delivery, pregnancy outcome by maternal/paternal exposure and by prospective/retrospective case definition, fetal outcome, infant status, and congenital abnormalities

- It will be considered that the educational materials have been successful if more than 80% of responses to the survey are correct. The number of pregnancy reports will be considered in this evaluation as well.
- Results of assessment of the effectiveness of risk minimisation activities will be presented in the PSURs.

3. Patient brochures integrated with reminder card

Objective

To inform patients about important safety information regarding pregnancy for patients taking Odomzo® (sonidegib) capsules.

Rationale for the additional risk minimisation activity:

Patient brochures integrated with reminder card are implemented to minimize this risk regarding pregnancy for patients taking Odomzo® (sonidegib) capsules.

The brochure aims to provide adequate patient education on:

- Sonidegib potential adverse events (reproductive toxicity - teratogenicity) and impaired fertility
- What to do before, during and after treatment
- Recommended forms of contraception
- What to do if pregnancy occurs

In addition, the brochure contains recommendations to contact the physician in case of additional questions or if there are side effects. Patient information packs are prepared nationally, in line with each member state's national regulations and legislations, and language.

Target audience and planned distribution path:

- The brochure is provided to the physician for distribution to the patient after Odomzo® is prescribed to them.
- The educational material will be distributed in the EU from the first launch of this product
- Local Sun Pharma representatives are responsible to convey the key safety messages into the local versions of the educational materials and to distribute it in line with national requirements
- Educational material will be review annually for a period of 5 years
- Further details of educational materials can be found in Annex 6

Plans to evaluate the effectiveness of the interventions and criteria for success:

- The effectiveness of the education material for HCPs will be assessed in agreement with the National Competent Authorities prior to launch
- This may include a physician survey on their knowledge of the risks associated with sonidegib.

- In addition, pregnancy exposures to sonidegib that are reported to occur in female patients or in the female partners of male patients will be actively collected and analysed
- Descriptive statistics will be the primary approach for summarizing data, including subject's age, gender, concomitant medication, medical and obstetric history, indication for and duration of sonidegib treatment, weeks of gestational age at exposure, type of delivery, pregnancy outcome by maternal/paternal exposure and by prospective/retrospective case definition, fetal outcome, infant status, and congenital abnormalities
- It will be considered that the educational materials have been successful if more than 80% of responses to the survey are correct. The number of pregnancy reports will be considered in this evaluation as well.
- Results of assessment of the effectiveness of risk minimisation activities will be presented in the PSURs.

4. Patient counseling form

Objective

Provide counselling to minimize the risk of teratogenicity with Odomzo® (sonidegib) capsules.

Rationale for the additional risk minimisation activity:

Patient counseling form is implemented to minimize this risk.

Target audience and planned distribution path:

- Patient and Health Care Professionals.
- The educational material will be distributed in the EU from the first launch of this product
- Educational material will be review annually for a period of 5 years
- Further details of educational materials can be found in Annex 6

Plans to evaluate the effectiveness of the interventions and criteria for success:

- The effectiveness of the education material for HCPs will be assessed in agreement with the National Competent Authorities prior to launch
- This may include a physician survey on their knowledge of the risks associated with sonidegib.
- In addition, pregnancy exposures to sonidegib that are reported to occur in female patients or in the female partners of male patients will be actively collected and analysed
- Descriptive statistics will be the primary approach for summarizing data,

including subject's age, gender, concomitant medication, medical and obstetric history, indication for and duration of sonidegib treatment, weeks of gestational age at exposure, type of delivery, pregnancy outcome by maternal/paternal exposure and by prospective/retrospective case definition, fetal outcome, infant status, and congenital abnormalities

- It will be considered that the educational materials have been successful if more than 80% of responses to the survey are correct. The number of pregnancy reports will be considered in this evaluation as well.
- Results of assessment of the effectiveness of risk minimisation activities will be presented in the PSURs.

5. Pregnancy Prevention Program

Objective

To implement a set of interventions aiming to minimise pregnancy exposure during treatment with a medicinal product with known or potential teratogenic effects.

Rationale for the additional risk minimisation activity

To educate healthcare providers and patients about the teratogenic risks associated with sonidegib and the need to avoid foetal exposure.

To ensure that female patients are not pregnant when starting therapy or do not become pregnant during the course and/or soon after stopping the therapy. It could also target male patients when use of a medicinal product by the biological father might have a negative effect on the pregnancy outcome. A PPP combines the use of educational tools with interventions to control appropriately access to the medicine.

Pregnancy Prevention Program, consisting of:

- DHCP letter
- HCP educational material with integrated HCP reminder card
- Patient educational material with integrated patient reminder card
- Verification of counseling form for women of childbearing potential, women of non-childbearing potential and for males
- Verification of pregnancy by a test supervised by a health care professional is required within 7 days prior to initiation of sonidegib treatment and monthly during treatment by means of a test performed by a healthcare professional.
- Content to include background information on sonidegib with teratogenic risks associated
- Need for adequate contraception use (one highly effective methods, and a barrier method)
- Prescription duration limited to one month

- Information to be followed in the event of a pregnancy

Educational material will be review annually for a period of 5 years.
The educational material will be distributed in the EU from the first launch of this product

Further details of educational materials can be found in Annex 6

Target audience and planned distribution path:

- Health Care Professionals and patients
- The educational material will be distributed in the EU from the first launch of this product
- Educational material will be review annually for a period of 5 years
- Further details of educational materials can be found in Annex 6

Plans to evaluate the effectiveness of the interventions and criteria for success:

- The effectiveness of the education material for HCPs will be assessed in agreement with the National Competent Authorities prior to launch
- This may include a physician survey on their knowledge of the risks associated with sonidegib.
- In addition, pregnancy exposures to sonidegib that are reported to occur in female patients or in the female partners of male patients will be actively collected and analysed
- Descriptive statistics will be the primary approach for summarizing data, including subject's age, gender, concomitant medication, medical and obstetric history, indication for and duration of sonidegib treatment, weeks of gestational age at exposure, type of delivery, pregnancy outcome by maternal/paternal exposure and by prospective/retrospective case definition, fetal outcome, infant status, and congenital abnormalities
- It will be considered that the educational materials have been successful if more than 80% of responses to the survey are correct. The number of pregnancy reports will be considered in this evaluation as well.
- Results of assessment of the effectiveness of risk minimisation activities will be presented in the PSURs.

V.3. Summary of risk minimization measures

Table Part V.3 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Muscle-related event	**Routine risk minimisation** -SmPC Section 4.2, 4.4, 4.8 **-**SmPC Section 4.2 summarizes recommendations for dose interruption and/or dose reduction of sonidegib therapy in the management of symptomatic CK elevations and muscle related adverse events -Prescription only medicine to be used by experienced physicians in the approved indication **Additional risk minimisation measures** None	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:> **-** Specific ADR follow-up form muscle related events <Additional pharmacovigilance activities:> **-**"PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"
Teratogenicity	**Routine risk minimisation** -SmPC Sections 4.3, 4.4 and 4.6 -Prescription only medicine **Additional risk minimisation measures** **-Odomzo Pregnancy Prevention Programme** (Educational material consisting of DHCP letter as well as educational brochure for physicians and patients/caregivers.)	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:> **-**none <Additional pharmacovigilance activities:> **-**Study EUPAS35766: "Physicians' knowledge on the risks associated with Odomzo®" **-**"PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"
Food interactions	**Routine risk minimization** **-**SmPC Sections 4.2, 4.3, 4.4, 4.5 and 5.2 -Prescription only medicine ne to be used by experienced physicians in the approved indication **Additional risk minimisation measures** None	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:> -none <Additional pharmacovigilance activities:> **-**none

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Interactions with strong CYP3A4inhibitors/CYP3A4inducer)	**Routine risk minimisation** **-**SmPC Section 4.4 and 4.5 -Prescription only medicine to be used by experienced physicians in the approved indication **Additional risk minimisation measures** **None**	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:> **-**none <Additional pharmacovigilance activities:> **-**none
Impaired fertility	**Routine risk minimisation** **-**SmPC Sections 4.6, 4.8 -Prescription only medicine **Additional risk minimisation measures** **-Odomzo Pregnancy Prevention Programme** (Educational material consisting of DHCP letter as well as educational brochure for physicians and patients/caregivers)	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:> **-**none <Additional pharmacovigilance activities:> -Study EUPAS35766: "Physicians' knowledge on the risks associated with Odomzo® **-**"PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"
Second primary malignancies	**Routine risk minimisation** **-**SmPC Section 4.6 and 4.8 -Prescription only medicine to be used by experienced physicians in the approved indication **Additional risk minimisation measures** None	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:> **-**none <Additional pharmacovigilance activities:> **-**"PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"
Post-natal developmental defects	**Routine risk minimisation** **-**SmPC Section 5.3 -Prescription only medicine to be used by experienced physicians in the approved indication **Additional risk minimisation measures** None	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:> **-**none <Additional pharmacovigilance activities:> **-**"PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Fractures	**Routine risk minimisation** **-**none -Prescription only medicine to be used by experienced physicians in the approved indication **Additional risk minimisation measures** **None**	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:> **-**none <Additional pharmacovigilance activities:> **-** "PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"
Interaction with sensitive BCRP substrates with low therapeutic index	**Routine risk minimisation** **-**SmPC Section 4.5 -Prescription only medicine to be used by experienced physicians in the approved indication **Additional risk minimisation measures** None	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:> **-**none <Additional pharmacovigilance activities:> **-**none
Interaction with drugs with a known risk of myopathy	**Routine risk minimisation** **-**SmPC Section 4.5 -Prescription only medicine to be used by experienced physicians in the approved indication **Additional risk minimisation measures** None	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:> **-**none <Additional pharmacovigilance activities:> **-**none
Cardiac events	**Routine risk minimisation** -Prescription only medicine to be used by experienced physicians in the approved indication **Additional risk minimisation measures** None	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:> **-**none <Additional pharmacovigilance activities:> **-**"PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"
Syncope	**Routine risk minimisation** **-** Prescription only medicine to be used by experienced physicians in the approved indication	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:> **-**none

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures None	<Additional pharmacovigilance activities:> **-**"PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"
Corneal disorders	**Routine risk minimisation** **-** Prescription only medicine to be used by experienced physicians in the approved indication **Additional risk minimisation measures** None	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:> **-**none <Additional pharmacovigilance activities:> **-**"PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"
Use in patients with severe renal impairment	**Routine risk minimisation** **-**SmPC Sections 4.2 and 5.2 -Prescription only medicine to be used by experienced physicians in the approved indication **Additional risk minimisation measures** **None**	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:> **-**none <Additional pharmacovigilance activities:> **-**"PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"
Use in races other than Caucasians	**Routine risk minimisation** **-**SmPC Section 5.2 -Prescription only medicine to be used by experienced physicians in the approved indication **Additional risk minimisation measures** None	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:> **-**none <Additional pharmacovigilance activities:> **-**none
Use in female patients of childbearing potential taking concomitant oral contraceptives	**Routine risk minimisation** **-**SmPC Section 5.2 -Prescription only medicine to be used by experienced physicians in the approved indication	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:> **-**none

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures None	<Additional pharmacovigilance activities:> **-**"PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"
Long-term safety in laBCC patients	**Routine risk minimisation** **-** Prescription only medicine to be used by experienced physicians in the approved indication **Additional risk minimisation measures** None	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:> **-**none <Additional pharmacovigilance activities:> **-**"PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"
Off-label use in in patients with Medulloblastom, BCC appropriate for surgery or radiotherapy and other cancers	**Routine risk minimisation** **-**SmPC Section 4.1 - Prescription only medicine to be used by experienced physicians in the approved indication **Additional risk minimisation measures** None	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:> **-**none <Additional pharmacovigilance activities:> **-**"PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"
Use in patients with anemia (haemoglobin of <9 g/dl)	**Routine risk minimisation** -Prescription only medicine to be used by experienced physicians in the approved indication **Additional risk minimisation measures** None	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:> **-**none <Additional pharmacovigilance activities:> **-**"PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"
Use in patients with recent myocardial ischemia and cardiac failure	**Routine risk minimisation** -Prescription only medicine to be used by experienced physicians in the approved indication **Additional risk minimisation measures** None	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:> **-**none <Additional pharmacovigilance activities:> **-**"PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"

Part VI: Summary of the risk management plan for Odomzo

(sonidegib as phosphate)

This is a summary of the risk management plan (RMP) for Odomzo 200 mg hard capsules. The RMP details important risks of Odomzo 200 mg hard capsules, how these risks can be minimised and how more information will be obtained about Odomzo 200 mg hard capsules's risks and uncertainties (missing information).

Odomzo 200 mg hard capsules summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Odomzo should be used.

This summary of the RMP for Odomzo 200 mg hard capsules should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Odomzo 200 mg hard capsules's RMP.

I. The medicine and what it is used for

Odomzo 200 mg hard capsules is authorised for the treatment of adult patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy. It contains sonidegib (phosphate) as the active substance and it is given by oral route.

II. Risks associated with the medicine and activities to minimise or further characterize the risks

Important risks of Odomzo 200 mg hard capsules, together with measures to minimize such risks and the proposed studies for learning more about Odomzo 200 mg hard capsules's risks are outlined below.

• Specific information such as warnings, precautions and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals

• The authorized pack sizes-the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly

• The medicine's legal status (with prescription) can help to minimise its risks.

Together these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment –so that immediate action can be taken as necessary. These measures constitute *routine Pharmacovigilance activities.*

If important information that may affect the safe use of Odomzo 200 mg hard capsules is not yet available, it is listed under "missing information" below.

II.A List of important risks and missing information

Important risks of Odomzo 200 mg hard capsules are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered.

Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Odomzo 200 mg hard capsules. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collect

List of important risks and missing information	
Important identified risks	• **Muscle related events** • **Reproductive toxicity (teratogenicity)Food interactions** • **Interactions with strong CYP3A4 inhibitors and CYP3A4 inducers**
Important potential risks	• **Impaired fertilitySecond primary malignancies** • **Post-natal developmental defects** • **Fractures** • **Interaction with sensitive BCRP substrates with low therapeutic index** • **Interactions with drugs with a known risk of myopathy** • **Cardiac events (myocardial ischemia, cardiac failure and cardiac death)** • **Syncope** • **Corneal disorders**
Missing information	• **Use in patients with severe renal impairment** • **Use in races other than Caucasians** • **Use in female patients of childbearing potential taking concomitant oral contraceptives** • **Long-term safety on laBCC patients** • **Off-label use in patients with medulloblastoma,**

	BCC appropriate for surgery or radiotherapy and other cancers • **Use in patients with anemia (hemoglobin of<9 g/dl)** • **Use in patients with recent myocardial ischemia or cardiac failure**

IIB Summary of important risks

Important identified risk: Muscle related events	
Evidence for linking the risk to the medicine	Muscle toxicity with CK elevation is a notable clinical toxicity with sonidegib and is believed to be a class effect for all inhibitors of the Hedgehogh signalling pathway (the blockade of the Hedgehog pathway, which is required for tissue regeneration/repair mechanism, could result in CK elevation in the event that an injury occurs); therefore muscle-related events are considered an important risk in the RMP and will be further assessed in the post-marketing setting. The classification of muscle related events as an identified risk is based on evidence from the clinical developmental programme.
Risk factors and risk groups	In the pivotal study, no particular related risk factors have been identified in terms of risk groups, or demographics neither for CK elevation and muscle-related findings, nor for those subjects reported with "rhabdomyolysis"; no life-threatening muscle-related events requiring hemodialysis have been reported with sonidegib in the Study A2201.
Risk minimisation measures	Routine risk minimization measures -SmPC Sections 4.2, 4.4, 4.8 -Prescription only medicine to be used by experienced physicians in the approved indication **-** Specific ADR follow-up form muscle related events <Additional risk minimisation measures> None

Additional Pharmacovigilance activities	-"PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"
Important identified risk: Reproductive toxicity (teratogenicity)	
Evidence for linking the risk to the medicine	Sonidegib was shown to be fetotoxic in rabbits as evidenced by abortion and/or complete resorption of fetuses and teratogenic resulting in severe malformations at ≥ 5 mg/kg/day at plasma exposure lower than the steady-state exposure at the recommended human dose. Teratogenic effects included vertebral, distal limb and digit malformations, severe craniofacial malformations and other severe midline defects. Fetotoxicity in rabbits was seen at low maternal doses (0.01 mg/kg/day) where maternal exposure was below the limit of detection (0.05 ng/mL) (Non-clinical overview).
Risk factors and risk groups	Women of childbearing age becoming pregnant and/or requiring treatment with sonidegib through pregnancy or female partners of male patients
Risk minimisation measures	Routine risk minimisatin measures: -SmPC Sections 4.3, 4.4 and 4.6 -Prescription only medicine to be used by experienced physicians in the approved indication Additional risk minimisation measures **-Odomzo Pregnancy Prevention Programme** (Educational material consisting of DHCP letter as well as educational brochure for physicians and patients/caregivers.)
Additional Pharmacovigilance activities	**-Study (EUPAS35766): "Physicians' knowledge on the risks associated with Odomzo®** -"PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"
Important identified risk: Food interaction	
Evidence for linking the risk to the medicine	Studies investigating the pharmacokinetic parameters of Odomzo 200 mg hard capsules have shown that the bioavailability of is increased in the presence of food

Risk minimisation measures	Routine risk minimisation measures -SmPC Sections 4.5, 5.2 -Prescription only medicine ne to be used by experienced physicians in the approved indication <Additional risk minimisation measures> None
Important identified risk: **Interactions with strong CYP3A4inhibitors/CYP3A4inducers**	
Evidence for linking the risk with the medicine	Studies of pharmacokinetic parameters have shown that Sonidegib undergoes metabolism primarily by CYP3A4, and concomitant administration of strong inhibitors or inducers of CYP3A4 can increase or decrease sonidegib concentrations significantly.
Risk minimisation measures	Routine risk minimisation measures -SmPC Section 4.5 -Prescription only medicine to be used by experienced physicians in the approved indication <Additional risk minimisation measures> None
Important potential risk: Impaired fertility	
Evidence for linking the risk to the medicine	Animal studies have shown that administering sonidegib could lead to a complete lack of fertility
Risk factors and risk groups	Women of childbearing age becoming pregnant and/or requiring treatment with sonidegib through pregnancy or female partners of male patients
Risk minimisation measures	Routine risk minimization -SmPC Sections 4.6, 4.8, 5.3 -Prescription only medicine to be used by experienced physicians in the approved indication Additional risk minimisation measures

	-Odomzo Pregnancy Prevention Programme (Educational material consisting of DHCP letter as well as educational brochure for physicians and patients/caregivers)
Additional Pharmacovigilance activities	**-Study (EUPAS35766): "Physicians' knowledge on the risks associated with Odomzo®** **-**"PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"
Important potential risk: Second primary malignancies	
Evidence for linking the risk to the medicine	Sonidegib was not genotoxic in studies conducted in vitro and in vivo. Carcinogenicity studies were performed with sonidegib in mice and rats. No carcinogenic potential was identified in either species.
Risk factors and risk groups	The excess risk of developing a second malignancy among cancer survivors can likely be attributed to factors including similar etiologies (e.g. lifestyle factors, environmental exposures), genetics, and the effects of treatment (Travis et al 2006, Mariotto et al 2007, Youlden and Baade 2011). Associations between specific sites of primary and secondary cancers have been noted. Among BCC patients, significantly increased risk was observed of lung, melanoma, non- Hodgkin lymphoma and mouth and pharynx cancers. As noted above, having a personal history of non-melanoma skin cancer, including BCC or SCC, is an independent risk factor for the development of secondary cancers (Chen et al 2008, Wheless et al 2010). Evidence from the literature also suggests that earlier age of non-melanoma skin cancer is associated with a higher risk of developing a secondary cancer (Chen et al 2008).
Risk minimisation measures	Routine risk minimization measures **-**SmPC Section 4.4 -Prescription only medicine to be used by experienced physicians in the approved indication Additional risk minimisation measures None
Additional Pharmacovigilance activities	**-**"PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"
Important potential risk: **Post natal developmental defects**	
	Evidence for this risk arises from the sonidegib's pharmacologic mechanism of action on developmental pathways as seen in rats and dogs.

Evidence for linking the risk to the medicine	The Hh pathway remains active during postnatal development in the root of growing teeth and in the epiphyseal plate of growing long bones. Inhibition of the Hh pathway by sonidegib disrupts normal proliferation and differentiation at these sites, resulting in abnormal tooth development and premature closure of the epiphyseal plate. The most striking effects were on growing bone and teeth and consisted of thinning or closure of growth plates in the sternum and femur and decreasing proliferating chondrocytes in the costochondral junction of ribs and of dentine dysplasia of the incisors and loss of incisors. Toxicology studies conducted on growing animals have shown that sonidegib has effect on bone metabolism and on growing teeth. It is estimated that these effects are unlikely to occur in adult humans due to the maturity of their skeletal system. There were no cases of post-natal developmental defects reported during the registration trial of sonidegib since the population studied was adult patients (aged >18 years). However, in Study X2104, three pediatric patients reported epiphyseal disorder, bone disorder, and chondropathy. The two pediatric patients with epiphyseal disorder and chondropathy were discontinued from the study due to the events. While data is still limited, this study provides early clinical evidence to what was observed in preclinical studies regarding this potential risk.
Risk factors and risk groups	Infants being breastfed by mothers receiving sonidegib and/or paediatric patients being treated in clinical studies with sonidegib for indications in oncology for which there are no other therapeutic alternatives.
Risk minimisation measures	Routine risk minimization measures -SmPC Section 5.3 -Prescription only medicine to be used by experienced physicians in the approved indication Additional risk minimisation measures None
Additional Pharmacovigilance activities	-"PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"
Important potential risk: Fractures	

Evidence for linking the risks to the medicine	Evidence arises from sonidegib clinical developmental programme.
Risk groups or risk factors	Given sonidegib's effect on growing bone, pediatric patients are at highest risk. The effect of sonidegib on mature bones is not known, since the toxicology studies were conducted in growing animals, however, these effects are not likely to occur in the adult cancer patient due to the maturity of their skeletal system.
Risk minimisation measures	Routine risk minimization measures -Prescription only medicine to be used by experienced physicians in the approved indication <Additional risk minimisation measures> None
Additional Pharmacovigilance activities	-"PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"
Potential identified risk: Interaction with sensitive BCRP substrates with low therapeutic index	
Evidence for linking the risks to the medicine	Studies of pharmacokinetic parameters have shown that Sonidegib is also a breast cancer resistance protein (BCRP) inhibitor
Risk groups or risk factors	Patients concomitantly using substrates of BCRP transporters should be carefully monitored for adverse drug reactions
Risk minimisation measures	Routine risk minimization measures -SmPC Section 4.5 -Prescription only medicine to be used by experienced physicians in the approved indication <Additional risk minimisation measures> None

Important potential risk: Interaction with drugs with a known risk of myopathy	
Evidence for linking the risks to the medicine	Evidence of interaction with drugs with a known risk of myopathy arises from the sonidegib's pharmacological mechanism of action. Muscle toxicity (with CK elevation) is believed to be a class effect for all inhibitors of the Hedgehogh signaling pathway, therefore concomitant administration of drugs with a known risk of myopathy might lead to overlapping toxicities
Risk groups or risk factors	Patients concomitantly taking drugs with a known risk of myopathy
Risk minimisation measures	Routine risk minimization measures -SmPC Section 4.5 -Prescription only medicine to be used by experienced physicians in the approved indication <Additional risk minimisation measures> None
Important potential risk: Cardiac events	
Evidence for linking the risks to the medicine	Evidence for linking sonidegib administration with cardiac events arises from the review of published non-clinical data indicating that the inhibition of Hh-signalling results in myocardial ischemia, cardiac failure and cardiac death and that Hh signaling is protective against acute myocardial infarction (Paulis L et al 2015). Therefore, the potential for sonidegib to cause cardiac events cannot be excluded; particularly in patients with recent ischaemic injury, (a group of patients in which exposure to sonidegib is limited). However, there is no available information on the potential mechanism specifically between sonidegib and cardiac events based on preclinical data which extensively evaluated cardiovascular data.
Risk groups or risk factors	In the pivotal study, no particular related risk factors have been identified in terms of risk groups or demographics for those subjects with related cardiac events. However, there are various factors which can impact the risk for cardiac events in general such as the presence of the following history: diabetes, hypercholesterolemia, hypertension, previous myocardial ischemia and smoking history.

Risk minimisation measures	Routine risk minimization measures -Prescription only medicine to be used by experienced physicians in the approved indication <Additional risk minimisation measures> None
Additional Pharmacovigilance activities	-"PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"
Important potential risk: Syncope	
Evidence for linking the risks to the medicine	Evidence linking sonidegib administration to syncope, arises from the clinical developmental programme. However, no definitive signal has risen from the analysis of safety information available to date and no clear association with sonidegib has been made. In the general population, syncope is common in patients with co-morbidities or concurrent medications affecting the heart rate. These events are infrequent in patients taking Odomzo.
Risk groups or risk factors	Several etiologic factors have been noted to contribute to syncope in cancer patients, the most common being orthostatic hypotension, with cardiac causes assuming a secondary role. Other causes are drugs, vasovagal reactions, and cerebrovascular disease. Patients with head and neck tumors, thyroid tumors, and cervical lymphadenopathy can develop recurrent syncope related to carotid sinus hypersensitivity. Syncope in patients with head and neck tumors can occur through several mechanisms: glossopharyngeal, neuralgia– asystole syndrome, carotid sinus syndrome, and glossopharyngeal-related reflex cardiogenic syncope without neuralgic pain.
Risk minimisation measures	Routine risk minimisation measures - Prescription only medicine to be used by experienced physicians in the approved indication <Additional risk minimisation measures> None

Additional Pharmacovigilance activities	-"PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"
Important potential risk: Corneal disorders	
Evidence for linking the risks to the medicine	Evidence linking corneal disorder to sonidegib arises from the clinical developmental programme. However, no definitive signal has risen from the analysis of safety information available to date and no clear association with sonidegib has been made.
Risk groups or risk factors	Contact lens wearers are at greatest risk of developing ulcerative keratitis. Other risk factors for ulcerative keratitis include previous eye disease (except myopia), nonsurgical ocular trauma and HIV infection.
Risk minimisation measures	Routine risk minimisation measures - Prescription only medicine to be used by experienced physicians in the approved indication <Additional risk minimisation measures> None
Additional Pharmacovigilance activities	-"PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"
Missing information: Use in patients with severe renal impairment	
Risk minimisation measures	Routine risk minimisation measures -SmPC Sections 4.2 and 5.2 -Prescription only medicine to be used by experienced physicians in the approved indication <Additional risk minimisation measures> None

Additional Pharmacovigilance activities	-"PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"
Missing information: Use in races other than Caucasians	
Risk minimisation measures	Routine risk minimization measures -SmPC Section 5.2 -Prescription only medicine to be used by experienced physicians in the approved indication <Additional risk minimisation measures> None
Missing information: Use in female patients of childbearing potential taking concomitant oral contraceptives	
Risk minimisation measures	Routine risk minimization measures -SmPC Section 5.2 -Prescription only medicine to be used by experienced physicians in the approved indication <Additional risk minimisation measures> None
Additional Pharmacovigilance activities	- PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"
Missing information: Off-label use in in patients with Medulloblastoma, BCC appropriate for surgery or radiotherapy and other cancers	
Risk minimisation measures	Routine risk minimisation measures -SmPC Section 4.1 - Prescription only medicine to be used by experienced physicians in the approved indication <Additional risk minimisation measures> None

Additional Pharmacovigilance activities	-"PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"
Missing information: Use in patients with anemia (haemoglobin of <9 g/dl)	
Risk minimisation measures	Routine risk minimization measure -Prescription only medicine to be used by experienced physicians in the approved indication <Additional risk minimisation measures> None
Additional Pharmacovigilance activities	-"PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"
Missing information: Use in patients with recent myocardial ischemia and cardiac failure	
Risk minimisation measures	Routine risk minimisation measures -SmPC Section 4.1 -Prescription only medicine to be used by experienced physicians in the approved indication <Additional risk minimisation measures> None
Additional Pharmacovigilance activities	-"PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"
Missing information: Long-term safety in laBCC patients	
Risk minimisation measures	Routine risk minimisation measures - Prescription only medicine to be used by experienced physicians in the approved indication Additional risk minimisation measures None
Additional Pharmacovigilance activities	-"PASS EUPAS28453 to assess the long-term safety and tolerability of Odomzo"

II. C Post-authorisation development plan

II.C. 1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Odomzo 200 mg hard capsules.

II.C. 2 Other studies in post-authorisation developmental plan

1. PASS number EUPAS35766 -Physicians' knowledge on the risks associated with Odomzo® exposure after the implementation of a risk minimization program

Purpose of the study: To assess health care professionals' knowledge of the risk of abnormal development of unborn babies associated with the use of Odomzo during pregnancy and of reduced ability to have children, after supplying educational materials to healthcare professionals.

2. PASS number EUPAS28453 A non-interventional, multi-national, multi-center post-authorization safety study (PASS) to assess the long-term safety and tolerability of Odomzo® (sonidegib) administered in patients with locally advanced basal cell carcinoma (laBCC)

Purpose of the study: This long-term PASS is to further characterize the long term safety and tolerability profile of sonidegib under real-world (routine clinical practice) conditions.

Part VII: Annexes

Annex 1 – EudraVigilance Interface

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Annex 4 - Specific adverse drug reaction follow-up forms

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Annex 7 - Other supporting data (including referenced material)

Annex 8 – Summary of changes to the risk management plan over time

Annex 4- Specific adverse drug reaction follow-up form

Sonidegib -Targeted follow-up checklist for muscle-related events

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Event Description:

Did the patient present with any of the following signs or symptoms? *(Check all that apply)*

☐ Muscle tenderness	☐ Muscle swelling	☐ Fatigue
☐ Muscle stiffness	☐ Walking difficulty	☐ Joint pain
☐ Muscle aching (myalgia)	☐ Respiratory difficulty	☐ Acute renal failure
☐ Muscle weakness	☐ Dark or red color urine	☐ Disseminated intravascular coagulation
☐ Muscle spasms	☐ General weakness	☐ Compartment syndrome
☐ Muscle hypotonicity	☐ Frequent falls	☐ Thyroid disorder (hypo/ hyperthyroidism)
☐ Muscle hypertonicity	☐ Poor balance	☐ None of the above

Were abnormalities detected in any of the following diagnostic tests? *(Check all that apply and please specify which test(s), dates and results)*

☐ Electrolyte levels (i.e. hyperkalemia, hypocalcaemia)

☐ CPK, myoglobin, aldolase, albumin (hypoalbuminaemia)

☐ Urinalysis including casts, hemoglobin, myoglobin

☐ Renal tests indicating renal insufficiency (Serum creatinine, BUN)

☐ Muscle biopsy

☐ None of the above

Patient History:

Had the patient been exposed to hazardous toxins in the past?

☐ Yes *(please describe)*: ☐ No ☐ Unknown

_____

Does the patient have evidence of any of the following? *(Check all that apply)*

☐ Metabolic or genetic disorders *(e.g. disorders of muscle carbohydrate metabolism, carnitine palmitoyltransferase deficiency)*	☐ Exertional rhabdomyolysis	
☐ Genetic abnormality *(e.g. hereditary metabolic abnormality)*	☐ Crush injury or trauma	☐ Viral infection (e.g. EBV, CMV, HIV, Herpes virus)
☐ Endocrine abnormality (e.g. diabetic ketoacidosis)	☐ Hypothermia	☐ Arterial thrombosis
☐ Alcoholism or alcohol abuse *(please specify):*	☐ Hyperthermia	☐ Bacterial infection
☐ Drug or substance abuse *(please specify):*	☐ Malignant hyperthermia	☐ Seizures/Epilepsy
☐ Snake or insect envenomation *(please specify):*	☐ Neuroleptic malignant syndrome	☐ None of the above

Has the patient recently taken any of the following? (*Check all that apply)*

☐ HMG-CoA reductase inhibitors (statins)	☐ Nucleoside reverse transcriptase inhibitors (NRTIs)	☐ Injection of iron-dextran
☐ Gemfibrazole	☐ Corticosteroids	☐ Niacin
☐ Cyclosporine	☐ Erythromycin	☐ Itraconazole
☐ MAOIs (esp. in combination with SSRIs, lithium, tri-cyclic antidepressants)	☐ Neuroleptics (phenothiazines)	☐ SSRIs/SNRIs

☐ None of the above

Was there any evidence of drug-drug-interactions leading up to this event?

☐ Yes (*please specify, including medications)*:

_____

☐ No

☐ Unknown

Annex 6 – Details of proposed additional risk minimization activities

Organization of material

The Odomzo (sonidegib) educational materials are supplied as a physician education information pack, which contains:

- DHCP letter
- Physician brochures integrated with reminder card
- Patient brochures integrated with reminder card
- Verification of counselling form

Objective

Educational material has been developed for physicians and patients in order to support the safe and effective use of sonidegib. The material provides information on how to safely prescribe sonidegib. It highlights the key safety messages by describing signs and symptoms of potential adverse reactions, thereby ensuring rapid identification and treatment of these events.

Physician education information packs are provided to all facilities where sonidegib is expected to be used.

The legal status of sonidegib is as a prescription-only medicine to be administered by qualified physicians. This restriction reduces the potential risks associated with off-label use of the product and increases the likelihood for patients to be appropriately monitored and treated.

Details of proposed educational program

The physician information has been provided as a letter (DHCP letter), an educational brochure, and a verification of counseling form.

To ensure that patients are adequately informed about sonidegib, a patient brochure for pregnancy prevention has been developed. The brochure is provided to the physician for distribution to the patient after Odomzo® is prescribed to them.

The brochure aims to provide adequate patient education on:

1. Sonidegib potential adverse events (reproductive toxicity - teratogenicity) and impaired fertility
2. What to do before, during and after treatment
3. Recommended forms of contraception
4. What to do if pregnancy occurs

In addition, the brochure contains recommendations to contact the physician in case of additional questions or if there are side effects. Patient information packs are prepared nationally, in line with each member state's national regulations and legislations, and language.

A verification of counseling form is also provided to the physicians to document that the patients have been counseled by their physicians about the risks associated with Odomzo treatment, including the risk of exposure to the unborn baby and/or infant during pregnancy and breastfeeding.

Key Safety Messages:

1. Health care providers

The following are key safety messages for health care providers, based on the risks that require "additional risk minimization measures" listed as 'educational material':

Reproductive toxicity (teratogenicity) **and impaired fertility:**

The following are the key messages to be communicated:

For Females:

- Sonidegib may cause embryo-fetal death or severe birth defects when administered to a pregnant woman.
- Sonidegib must not be used during pregnancy.
- Women who are pregnant or breast-feeding must not be prescribed sonidegib.
- Women of childbearing potential who will not or cannot practice the recommended pregnancy prevention measures must not be prescribed sonidegib.
- All women of childbearing potential are required to undergo a healthcare provider-administered pregnancy test within 7 days prior to starting sonidegib treatment, and subsequently, medically supervised monthly pregnancy tests.
- All women of childbearing potential must use two methods of contraception, including one highly effective method and a barrier method.
- Pregnancy precautions must be taken for 20 months after the last dose of sonidegib.

For Males:

- Men should not father a child or donate semen while taking sonidegib and for at least 6 months after ending treatment.
- Male patients must always use a condom, even after a vasectomy, when having sexual intercourse with a female partner and for 6 months after ending treatment to prevent exposure of female partners to the medicinal product via seminal fluid.

About Infertility:

- The potential for sonidegib to cause infertility in male and female patients is unknown.
- Based on findings from animal studies, male and female fertility may be compromised with sonidegib.
- Fertility preservation options should be discussed prior to starting treatment with sonidegib with any patient wanting to maintain reproductivity after treatment.

Pregnancy prevention:

The following are the key messages to be communicated:

- Sonidegib may cause severe birth defects.
- Sonidegib may lead to the death of a baby before it is born or shortly after being born.
- You or your partner must not become pregnant while taking sonidegib.
- You must follow the contraception advice during and for 20 months after the last dose of sonidegib.
- Sexually active males being treated with sonidegib must use a condom during intercourse, regardless of their vasectomy status. They should not father a child or donate semen while taking sonidegib or for at least 6 months after ending treatment.

All Patients:

- All patients should dispose of any unused capsules at the end of treatment in accordance with local requirements (if applicable, e.g. by returning the capsules to their pharmacist or physician)
- All patients should be advised never to give sonidegib to another person
- All patients should be advised not to donate blood during treatment, or for at least 20 months after the final dose

2. Patients:

Patient educational material:

• Summary of important safety information regarding pregnancy for patients taking Odomzo capsules

• Important things to know about Odomzo:

-Indication

-Summary of mode of action

-Risk of fetal death and birth defects

• Important things to know before starting treatment with Odomzo

• Important things to know during treatment with Odomzo:

-Information on how to avoid pregnancy (including contraceptive measures and regularly monitoring for) and for how long after stopping treatment

-Things to do if the patient/patient's partner has become pregnant

-Information on contraindications: pregnancy, breastfeeding, blood and semen donation

-Information on disposal of unused capsules

-Information on keeping the drug out of the sight and reach of children

• Important things to know after treatment with Odomzo:

-Disposal of unused capsules after end of treatment

-Women: continue to follow instructions during treatment with Odomzo for 20 months after final dose

-Men: continue to follow instructions during treatment with Odomzo for 6 months after final dose

-Common side effects

-Call for reporting

Patient reminder card:

• Contraindications for taking Odomzo: pregnancy, breastfeeding and not using pregnancy prevention measures

• Things to do if patient/patient's partner becomes pregnant

• Contraception advice

• Information on pregnancy testing before and while on therapy

• After treatment information on disposal of unused capsules and contraindication to blood donation

Verification of counseling form for women of childbearing potential, women of non-childbearing potential and for males:

- Patient's details
- Pretreatment pregnancy test results (negative/positive)
- Date of pretreatment pregnancy test
- Patient confirmation (signed)
- Physician or Healthcare provider confirmation (signed)
- All patients: contraindications while on treatment
- Women of childbearing potential:

- Contraindications during and after treatment (pregnancy, breastfeeding, need for pregnancy testing, adequate contraception methods, advice if patient becomes pregnant)

- Male patients:

- Things to do during and after therapy (contraception methods, reporting if female partner becomes pregnant, contraindication to semen donation)