EU RISK MANAGEMENT PLAN

for

VORANIGO (Vorasidenib)

RMP version to be assessed as part of this application:	
RMP Version number:	1.0
Data lock point for this RMP:	06 September 2022
Date of final sign-off:	18 July 2025
Rationale for submitting an updated RMP:	Not applicable
Summary of significant changes in this RMP:	Not applicable
Other RMP versions under evaluation:	Not applicable
RMP Version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable
Details of the currently approved RMP:	Not applicable
Version number:	Not applicable
Approved with procedure:	Not applicable
Date of approval (opinion date):	Not applicable

EU QPPV name: **Dr. Fairouz SMAIL, MD.**

EU QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

Table of content

List of In-Text Tables

List of Abbreviations

Abbreviation	Definition
2-HG	2-Hydroxyglutarate
ADME	Absorption, distribution, metabolism, and excretion
ADR	Adverse Drug Reactions
AIDS	Acquired immunodeficiency syndrome
ALF	Acute Liver Failure
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration-time curve
BALB/c	Bagg albino
BIRC	Blinded Independent Review Committee
CIOMS	Council for International Organizations of Medical Sciences
CI	Confidence interval
C_{max}	Maximum observed concentration
CMV	Cytomegalovirus
CNS	Central nervous system
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DDI	Drug-Drug Interaction
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
EBV	Epstein-Barr virus
ECG	Electrocardiogram
EEA	European Economic Area
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
GLP	Good laboratory practice
GGT	Gamma-glutamyl transferase
HBV	hepatitis B virus
HCV	hepatitis C virus
hERG	Human ether-à-go-go related gene
HGG	High-grade glioma
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonisation
IC_{50}	Concentration of drug that achieved half-maximal inhibition
IDH	Isocitrate dehydrogenase
IDH1, IDH2	Isocitrate dehydrogenase 1, isocitrate dehydrogenase 2

INN	International Non-Proprietary Name
I.R.I.S	Institut de Recherches Internationales Servier
LGG	Low-grade glioma
LVEF	Left ventricular ejection fraction
MAA	Marketing Authorisation application
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NOAEL	No Observed Adverse Effect Level
ODWG	Organ Dysfunction Working Group
PFS	Progression-free survival
PK	Pharmacokinetic
PL	Package Leaflet
PT	Preferred term
PXR	Pregnane X Receptor
QD	Once daily
QPPV	Qualified person in pharmacovigilance
QTc	Corrected QT interval
QTcF	Corrected QT interval using Fridericia's formula
RARECARE	Surveillance of Rare Cancers in Europe
RMP	Risk management plan
ROS	Reactive oxygen species
RUCAM	Roussel Uclaf Causality Assessment Method
SAE	Serious adverse event
SmPC	Summary of Product Characteristic
SMQ	Standardised MedDRA Query
SM	Systemic mastocytosis
TEAE	Treatment emergent adverse event
TTNI	Time to next intervention
ULN	Upper limit of normal
US	United States
WHO	World Health Organization

Part I: Product(s) Overview

Table 1: Product Overview

Active substance (INN or common name)	Vorasidenib
Pharmacotherapeutic group (ATC Code)	Antineoplastic agents; other antineoplastic agents ATC code: L01XM04
Marketing Authorisation Holder	Les Laboratoires Servier
Medicinal products to which this RMP refers	One
Invented name in the European Economic Area (EEA)	Voranigo
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class**: selective inhibitor of the neomorphic activity of mutant isocitrate dehydrogenase (IDH)1 (R132) and IDH2 (R172) proteins.
	Summary of mode of action: Vorasidenib is an inhibitor that targets the mutant IDH1 and IDH2 enzymes. In patients with astrocytoma or oligodendroglioma, IDH1 and IDH2 mutations lead to overproduction of oncogenic metabolite 2- hydroxyglutarate (2-HG), resulting in impaired cellular differentiation contributing to oncogenesis. Inhibition of the IDH1- and IDH2-mutated proteins by vorasidenib inhibits the abnormal production of 2-HG leading to differentiation of malignant cells and a reduction in their proliferation. Pre-clinical studies investigating the ability of vorasidenib to decrease tumor size were not performed.
Hyperlink to the Product Information	Module 1.3.1 Product Information
Indication in the EEA	Voranigo as monotherapy is indicated for the treatment of predominantly non-enhancing Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation in adult and adolescent patients aged 12 years and older and weighing at least 40 kg who only had surgical intervention and who are not in immediate need of radiotherapy or chemotherapy.

Dosage in the EEA	Current: The recommended dose of Voranigo in adults and adolescents 12 years of age and older is 40 mg once daily for patients weighing at least 40 kg. No dose recommendation can be made in patients weighing less than 40 kg, because of lack of clinical data in this population.
Pharmaceutical forms and strengths	10 mg film-coated tablet • Each film coated tablet contains 10 mg of vorasidenib (as hemicitric acid, hemihydate). 40 mg film-coated tablet • Each film coated tablet contains 40 mg of vorasidenib (as hemicitric acid, hemihydate).
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

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

Indication - Grade 2 astrocytoma or oligodendroglioma

Voranigo as monotherapy is indicated for the treatment of predominantly non-enhancing Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation in adult and adolescent patients aged 12 years and older and weighing at least 40 kg who only had surgical intervention and who are not in immediate need of radiotherapy or chemotherapy.

Incidence and Prevalence

Gliomas are defined as neuroepithelial tumors that originate from glial cells in the central nervous system (CNS) and are the most common form of primary malignant brain tumors. They are either astrocytic, oligodendrocytic, or ependymal, and are typically malignant (NBTS, 2022). The European annual incidence of glioma is estimated to be approximately 5.35 new cases/100 000 individuals (Orphanet, 2022) and 5.58/100 000 individuals (RARECARENet). The complete prevalence in Europe is approximately 2.6/10 000 individuals (Crocetti, 2012; Orphanet, 2022).

Isocitrate dehydrogenase-1 (IDH1) and isocitrate dehydrogenase-2 (IDH2) mutations occur early in gliomagenesis and IDH1 mutations are the most frequent genetic events in Grade 2 and 3 diffuse gliomas, occurring in approximately 80% of cases, while IDH2 mutations are far less frequent (approximately 4%) (Cohen, 2013). Historically, gliomas were categorized by a histopathological grading system (Grades 1-4). Per the World Health Organization (WHO) 2016 and 2021 classifications, gliomas are now classified based on molecular features in addition to histology. In addition to the presence of an isocitrate dehydrogenase mutation, oligodendrogliomas are defined by the presence of 1p19q codeletion and are histologically classified as Grade 2 or 3 tumors. Conversely, astrocytomas are defined by the lack of the 1p19q codeletion and are histologically classified as Grade 2, 3, or 4 (WHO 2021).

Demographics of the population in the proposed indication - age, gender, racial and/or ethnic origin

IDH-mutant diffuse gliomas are more commonly diagnosed in younger patients, including a range of adolescents in their late teens. The mean age of diagnosis is 45 years for patients with oligodendrogliomas and 38 years for patients with astrocytomas (Brat, 2015). Incidence of diffuse gliomas was higher in white compared to black and higher in males compared to females (Ostrom, 2022).

Risk factors for the disease

There are no known risk factors for IDH-mutant gliomas.

The main existing treatment options

There are currently no approved therapies for Grade 2 IDH mutant gliomas, and most treatments used are adopted from the higher-grade setting (Dietrich, 2022, Van Den Bent, 2011). Following maximal safe resection, the current standard of care for Grade 2 gliomas deemed high risk and Grade 3 gliomas involves radiation and chemotherapy. While these treatments result in survival benefits, they are toxic, non-curative, and associated with short-and long-term toxicities which can impact a patient's quality of life (McAleer, 2015; Varn, 2022 and Yu, 2021).

These therapies carry a risk of neurotoxicity, with the most common long-term complications being radiation necrosis, chemotherapy-associated leukoencephalopathy, and cognitive deficits (Klein, 2010). Neurocognitive impairment has also been described as not only a symptom related to the disease itself but also a side effect associated with radiation therapy and anti-seizure medications (Douw, 2009). These current treatments can also induce somatic alterations, leading to alkylating therapy-induced hypermutation or radiation-induced cell cycle alteration. These treatment-induced changes result in a more aggressive phenotype that is more resistant to available treatment with a more dismal prognosis (Varn, 2022; Yu, 2021; Touat, 2020). Therefore, there is an urgent unmet need for alternative therapies that target gliomas early in their development so that the use of more toxic treatments such as radiation and chemotherapy may be deferred.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

IDH mutant glioma patients may present with focal or generalised symptoms over days to years, depending on the speed of growth and location of the tumour. Tumours in functional areas will cause more obvious focal neurological deficits and tend to be discovered sooner on imaging (Lapointe, 2018). Frontal lobe tumours might cause weakness or dysphasia; parietal lobe tumours might cause numbness, hemineglect, or spatial disorientation; tumours involving the optic radiations might cause visual field defects. Tumours in the prefrontal lobe, temporal lobe, or corpus callosum often result in subtler cognitive dysfunction-personality changes, mood disorders, and short-term memory deficits (Lapointe, 2018). In approximately 50% of patients with IDH-mutant gliomas, tumours occur in frontal and prefrontal regions and present with new-onset seizures, which is the most common early symptom of the disease (Qi, 2014; Brat, 2015; Eckel-Passow, 2015). Although currently available treatments including surgery, RT, and/or chemotherapy may provide a PFS and survival benefit, they are not curative and these tumours eventually recur becoming more aggressive, and result in a decreased overall life expectancy for a young, otherwise healthy patient population, with an estimated median OS for Grade 2/3 diffuse gliomas ranging from 3 years to 14 years (Buckner, 2016; Lassman, 2022; Van Den Bent, 2011).

Important co-morbidities

These young patients do not usually suffer from significant non-glioma-related co-morbidities (Van Den Bent, 2022). However, they experience multiple tumour or treatment-related symptoms including seizures, headaches, fatigue, memory changes, cognitive decline, or other neurological dysfunctions depending on the tumour location (Dietrich, 2022; Van Den Bent, 2022). Many of these symptoms worsen over time due to diffuse infiltrative glioma growth or because of adverse effects from treatments such as surgery, radiation, chemotherapy, and antiepileptic medications (Dietrich, 2022; Van Den Bent, 2022).

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

Table 2: Key Safety Findings from Non-Clinical Studies and Relevance to Human Usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
Liver Vorasidenib led to hepatic effects at the lowest or tolerated doses tested in rats and monkeys during repeat-dose toxicity studies, with respective safety margins between monkey and human exposures of 8 for this target organ and no margin determined in rats. Those effects were restricted to signs suggestive of hepatic enzyme induction (higher liver weights and hepatocellular hypertrophy) without hepatocellular degeneration or necrosis. These findings were associated with liver enzyme elevation, mainly in the monkeys and rarely exceeding a 3-fold ratio over the controls, unless at very high exposures compared to humans (>65-fold the human reference exposure).	Most liver findings were suggestive of hepatic enzyme induction, and were not associated with hepatocellular degeneration or necrosis. Associated high liver enzyme elevation occurred at very high exposures compared to humans. Nevertheless, findings are relevant to humans, since hepatoxicity has been observed in humans and is considered an important identified risk.
Skin Vorasidenib induced skin toxicity in rats. After 28 days of treatment at 100 mg/kg/day, epidermal hyperplasia was observed, consisting of focally extensive to diffuse, even thickening of the stratum spinosum without rete peg formation or basal cell hyperplasia. There was no inflammation associated with those lesions. Hypertrophy of the sebaceous glands of the pilosebaceous units was noted in some of the same animals and was also considered related to vorasidenib treatment. In the 13-week toxicity study, higher incidences of epidermal hyperplasia were observed in all treated groups. After 4-week recovery period, epidermal hyperplasia was observed but the test-item relationship was uncertain. Therefore, the reversibility could not be assessed. At the lowest toxic dose, 5 mg/kg/day, the animal exposure remains 26-fold higher compared to the human exposure, which is significant. In monkeys, desquamation of various body surfaces was observed in one female in poor clinical status treated with 40 mg/kg/day in the 28-day study. There was no histological correlate and no clinical or microscopic observation of the skin in any other animal. Furthermore, this was not observed in the 13-week toxicity study, even at the highest dose, resulting in higher exposure compared to the 28-day study. Accordingly, the skin was not considered as a target of toxicity in that species.	The reversible skin effects observed in rats treated with vorasidenib could be relevant for human therapeutic use but are manageable.
Gastro-intestinal tract In rats only, during the 28-day study, vorasidenib-related findings were noted in the gastro-intestinal tract in all treated groups for females and at 30 and 100 mg/kg/day for male. They consisted of thickened glandular or non-glandular stomach correlating with erosions, ulcers, oedema, inflammation, epithelial degeneration and/or hyperplasia at microscopic examination. Few microscopic observations were also noted in the duodenum including erosion, minimal mucosal hyperplasia and neutrophilic infiltrates. Partial recovery was observed. No such findings were observed in the monkey nor in the 13-week study in rats performed at up to 50 mg/kg/day.	Gastrointestinal findings were observed inconsistently in a single rat study and not in the monkey studies. Such findings could be relevant to humans but are manageable.

Skeletal muscle In the 13-week toxicity study in rats, several animals treated with vorasidenib at 50 mg/kg/day, and to a lesser extent at 15 mg/kg/day, displayed clinical signs such as decreased muscle tone, or abnormal gait. This correlated, at microscopic examination, with skeletal muscle atrophy consistent with a neurogenic origin. Atrophy was characterised by focally extensive groups of muscle fibers that had a smaller diameter and often an angular profile on cross section. There was no inflammation or muscle necrosis associated with the atrophy. Often, small nerve branches within the affected section of the muscle showed axonal atrophy, myelin digestion chambers and/or dilated myelin sheaths. The incidence and severity of these findings were dose-related, remaining minimal at 5 mg/kg and mild to moderate at 15 and 50 mg/kg/day. Notably, smooth muscle, diaphragm (when collected), tongue and heart were normal, and sciatic nerve and spinal cord did not show evidence of vorasidenib related axonal degeneration. At the end of the recovery, skeletal muscle atrophy was still observed in the 15 and 50 mg/kg/day groups, but with lower incidence and/or severity. No clinical or microscopic signs of muscular toxicity were observed in any of the monkey studies.	The skeletal muscle atrophy was noted from a dose leading to a 26-fold higher plasma exposure vs. human exposure. No threshold was determined. Such findings could be relevant to humans.
Kidneys In rats treated for 28 days, only a slight decrease in kidney weight was observed, without microscopic or clinical pathology correlation. After 13 weeks of treatment, tubular degeneration was observed in the kidney, mainly at 50 mg/kg/day, with higher incidence in females compared to males. This was also present in isolated animals (1 or 2 per group) and with a minimal grade, at 5 or 10 mg/kg/day. This was not correlated with relevant increase in plasma creatinine or urea levels, but marginal increases in electrolytes in urinary excretion were observed mainly at 15 mg/kg/day. Mixed cell infiltrates in the renal pelvic epithelium (at ≥15 mg/kg/day, females) and in the urinary bladder (50 mg/kg/day, females) were also observed. At the end of the 4-week recovery period, microscopic changes were still observed with similar incidence and/or severity, thus not considered reversible. No effect was observed on kidneys in treated cynomolgus monkeys at any dose and treatment duration.	The kidney histomorphological findings were observed at an exposure 26--fold higher in animals compared to the human exposure. No threshold was determined. Such findings could be relevant to humans.
Mammary gland In the 13-week study in rats, minimal and mild atrophy of mammary gland was observed for males given doses ≥ 5 mg/kg/day and females dosed at 50 mg/kg/day. Under the conditions of this study, a high incidence of mammary gland atrophy was also observed in control rats questioning about the relevance of this finding.	Mammary gland atrophy was observed inconsistently in a single rat study (13-week) but not in the monkey studies. The relevance of this findings for humans remains unclear.
QT prolongation In the 28-day toxicity study in monkeys, a marginal QTc (Corrected QT interval) prolongation of 32 msec was noted in a single high-dose (40 mg/kg/day group) male. The low magnitude of this prolongation was considered as physiologically irrelevant but a relationship with vorasidenib could not be ruled	This single and minimal QTc prolongation remained an isolated finding in the non-clinical cardiovascular evaluation of vorasidenib. However, QT prolongation could not be excluded in

out since this male displayed the highest plasma Maximum observed concentration (C_{max})on Day 27. There were no other vorasidenib-related changes in electrocardiography parameters or traces. In the 13-week study, there were no vorasidenib-related abnormalities in frequency, rhythm or waveform morphology, nor on conduction times. In addition, vorasidenib did not elicit any *in vitro* alert regarding human ether-a-go-go-related gene (hERG) or other cardiac ion channels. Therefore, this single and minimal QTc prolongation remained an isolated finding in the preclinical cardiovascular evaluation of vorasidenib.	human therapeutic use, and is considered an important potential risk per conservative approach.
Reproductive and developmental toxicity	
Reproductive organs During 28-day study in female rats, loss of estrous cyclicity, organ atrophy, and lower ovary/oviduct weights were observed in the high dose group associated with effects on uterus (decreased weight, atrophy), ovary (decreased corpora lutea, increased atretic follicles), cervix (atrophy, mucification) and vagina (atrophy, mucification). None of the animals in the 100 mg/kg/day group had a normal estrous cycle. Almost all females were in persistent diestrous, implying that the animals had not ovulated for at least several cycles and one female was noted as being in metestrus. In males, weights of epididymis, seminal vesicle/prostate, and testis were decreased in the 100 mg/kg/day group. Findings were observed on testis (degeneration of the seminiferous tubules), epididymis (cellular luminal debris, 100 mg/k/day), prostate (atrophy of the epithelium ≥30 mg/kg/day), and seminal vesicles (atrophy of the epithelium ≥10 mg/kg/day). Atrophy of the secondary sex organs and altered estrous cyclicity was commonly observed with significant body weight loss and/or stress, and these effects may have contributed to the microscopic findings in the accessory sex organs at 100 mg/kg/day. At the lowest tested dose of 5 mg/kg/day, the findings were observed at an exposure 26-fold higher compared to human exposure at 50 mg daily dose. At the recovery necropsy, the vorasidenib- related changes in organ weights were partially recovered on seminal vesicle/prostate weights and epididymis in males and on ovaries/oviduct and uterus in females. In the high dose groups of males and females, changes in organ weights were also noted. Of note, the reversible effects on the reproductive organs may not be evidenced as the duration of the recovery periods (14 or 28 days) did not cover the full spermatogenic cycle or follicular development and growth. Effects on reproductive organs were also observed during the 13-week repeat-dose toxicity study in male and female rats. In cynomolgus monkeys, no toxicological significant findings were noted at doses up to the MTD after 13-week treatment.	Impairment of fertility is considered an important potential risk of Vorasidenib.
Embryo-foetal development During an embryo-foetal development study, daily oral doses of 10, 25, and 75 mg/kg/day vorasidenib were administered to pregnant Sprague Dawley rats throughout organogenesis. Maternal toxicity was observed at 75 mg/kg/day and the dose of 25 mg/kg/day was defined as the NOAEL (No Observed Adverse	Use during pregnancy (embryo-foetal development toxicity) is considered an important potential risk of vorasidenib.

Effect Level). In litters, fetotoxicity was observed at 25 and 75 mg/kg/day with a higher incidence of early resorptions and visceral malformations (malpositioned kidney and testis at 75 mg/kg/day). Dose-related lower foetal weight and delayed ossification were observed in all treated groups. The NOAEL for embryo-foetal development was set at 10 mg/kg/day. In rabbits, daily oral administration of 2, 6 and 18 mg/kg/day vorasidenib to pregnant females throughout organogenesis was associated with reduction of body weight in all treated groups and maternal toxicity in the high dose group (18 mg/kg/day). The NOAEL for maternal toxicity was set at 6 mg/kg/day. In litters, no direct fetotoxicity was noted, only lower foetal weight with delayed ossification was observed at 6 mg/kg/day and a slightly higher incidence of late resorptions occurred at 18 mg/kg/day, consistent with the severity of the maternal toxicity. The NOAEL for embryo-foetal development was set at 6 mg/kg/day.	
Genotoxicity A genotoxicity assessment of vorasidenib and AGI-69460 was performed through in vitro bacterial reverse mutation assay, human peripheral blood lymphocyte micronucleus assay and in vivo micronucleus assay. Vorasidenib and its major circulating metabolite, AGI-69460 were not mutagenic in *in vitro* bacterial reverse mutation (Ames) assays, were not clastogenic in an *in vitro* human lymphocyte micronucleus assay or in an *in vivo* rat bone marrow micronucleus assay. Regarding AGI-69460, a Comet assay in liver combined with *in vivo* rat bone marrow micronucleus assay, demonstrated no induction of DNA damage and completely excluded genotoxic potential for this metabolite.	None
Carcinogenicity Kupffer cell hyperplasia in monkey was observed during repeat-dose studies. No results of carcinogenicity studies are available yet and long-term clinical safety data are insufficient to characterise this risk. Safety margins are calculated from steady state animal plasma exposures *vs*. human exposure at 50 mg/day[1].	A carcinogenicity risk in humans could not be excluded and is considered an important potential risk.
Safety pharmacology	
Potential effects of vorasidenib on cardiovascular and central nervous systems were evaluated. Vorasidenib and its major circulating metabolite AGI-69460 do not inhibit the rapidly activating delayed rectifier potassium current at the highest concentration tested (IC50 >12.3 µM and >30 µM, respectively). ECG (Electrocardiogram) assessment was included in the 28-day and 13-week cynomolgus monkey studies. A marginal prolongation of the QTc (32 msec) was identified in one male monkey administered the non-tolerable vorasidenib dose of 40 mg/kg/day in the 28-day study. There were no effects on ECG parameters in the 13-week study. A modified Irwin test was conducted on Sprague-Dawley rats as part of the 28-day repeat-dose toxicology and demonstrated no adverse effects. Regarding the respiratory system, there were no treatment-related clinical observations in rat and cynomolgus monkey during 28-day and 13-week studies.	This single and minimal QTc prolongation remained an isolated finding in the preclinical cardiovascular evaluation of vorasidenib. However, QT prolongation is considered an important potential risk.

Pharmacokinetic properties	
The pharmacokinetic (PK) profile of vorasidenib has been established using a combination of *in vitro* and *in vivo* experiments. Absorption, distribution, metabolism, and excretion (ADME) studies were performed in BALB/c (Bagg albino) mice, Sprague- Dawley rats, beagle dogs, and cynomolgus monkeys. *In vitro* experiments assessing ADME, drug-drug interaction (DDI) potential, and other specific properties were also performed. Vorasidenib incubation in human liver microsomes, recombinant Cytochrome P450 (CYP450) enzyme end human hepatocytes in the presence of CYP-selective chemical inhibitors indicate that CYP1A2 may be the major enzyme responsible for the hepatic metabolism of vorasidenib. Non-CYP pathways may contribute up to 30% of vorasidenib liver metabolic clearance. Vorasidenib, at clinically relevant concentrations, shows no evidence of direct inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5. Based on in vitro experiments, Vorasidenib is a strong inducer by means of pregnane X receptor (PXR) activation. Vorasidenib appeared to be an inducer of CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4/5, and UGT1A4 in vitro. Autoinduction of vorasidenib metabolism was not observed in vitro in a human hepatocyte study. Vorasidenib is not a substrate of P-gp, BCRP, OATP1B1, or OATP1B3. Vorasidenib is not an inhibitor of P-gp, but it is an inhibitor of BCRP (IC50 of 1.22 μM). At clinically relevant concentrations, vorasidenib is not anticipated to cause any drug-drug interaction with substrates of these transporters.	Based on in vitro experiments Vorasidenib is a strong inducer by means of pregnane X receptor (PXR) activation and may affect the plasma exposure of co-administered medicines that are metabolized or transported by enzymes or transporters whose expression is mediated by PXR. Co-administration of vorasidenib with strong CYP1A2 inhibitors may increase vorasidenib plasma concentration. Co-administration of vorasidenib with moderate CYP1A2 inducers may decrease vorasidenib plasma concentration. Co-administration of vorasidenib with CYP2C19 substrates with narrow therapeutic index or CYP3A4 substrates with narrow therapeutic index may decrease the plasma concentrations of these medicinal products. Co-administration of vorasidenib with sensitive substrates of CYP3A4 without narrow therapeutic index may decrease the plasma concentrations of these medicinal products.

[1] Based on the results from the relative bioavailability study, population PK simulations, and available clinical PK data from the vorasidenib Phase 1 studies, steady-state AUCs of 40 mg QD of the film-coated tablet formulation are projected to be comparable to those of 50 mg QD of the uncoated tablet formulation.
IC^{50}Concentration of drug that achieved half-maximal inhibition

Conclusions from the non-clinical development program:

Non-clinical findings with relevance for use in humans include hepatotoxicity, potential impairment of fertility, use during pregnancy (embryo-foetal development toxicity), QT prolongation and carcinogenicity.

Safety concern based on non-clinical findings that has relevance for human usage and has been confirmed by clinical data:

- Hepatotoxicity (Important identified risk).

Safety concerns based on non-clinical findings that have relevance for human usage and for which there were no available clinical data to allow evaluation of these risks in humans:

- Impairment of fertility (Important potential risk),
- Use during pregnancy (embryo-foetal development toxicity) (Important potential risk),
- QT prolongation (Important potential risk),
- Carcinogenicity (Important potential risk).

Part II: Module SIII - Clinical trial exposure

The vorasidenib clinical development programme was initiated in 2015, with a Development International Birth Date of 30 April 2015, and investigated as a single-agent therapy for the treatment of subjects with cancers that harbor IDH1 or IDH2 mutations, including solid tumours and haematologic malignancies. All studies of vorasidenib were conducted in accordance with the ethical principles of Good Clinical Practice, according to the International Council for Harmonisation (ICH) Harmonised Tripartite Guideline E6.

The pivotal study for this marketing application is AG881-C-004, which is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study of vorasidenib in subjects with residual or recurrent Grade 2 glioma with an IDH1 or IDH2 mutation. The primary objective of the study was to demonstrate the efficacy of vorasidenib based on radiographic progression-free survival (PFS) per a blinded independent review committee (BIRC) compared with placebo in subjects with residual or recurrent Grade 2 oligodendroglioma and astrocytoma with an IDH1 or IDH2 mutation who have undergone surgery as their only treatment. The key secondary objective of the study was to demonstrate the efficacy of vorasidenib based on time to next intervention (TTNI) compared with placebo. In this study subjects were randomized 1:1 to receive vorasidenib 40 mg QD or matched placebo.

In addition to this pivotal study, supporting safety data from two Phase 1 studies are provided for the proposed indication and dose of 40 mg QD vorasidenib. Study AG881-C-002, which is a Phase 1, multicenter, open-label, dose-escalation and expansion, safety, pharmacokinetic, pharmacodynamic, and clinical activity study in subjects with advanced solid tumors including gliomas. In that study subjects with glioma received doses of 10 mg QD up to 300 mg QD. Study AG120-881-C-001 is a Phase 1, multicenter, randomized, controlled, open-label, perioperative study to measure the 2-HG concentration in resected brain tumours following treatment with ivosidenib (S095031, previously known as AG-120) or vorasidenib in subjects with glioma. In that study, subjects received either 10 mg QD or 50 mg QD vorasidenib.

The safety profile of vorasidenib in subjects with hematologic malignancies is expected to differ from that in subjects with solid tumors due to fundamental differences in disease characteristics and response to mutant IDH-directed therapy. Therefore, these data were not pooled and the safety in this population is discussed separately.

In the following tables, data are presented for Study AG120-881-C-001 with a data cutoff of 30 May 2022, Study AG881-C-002 with a data cutoff of 17 October 2022 and Study AG881-C-004 with a data cutoff of 06 September 2022. Glioma Overall- vorasidenib 40mg included data from subjects with glioma treated with vorasidenib 40 mg QD (or 50 mg QD uncoated) in Study AG881-C-004, post crossover data from subjects initially randomized to placebo and treated with vorasidenib 40 mg QD after crossover in Study AG881-C-004, data from subjects treated with vorasidenib 50 mg QD in Study AG120-881-C-001, and data from subjects treated with vorasidenib 50 mg QD in Study AG881-C-002. Glioma Overall – All Doses contains data from subjects with glioma treated with vorasidenib 40mg QD in Study AG881-C-004, post crossover data from subjects initially randomized to placebo and treated with vorasidenib 40mg QD after crossover in Study AG881-C-004, and data from subjects treated with vorasidenib at any dose in Study AG120-881-C-001 and Study AG881-C-002.

Table 3: Duration of Exposure in Glioma

	Glioma Overall - Vorasidenib 40 mg N = 244		Glioma Overall - All Doses N = 295	
Duration of Exposure	**Persons n (%)**	**Total Person Time (Years)**	**Persons n (%)**	**Total Person Time (Years)**
< 1 month	12 (4.9)	0.7	17 (5.8)	1.0
1 to < 3 months	20 (8.2)	3.5	28 (9.5)	4.8
3 to < 6 months	22 (9.0)	8.0	29 (9.8)	10.6
6 to < 12 months	83 (34.0)	61.7	91 (30.8)	68.0
12 to < 24 months	84 (34.4)	115.7	89 (30.2)	122.9
24 to < 36 months	13 (5.3)	28.8	15 (5.1)	33.6
>=36 months	10 (4.1)	39.9	26 (8.8)	108.5
Total	244	258.4	295	349.3

Total Person Time = sum of person time for each subject in the category.
Person time in years: (Date of last dose – Date of first dose + 1)/365.25; for subjects who are still on treatment at data cut-off, the date of the last dose will be the last dosing date or a pre-specified data cut-off date, whichever is earlier.
For Study AG120-881-C-001 subjects, person time is the sum of pre-surgery person-time in years and post-surgery person-time in years.
Source: RMP Table 18.3.4.1.

Table 4: Exposure by Dose in Glioma

	Glioma Overall - All Doses N = 295	
Dose Level [2]	**Persons n (%)**	**Total Person Time (Years) [1]**
10 mg QD	16 (5.4)	39.9
25 mg QD	6 (2.0)	11.6
40 mg QD coated (and 50 mg QD uncoated)	244 (82.7)	258.4
100 mg QD	10 (3.4)	18.6
200 mg QD	14 (4.7)	19.3
300 mg QD	5 (1.7)	1.4
Total	295	349.3

[1] Total Person Time = sum of person time for each subject in the category. Person time in years: (Date of last dose – Date of first dose + 1)/365.25; for subjects who are still on treatment at data cut-off, the date of the last dose will be the last dosing date or a pre-specified data cut-off date, whichever is earlier. For Study AG120-881-C-001 subjects, person time is the sum of pre-surgery person-time in years and post-surgery person-time in years.
[2] Subjects are classified according to the assigned dose level if it was received at least once, or the first dose level received if the assigned treatment was never received.
Source: RMP Table 18.3.4.2.

Table 5: Exposure by Age Group and Gender in Glioma

	Glioma Overall - Vorasidenib 40 mg N = 244				Glioma Overall - All Doses N = 295			
Age Group [2]	**Persons n (%)**		**Total Person Time (Years) [1]**		**Persons n (%)**		**Total Person Time (Years) [1]**	
	Male	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
12 - <18 years	0	0	--	--	1 (0.3)	0	1.0	--
18 - <40 years	69 (28.3)	50 (20.5)	76.6	40.2	77 (26.1)	59 (20.0)	85.5	51.0
40 - <65 years	71 (29.1)	52 (21.3)	77.6	61.2	88 (29.8)	64 (21.7)	105.3	93.6
>=65 years	1 (0.4)	1 (0.4)	1.8	1.0	3 (1.0)	3 (1.0)	8.5	4.5
Total	141	103	156.0	102.4	169	126	200.2	149.1

[1] Total Person Time = sum of person time for each subject in the category. Person time in years: (Date of last dose – Date of first dose + 1)/365.25; for subjects who are still on treatment at data cut-off, the date of the last dose will be the last dosing date or a pre-specified data cut-off date, whichever is earlier. For Study AG120-881-C-001 subjects, person time is the sum of pre- surgery person-time in years and post-surgery person-time in years.
[2] Age is derived based on the date of signing informed consent, except for post-crossover patients in Study AG881-C-004 where age is derived based on crossover date.
Source: RMP Table 18.3.4.3.

Table 6: Exposure by Race in Glioma

	Glioma Overall - Vorasidenib 40 mg N = 244		Glioma Overall - All Doses N = 295	
Race	**Persons n (%)**	**Total Person Time (Years)**	**Persons n (%)**	**Total Person Time (Years)**
White	190 (77.9)	205.5	230 (78.0)	281.8
Asian	7 (2.9)	6.7	8 (2.7)	9.9
Black or African American	2 (0.8)	2.8	3 (1.0)	2.8
American Indian or Alaska Native	1 (0.4)	0.7	1 (0.3)	0.7
Native Hawaiian or Other Pacific Islander	1 (0.4)	3.7	1 (0.3)	3.7
Other	2 (0.8)	2.7	2 (0.7)	2.7
Unknown *	41 (16.8)	36.4	50 (16.9)	47.8
Total	244	258.4	295	349.3

Total person time = sum of person time for each subject in the category. Person time in years: (Date of last dose – Date of first dose + 1)/365.25; for subjects who are still on treatment at data cut-off, the date of the last dose will be the last dosing date or a pre-specified data cut-off date, whichever is earlier. For Study AG120-881-C-001 subjects, person time is the sum of pre-surgery person-time in years and post-surgery person time in years and post-surgery person-time in years.

**The Unknown category includes both Unknown and Not Reported.*

Source: RMP Table 18.3.4.4.

Table 7: Exposure by Ethnicity in Glioma

	Glioma Overall - Vorasidenib 40 mg N = 244		Glioma Overall - All Doses N = 295	
Ethnicity	**Persons n (%)**	**Total Person Time (Years)**	**Persons n (%)**	**Total Person Time (Years)**
Hispanic or Latino	15 (6.1)	14.0	18 (6.1)	14.6
Not Hispanic or Latino	186 (76.2)	206.4	224 (75.9)	279.5
Unknown*	43 (17.6)	38.0	53 (18.0)	55.2
Total	244	258.4	295	349.3

Total Person Time = sum of person time for each subject in the category. Person time in years: (Date of last dose – Date of first dose + 1)/365.25; for subjects who are still on treatment at data cut-off, the date of the last dose will be the last dosing date or a pre-specified data cut-off date, whichever is earlier. For Study AG120-881-C-001 subjects, person time is the sum of pre- surgery person-time in years and post-surgery person-time in years.

**The Unknown category includes both Unknown and Not Reported.*

Source: RMP Table 18.3.4.5.

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

SIV.1 Exclusion criteria in the pivotal clinical study within the development program

The exclusion criteria from Study AG881-C-004 that are related to ongoing or recent conditions, or treatments that may impact the safety and efficacy assessment of vorasidenib are listed below and not discussed further.

Subjects were excluded if they:

- Have had any prior anticancer therapy other than surgery (biopsy, sub-total resection, gross total resection) for treatment of glioma including systemic chemotherapy, radiotherapy, vaccines, small-molecules, IDH inhibitors, investigational agents, etc.
- Have high-risk features as assessed by the Investigator, including brainstem involvement either as primary location or by tumour extension, clinically relevant functional or neurocognitive deficits due to the tumour in the opinion of the Investigator (deficits resulting from surgery are allowed), or uncontrolled seizures (defined as persistent seizures interfering with activities of daily life AND failed 3 lines of antiepileptic drug regimens including at least 1 combination regimen).
- Have concurrent active malignancy except for a) curatively resected nonmelanoma skin cancer

or b) curatively treated carcinoma in situ. Subjects with previously treated malignancies are eligible provided they have been disease-free for 3 years at Screening.

- Have an active infection that requires systemic anti-infective therapy or with an unexplained fever >38.5°C within 7 days of C1D1.
- Have significant active cardiac disease within 6 months before the start of study treatment, including New York Heart Association Class III or IV congestive heart failure, myocardial infarction, unstable angina, and/or stroke.
- Have left ventricular ejection fraction (LVEF) <40% by echocardiogram (or by other methods according to institutional practice) obtained within 28 days before the start of study treatment.
- Are taking therapeutic doses of steroids for signs/symptoms of glioma. Subjects taking physiologic doses (defined as equivalent of ≤10 mg prednisone daily) for medical conditions not related to glioma were permitted.
- Have known active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, known positive human immunodeficiency virus antibody results, or AIDS (Acquired immunodeficiency syndrome)-related illness. Subjects with a sustained viral response to HCV treatment or immunity to prior HBV infection were permitted. Subjects with chronic HBV that is adequately suppressed by institutional practice were permitted.
- Have known active inflammatory gastrointestinal disease, chronic diarrhea, previous gastric resection or lap band dysphagia, short-gut syndrome, gastroparesis, or other condition that limits the ingestion or gastrointestinal absorption of drugs administered orally. Gastroesophageal reflux disease under medical treatment was allowed (assuming no drug interaction potential).
- Have any other acute or chronic medical or psychiatric condition, including recent (within 12 months of C1D1) or active suicidal ideation or behavior, or a laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this study.

The remaining exclusion criteria from Study AG881-C-004 are presented below along with additional reason for exclusion and rationale for inclusion or not as missing information:

Subject was pregnant or breastfeeding

Reason for exclusion: Female subjects who become pregnant while on the study will be immediately discontinued from study treatment. To minimise risk to pregnant women and nursing mothers and their offspring, women of childbearing potential and males with partners of childbearing potential were instructed to use effective contraception during treatment with vorasidenib and for at least 3 months after the last dose.

Is it considered to be included as missing information? Yes (for use during breastfeeding).

Rationale: The mean age of diagnosis is 45 years for patients with oligodendrogliomas and 38 years for patients with astrocytomas (Brat, 2015). It is therefore anticipated that vorasidenib will be used in women of childbearing potential. Nonclinical studies have shown embryo-foetal toxicity at non-tolerable doses. It is not known whether adverse pregnancy outcomes or adverse events associated with breastfeeding may occur. [redacted]

There are no data on the presence of vorasidenib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Based on this, use during breastfeeding is considered as a missing information. Because of the potential for adverse reactions in breastfed children, women should not breastfeed during treatment with vorasidenib and for 2 months after the last dose.

The safety of vorasidenib is not known in these populations, and as there is a risk of possible harm to use during pregnancy based on nonclinical studies. Use during pregnancy (embryo-foetal development toxicity) is an important potential risk of vorasidenib. This safety concern has been described in the SmPC (Summary of Product Characteristic).

Subject is taking any medications that are CYP2C8, CYP2C9, CPY2C19, or CYP3A substrates with a narrow therapeutic index (Subjects should be transferred to other medications before receiving the first dose of study drug)

Reason for exclusion: These medications were prohibited during treatment with vorasidenib. Based on in vitro studies, vorasidenib may have the potential to induce the activity of these enzymes, thereby reducing the exposure to, and therapeutic effects of, medications metabolized by these enzymes. Subjects taking sensitive CYP2C8, CYP2C9, CYP2C19 and CYP3A substrates with a narrow therapeutic index were excluded from the clinical development programme for efficacy and safety reasons.

Is it considered to be included as missing information? No.

Rationale: Based on the Physiologically-Based Pharmacokinetic modeling, vorasidenib is predicted to have an induction effect on sensitive CYP2C19 and CYP3A4 substrates and may decrease the plasma concentrations and therapeutic effect of these medications. Subjects should avoid taking CYP2C19 and CYP3A4 substrates that have a narrow therapeutic index. Subjects taking CYP3A4, substrates without a narrow therapeutic index should consider alternative medications. Subjects taking hormonal contraceptives should consider alternative methods of contraception. The effect of vorasidenib on other medicinal products has been adequately covered in the SmPC.

Subject has a heart-rate corrected QT interval using Fridericia's formula (QTcF) ≥450 msec or other factors that increase the risk of QT prolongation or arrhythmic events (eg, heart failure, hypokalemia, family history of long QT interval syndrome)

Reason for exclusion: In the 28-day toxicity study in monkeys, a marginal QTc prolongation of 32 msec was noted in a single high-dose (40 mg/kg/day group) male. The low magnitude of this prolongation was considered as physiologically irrelevant but a relationship with vorasidenib could not be ruled out since this male displayed the highest plasma Cmax on study Day 27. Based on these data, QT prolongation was considered as an important potential risk in the vorasidenib clinical development program.

Is it considered to be included as missing information? No.

Rationale: The potential for QT prolongation with vorasidenib was evaluated in three open-label studies in patients with advanced hematologic malignancies, advanced solid tumors including gliomas, or low-grade glioma with an IDH1 or IDH2 mutation. No large mean changes in the QT/QTc interval were observed following treatment with vorasidenib. Electrocardiogram QT prolongation events observed in subjects with glioma treated with vorasidenib were infrequent, predominantly low-grade, nonserious, and self-limited requiring no action with study treatment. In addition, the data from a concentration-QT modeling demonstrated negative effect on concentration QT of vorasidenib. However, QT prolongation is considered an important potential risk of vorasidenib, per conservative approach.

Subject with known hypersensitivity to any of the components of vorasidenib

Reason for exclusion: Subjects with known hypersensitivity to any of the components of vorasidenib were excluded from the clinical development program for safety reasons. Subjects with a known hypersensitivity would be at a higher risk of subsequent serious systemic hypersensitivity reactions with re-exposure.

Is it considered to be included as missing information? No.

Rationale: The hypersensitivity to the medicinal product has been adequately covered in the SmPC. Vorasidenib is contraindicated for patients having hypersensitivity to the vorasidenib active substance or to any of the excipients.

Subject <12 years of age were not included in the pivotal study

Reason for exclusion: To date, IDH1 and IDH2 mutant glioma has only been reported as isolated single cases in paediatric patients <12 years of age. IDH1 mutations are occasionally found in adolescents ≥12 years and older of age but they are rare, both in subpopulations with low-grade glioma (LGG) or high-grade glioma (HGG). IDH2 mutations are rarer still, with only a few cases having been reported.

Is it considered to be included as missing information? No.

Rationale: Considering the rarity of IDH mutations in adult-type gliomas occurring in paediatric patients under 12 years of age, this population is not considered as a target population.

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

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, or adverse reactions with a long latency.
The Adverse Drug Reactions (ADRs) due to prolonged exposure and long latency periods may not have been detected during the Clinical Trial program of vorasidenib.

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

Table 8: Exposure of special populations included or not in clinical trial development program

<table>
<tr><th>Type of special population</th><th>Exposure</th></tr>
<tr><td>Pregnant women</td><td rowspan="2">Not included in the clinical development program.</td></tr>
<tr><td>Breastfeeding women</td></tr>
<tr><td colspan="2">Patients with relevant comorbidities:</td></tr>
<tr><td>Patients with hepatic impairment</td><td>
Baseline Liver Function in Glioma
<table>
<tr><th colspan="3">Baseline Liver Function by NCI ODWG Criteria [1]</th></tr>
<tr><th rowspan="2">Liver Function</th><th colspan="2">Glioma Overall - All Doses [2] N = 295</th></tr>
<tr><th>Persons n (%)</th><th>Total Person Time (Years) [3]</th></tr>
<tr><td>Normal</td><td>265 (89.8)</td><td>319.1</td></tr>
<tr><td>Mild</td><td>30 (10.2)</td><td>30.3</td></tr>
<tr><td>Moderate</td><td>0</td><td>--</td></tr>
<tr><td>Severe</td><td>0</td><td>--</td></tr>
<tr><td>Unknown</td><td>0</td><td>--</td></tr>
<tr><td>Total</td><td>295</td><td>349.3</td></tr>
</table>
Source: RMP Table 18.3.4.6.
[1] Baseline liver function based on NCI (National Cancer Institute) ODWG (organ dysfunction working group) criteria for hepatic impairment: Normal (total bilirubin <=ULN and ALT/AST (Aspartate aminotransferase) <=ULN); Mild (total bilirubin <=ULN and ALT/AST >ULN; or total bilirubin >1.0x - 1.5xULN); Moderate (total bilirubin >1.5x - 3x ULN); Severe (total bilirubin >3x ULN).
[2] Glioma Overall – All Doses: contains data from subjects with glioma treated with vorasidenib. This includes data from subjects treated with vorasidenib in Study AG881-C-004, post crossover data from subjects initially randomized to placebo and treated with vorasidenib after crossover in Study AG881-C-004, data from subjects treated with vorasidenib at any dose in Study AG120-881-C-001, and data from subjects treated at any dose with vorasidenib in Study AG881-C-002.
[3] Total Person Time = sum of person time for each subject in the category. Person time in years: (Date of last dose – Date of first dose + 1)/365.25; for subjects who are still on treatment at data cut-off, the date of the last dose will be the last dosing date or a pre-specified data cut-off date, whichever is earlier. For Study AG120-881-C-001 subjects, person time is the sum of pre-surgery person-time in years and post-surgery person-time in
</td></tr>
</table>

<table>
<tr><td></td><td>years.
For post-crossover patients in Study AG881-C-004, baseline is derived based on the start of post-crossover study treatment.</td></tr>
<tr><td>Patients with renal impairment</td><td>
Baseline Renal Function in Glioma
Baseline Renal Function by Creatinine Clearance (mL/min) and eGFR (mL/min/1.73m^2)
<table>
<tr><td></td><td colspan="2">Glioma Overall - All Doses [1] N = 295</td></tr>
<tr><td>Creatinine Clearance (mL/min) [3]</td><td>Persons n (%)</td><td>Total Person Time (Years) [2]</td></tr>
<tr><td>Normal (>=90)</td><td>262 (88.8)</td><td>280.4</td></tr>
<tr><td>Mild (60-<90)</td><td>31 (10.5)</td><td>64.2</td></tr>
<tr><td>Moderate (30-<60)</td><td>2 (0.7)</td><td>4.7</td></tr>
<tr><td>Severe (15-<30)</td><td>0</td><td>--</td></tr>
<tr><td>Unknown</td><td>0</td><td>--</td></tr>
<tr><td>Total</td><td>295</td><td>349.3</td></tr>
<tr><td>eGFR (mL/min/1.73m^2) [4]</td><td>Persons n (%)</td><td>Total Person Time (Years) [2]</td></tr>
<tr><td>Normal (>=90)</td><td>188 (63.7)</td><td>199.2</td></tr>
<tr><td>Mild (60-<90)</td><td>9 (33.6)</td><td>134.1</td></tr>
<tr><td>Moderate (30-<60)</td><td>8 (2.7)</td><td>16.0</td></tr>
<tr><td>Severe (15-<30)</td><td>0</td><td>--</td></tr>
<tr><td>Unknown</td><td>0</td><td>--</td></tr>
<tr><td>Total</td><td>295</td><td>349.3</td></tr>
</table>
Source: RMP Table 18.3.4.6.
[1] Glioma Overall – All Doses: contains data from subjects with glioma treated with vorasidenib. This includes data from subjects treated with vorasidenib in Study AG881-C-004, post crossover data from subjects initially randomized to placebo and treated with vorasidenib after crossover in Study AG881-C-004, data from subjects treated with vorasidenib at any dose in Study AG120-881-C-001, and data from subjects treated at any dose with vorasidenib in Study AG881-C-002.
[2] Total Person Time = sum of person time for each subject in the category. Person time in years: (Date of last dose – Date of first dose + 1)/365.25; for subjects who are still on treatment at data cut-off, the date of the last dose will be the last dosing date or a pre-specified data cut-off date, whichever is earlier. For Study AG120-881-C-001 subjects, person time is the sum of pre- surgery person-time in years and post-surgery person-time in years.
[3] Baseline renal function based on creatinine clearance (ml/min) is calculated as: (140-age) * baseline weight (kg) * (0.85 if female)/ (72 * baseline serum creatinine [mg/dL]).
[4] Baseline renal function based on eGFR (estimated glomerular filtration rate) is calculated as: eGFR (mL/min/1.73 m^2) = 175 * (Scr)^(-1.154) * (Age)^(-0.203) * (0.742 if female) * (1.212 if African American), where Scr is SI unit of serum creatinine (µmol/L). The conversion factor for serum creatinine is 1 µmol/L= 0.01131222 mg/dL.
For post-crossover patients in Study AG881-C-004, baseline is derived based on the start of post-crossover study treatment.
</td></tr>
<tr><td>Patients with cardiovascular impairment</td><td>Patients with severe cardiovascular impairment were not included in the clinical development program.</td></tr>
<tr><td>Immunocompromised patients</td><td>Immunocompromised patients were not specifically excluded from clinical studies unless they had HIV (Human Immunodeficiency Virus)/AIDS. Based on the targeted patient population in the pivotal study, glioma patients who had surgery as their only treatment are unlikely to be immunocompromised unless due to a pre-existing comorbidity, which was limited as these young otherwise healthy subjects rarely have other co-morbidities. As such, the exposure to vorasidenib in immunocompromised patients cannot be reliably quantified.</td></tr>
</table>

Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable.
Population with relevant different ethnic origin	There are no relevant different ethnic origins.
Subpopulations carrying relevant genetic polymorphisms	There are no relevant identified polymorphisms.

Part II: Module SV - Post-authorisation experience

Not applicable.

SV.1 Post-authorisation exposure

The first Marketing Authorisation Application (MAA) has been granted in the United States of America on August 06th, 2024. Then several other countries granted a Marketing Authorisation including Canada on August 27th, 2024; Australia on September 11th, 2024; the United Arabic Emirates on September 25th, 2024; Switzerland on November 15th, 2024 and Israel on November 26th, 2024.

SV.1.1 Method used to calculate exposure

The method used to estimate patient exposure for vorasidenib is based on mean daily dosage of 1 tablet of vorasidenib per day for the 40 mg dose-strength and 2 tablets for the 10 mg dose-strength, and months of 30.4 days, and use the following calculation formula:

Patient-Year (PY) = ((Number of boxes sold x Number of tabs per box)) / ((DDD*x 30,4 x 12))

*DDD is the daily dose recommended: 1 tablet for vorasidenib 40 mg dose-strength and 2 tablets for the 10 mg dose-strength.

SV.1.2 Exposure

Since the first Marketing Authorization (06 August 2024) up to 05 May 2025, this estimated exposure is 1702 Patient-year (PY).

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

Potential for misuse for illegal purposes.

Given the pharmacological properties of vorasidenib and its indication, the potential for misuse or abuse for illegal purposes is negligible. No potential for drug dependence or drug abuse has been noted for vorasidenib in any of the clinical studies.

Part II: Module SVII - Identified and potential risks

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

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

1. Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

Glioma specific risks with minimal clinical impact on patients

- Abdominal pain,
- Diarrhoea,
- Decreased appetite,
- Dizziness,
- Dyspnoea,
- Fatigue,
- Gastro-oesophageal reflux disease,
- Gamma-glutamyltransferase (GGT) increased,
- Hyperglycaemia,
- Hypophosphataemia,
- Platelet count decreased,
- Alkaline phosphatase (ALP) increased.

IDH mutant glioma is a diagnosis associated with a significant reduction in life expectancy. Patients with glioma would be treated in a clinical oncology setting equipped to recognise, and to manage appropriately, the complications of treatment listed in this section.

2. Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

None.

3. Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised):

The risks associated with vorasidenib that require no further characterisation and are adequately described in the product information are:

- Hypersensitivity.
- Drug interactions (co administration of vorasidenib with strong CYP1A2 inhibitors; moderate CYP1A2 inducers; CYP2C19 and CYP3A substrates with narrow therapeutic index, and sensitive substrates of CYP3A without narrow therapeutic index).

4. Known risks that do not impact the risk-benefit profile:

None.

5. Other reasons for considering the risks not important:

None.

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

Important identified risks:

Hepatotoxicity

Liver findings suggestive of hepatic enzyme induction have been observed in the non-clinical studies.

Liver enzyme elevations (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) was added as an important identified risk of vorasidenib during the Phase 1 studies in subjects with hematologic malignancies and solid tumours including glioma. Liver enzyme elevations are among the

most common adverse events reported in clinical studies, including the pivotal study. These events were mostly Grade 1 or 2 and were reversible to Grade 1 or baseline with dose modifications, including dose reductions and interruptions, or drug discontinuations and supportive care, which, in rare cases included hospitalization for monitoring liver function and administration of symptom-directed treatments.

[redacted] Hepatotoxicity is considered an important identified risk of vorasidenib for patients with Gade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation.

Risk-benefit impact:

Patients with Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation have a poor prognosis with a serious unmet medical need for safe and effective targeted therapies. The benefit of vorasidenib as an effective treatment in this population outweighs the risk of hepatotoxicity which can be managed in clinical practice through close monitoring of liver function in conjunction with temporary interruption or permanent discontinuation of vorasidenib treatment as per SmPC sections 4.2, 4.4 and 4.8, and PL sections 2 and 4.

Important potential risks:

Impairment of Fertility

Fertility studies have not been conducted with vorasidenib according to ICH S9 guidance. Effects on reproductive organs were seen in male and female rats during repeat-dose toxicity studies at non-tolerable dose levels. Male and female patients should be instructed on the potential impact of vorasidenib on fertility. However, there are currently no clinical data available to confirm the potential impact on fertility in humans.

Risk-benefit impact:

The benefit of vorasidenib as an effective treatment for Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation may outweigh the potential risk of impairment of fertility which can be managed through provision for women and men to seek reproductive counselling as per SmPC sections 4.4, 4.6 and PL section 2.

Use during pregnancy (embryo-foetal development toxicity)

Evidence for use during pregnancy (embryo-foetal development toxicity) is based on non-clinical studies, which may be relevant for humans. In the absence of evidence of the effects on the foetus in humans, embryo-foetal toxicity is considered an important potential risk for vorasidenib. In animal embryo-foetal toxicity studies, oral administration of vorasidenib to pregnant rats caused embryo-foetal development toxicity at 61 times the steady state clinical exposure based on the Area under the concentration-time curve (AUC) at the therapeutic daily dose. Vorasidenib was associated with maternal toxicity, early or late resorptions, lower foetal weights, delayed skeletal ossification and visceral malformations in rats (kidney and testis). No direct fetotoxicity was observed in pregnant rabbits at 11 times the steady state clinical exposure based on the AUC at the therapeutic daily dose. Based on these studies, vorasidenib could cause foetal harm when administered to women during pregnancy.

[redacted]

Risk-benefit impact:

The benefit of vorasidenib as an effective treatment for Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation may outweigh the potential risk of embryo-foetal toxicity which may be prevented by the use of effective contraception. Specific guidance is included in SmPC sections

4.4, 4.5 and 4.6, as well as in section 2 of PL that provides instructions on the timeframe to follow the respective pregnancy prevention measures.

QT prolongation

QT prolongation was initially considered an important potential risk of vorasidenib based on non-clinical findings of marginal QTc prolongation of 32 msec in a single high-dose-group (40 mg/kg/day) male monkey in the 28-day toxicity study. A detailed review of clinical data across Studies AG881-C-001, AG881-C-002, AG120-881-001, and AG881-C-004 of the preferred term (PT) Electrocardiogram QT prolonged, as well as analysis of treatment-emergent adverse events (TEAEs) within the broad standard Medical Dictionary of Regulatory Activities (MedDRA) Query (SMQ) Torsade de Pointes/QT prolongation, showed no concerning findings regarding predisposition, including the underlying disease or relevant cardiac comorbidities. All TEAEs of electrocardiogram QT prolonged were non-serious; events were predominantly low-grade and asymptomatic. TEAEs were manageable and self-limited with no dose interruption or modification. Review of these data led the Applicant to no longer consider QT prolongation to be an important potential risk or potential risk of vorasidenib. However, given the potential class effect of IDH1/2 inhibitors, the modest hERG blockade, and the relatively limited sample size of the pivotal study, QT prolongation is still considered as important potential risk.

Risk-benefit impact:

Patients with Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation are facing unmet medical need for safe and effective targeted therapies. The benefit of vorasidenib in these patients outweighs the risk of asymptomatic, low grade and self-limited electrocardiogram QT prolonged that has been observed during the clinical development of vorasidenib and which can be managed in clinical practice.

Carcinogenicity

Kupffer cell hyperplasia has been observed in monkey during repeat-dose studies. No evidence of genotoxic potential for vorasidenib and its main metabolite, AGI-69460 were demonstrated during *in vitro* and *in vivo* genotoxicity studies. Carcinogenicity studies on vorasidenib are planned in rats and transgenic mice. Long-term clinical safety data are insufficient to characterise this risk.

Risk-benefit impact:

The important potential risk of carcinogenicity with vorasidenib as an effective treatment for Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation is not fully characterised yet. Subsequent carcinogenicity studies will be performed in rats and transgenic mice dosed with vorasidenib to further characterise this potential risk. The potential risk of carcinogenicity is included in the SmPC section 4.4 and will be reassessed when additional data is available.

Missing information

Use during breastfeeding

There are no data on the presence of vorasidenib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for adverse reactions in breastfed children, women should not breastfeed during treatment with vorasidenib and for 2 months after the last dose. Corresponding guidances are included in SmPC section 4.6 and PL section 2.

Risk-benefit impact:

The benefit of vorasidenib as an effective treatment for Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation may outweigh the missing information on use during breastfeeding. Use during breastfeeding may be prevented by the use of effective contraception to avoid pregnancy. Breastfeeding can be started 2 months after the last dose of vorasidenib.

Use in the paediatric population 12 years and older

Oligodendroglial and astrocytic paediatric tumours that harbour IDH1/2 mutations tend to occur in older

adolescents (usually ≥16 years old but rarely after 12 years old) and show resemblance to adult counterparts following a similar clinical path with an indolent growth and a favourable prognosis (Packer 2017; Ryall 2017; Sturm 2017).

The efficacy and safety of vorasidenib were evaluated in the AG881-C-004 trial in adults and adolescents ≥ 12 years old weighing ≥ 40 kg with Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation, who had surgery as their only treatment, and were not in immediate need for chemotherapy or radiotherapy in the opinion of the investigator. [redacted] Population pharmacokinetic data demonstrated that age had no clinically meaningful effect on the pharmacokinetics of vorasidenib. The exposure of vorasidenib is expected to be similar between adults and adolescent patients aged 12 years and older.

Risk-benefit impact:

Overall, while clinical data are limited, based on the PK simulations and the expected similarities in exposure between adults and paediatrics, there are no expected differences in the safety outcomes between adults and adolescents (12 years and older). Relevant information is included in SmPC sections 5.1 and 5.2. The Applicant will conduct a paediatric clinical trial.

Long term safety > 12 months

The available data in subjects exposed to vorasidenib for >12 months and ≥24 months, showed no unexpected trends in the incidence or severity of TEAEs, and considering that vorasidenib does not demonstrate accumulation with long-term exposure, delayed toxicities or unexpected long-term safety concern are not anticipated. Since given the lack of non-clinical characterisation of deschloro-methyl sulfone (AGI-69460) the main metabolite of vorasidenib and the potential treatment duration of several years, long term safety > 12 months is considered as missing information. The Applicant will perform an ad hoc analysis of the data collected from the ongoing pivotal phase 3 study AG881-C-004.

Risk-benefit impact:

The benefit of vorasidenib as an effective treatment for Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation may outweigh the missing information on long term safety use. Subjects from the ongoing pivotal phase 3 Study AG881-C-004 (INDIGO) remaining on treatment will continue to be assessed for safety according to the study protocol, which is anticipated to continue up to 5 years after the last subject is enrolled. Results of these data will be integrated in the final AG881-C-004 clinical study report.

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

Not applicable.

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

Important Identified Risk: Hepatotoxicity

Drug-induced liver injury (DILI), refers to liver injury caused by drugs or other chemical agents, and represents a special type of adverse drug reaction. The incidence of DILI in the general population varies across countries. A lower incidence of DILI was observed in the United States than in Europe, while data from China indicated a considerably higher incidence. (Li, 2022). Hepatotoxicity is heterogeneous ranging from mild transaminase derangement to pronounced acute hepatitis and fulminant liver failure (Brennan, 2022).

Potential mechanisms:

The mechanism of action of vorasidenib inducing hepatotoxicity in glioma patients is not completely

understood. Idiosyncratic DILI is often mediated by the adaptive immune response. Meanwhile, some drugs and metabolites can directly damage mitochondria, produce ROS (Reactive oxygen species), and alter signaling pathway. To defend against the hazards induced by drugs, hepatocytes exhibit adaptive mechanisms including upregulation of Nrf2 signaling, mitophagy, and autophagy to cope with stress (Yuan, 2013).

Evidence source(s) and strength of evidence:

Liver findings suggestive of hepatic enzyme induction have been observed in the pre-clinical setting.

Liver enzyme elevations (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) was added as an important identified risk of vorasidenib during the Phase 1 studies in subjects with hematologic malignancies and solid tumours including glioma. Liver enzyme elevations are among the most common adverse events reported in clinical studies, including the pivotal study.

Evidence from these sources is considered to be a reliable predictor of how subjects will respond to treatment in clinical practice, by convention.

Characterisation of the risk:

The analysis of hepatotoxicity was based on the broad SMQ Drug-related hepatic disorders - comprehensive search with 2 additional preferred terms (blood albumin decreased and immune-mediated cholestasis), MedDRA v25.1, for subjects with glioma in Studies AG881-C-004, AG881-C- 002 and AG120-881-001.

The table below displays TEAEs within this search strategy in the overall glioma cohort treated with vorasidenib 40 mg QD, N = 244.

Table 9: Hepatotoxicity events

Hepatotoxicity events by PTs	Overall N = 244 n (%)
Subjects with any events	103 (42.2)
ALT increased	91 (37.3)
AST increased	65 (26.6)
GGT increased	33 (13.5)
Blood alkaline phosphatase increased	9 (3.7)
Blood bilirubin increased	6 (2.5)
Hepatic steatosis	3 (1.2)
Hypoalbuminaemia	2 (0.8)
Autoimmune hepatitis	1 (0.4)
Benign hepatic neoplasm	1 (0.4)
Bilirubin conjugated increased	1 (0.4)
Hepatic failure	1 (0.4)
Hepatic necrosis	1 (0.4)
INR increased	1 (0.4)

Source ISS Table 18.49.2.1 (PT)

In the overall glioma cohort treated with vorasidenib 40 mg QD (N=244), 103 (42.2%) subjects experienced at least 1 TEAE within the hepatotoxicity search strategy.

Table 10: Hepatotoxicity – Frequency (Glioma)

	Glioma Overall - Vorasidenib 40 mg N = 244 n(%)	**AG881-C-004 Vorasidenib 40 mg without Crossover [1] N = 167 n(%)**	**AG881-C-004 Vorasidenib 40 mg Post-crossover [2] N = 52 n(%)**	**AG881-C-004 Placebo [3] N = 163 n(%)**
Subjects with TEAEs, n (%)	103 (42.2)	73 (43.7)	15 (28.8)	34 (20.9)
Total number of TEAEs	449	328	50	90
Incidence rate - # of subjects with TEAEs per 100 person-years	39.87	39.54	62.56	21.31
95% CI (Confidence interval) for incidence rate*	32.86, 48.36	31.43, 49.73	37.71, 103.77	15.22, 29.82

[1] AG881-C-004 Vorasidenib 40 mg without Crossover: includes data from subjects in Study AG881-C-004 who were randomized to and treated with vorasidenib 40 mg QD (or 50 mg QD uncoated).
[2] AG881-C-004 Vorasidenib 40 mg Post-crossover: includes post crossover data from subjects initially randomized to placebo and treated with vorasidenib 40 mg QD after crossover in Study AG881-C-004.
[3] AG881-C-004 Placebo: includes data from subjects whose actual treatment was placebo in Study AG881-C-004. For subjects that subsequently cross over to receive vorasidenib 40 mg QD, only data before crossover is included.
Person-year: (Date of last dose – Date of first dose + 1)/365.25; for subjects who are still on treatment at data cut-off, the date of the last dose will be the last dosing date or a pre-specified data cut-off date, whichever is earlier. For AG120-881- C-001 subjects, person-year is the sum of pre-surgery person-time in years and post-surgery person-time in years.
**The estimate of incidence rate and the associated confidence interval is derived from Poisson Regression.*
Source: RMP Table 18.3.4.7.

In the overall glioma cohort treated with vorasidenib 40 mg QD (N=244), serious TEAEs within the hepatotoxicity search strategy were reported in 5 out of 244 (2%) subjects and all were assessed as related to study treatment by the investigator. In 32 (13.1%) subjects TEAEs within the hepatotoxicity search strategy led to treatment interruption, 13 (5.3%) subjects required a dose reduction, and 8 (3.3%) subjects required study treatment discontinuation. In most cases where a subject had a dose reduction, TEAEs were sufficiently managed with dose modification. Most of the events were resolved or 'resolving' at the time of the data cut-off. The median time to the first TEAE within the hepatotoxicity search strategy of all grades was 56 days (range: 1, 1122). The median time to resolution of all grades ALT increased was 50 days (range: 5, 1259), for all grades AST increased and all grades bilirubin increased it was 29 days (range: 4, 537 and range: 12, 142, respectively).

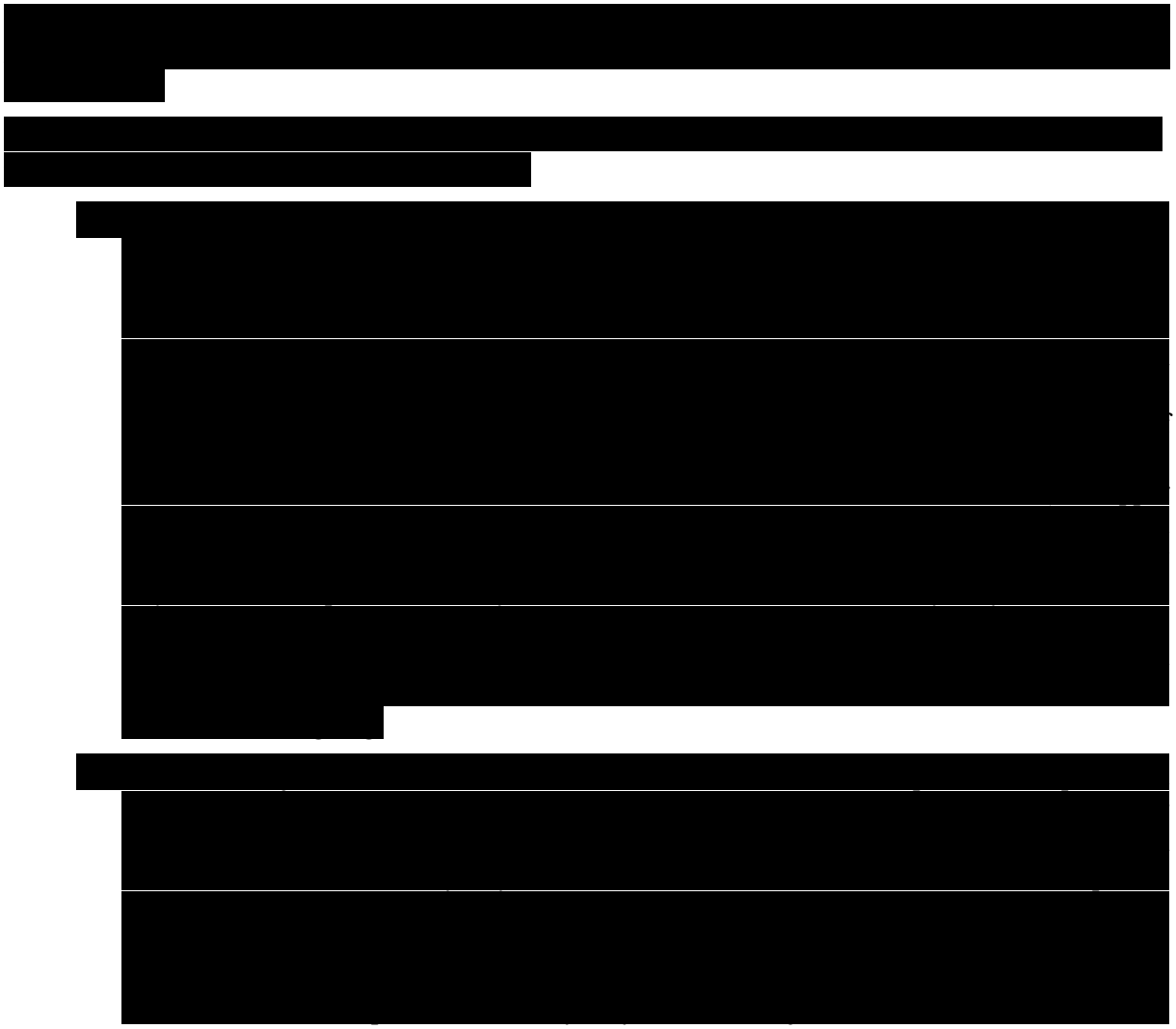
Table 11: Hepatotoxicity – Seriousness/Outcomes/Action Taken (Glioma)

	Glioma Overall - Vorasidenib 40 mg N = 244 n(%)	**AG881-C-004 Vorasidenib 40 mg without Crossover [1] N = 167 n(%)**	**AG881-C-004 Vorasidenib 40 mg Post-crossover [2] N = 52 n(%)**	**AG881-C-004 Placebo [3] N = 163 n(%)**
Subjects with TEAEs, n (%)	103 (42.2)	73 (43.7)	15 (28.8)	34 (20.9)
Seriousness [4], n (%)				
Serious	5 (2.0)	3 (1.8)	1 (1.9)	0
Nonserious	98 (40.2)	70 (41.9)	14 (26.9)	34 (20.9)
Outcomes [5], n (%)				
Unknown	2 (0.8)	0	1 (1.9)	0
Recovered/Resolved	49 (20.1)	34 (20.4)	6 (11.5)	29 (17.8)
Recovered/Resolved with sequelae	21 (8.6)	18 (10.8)	3 (5.8)	2 (1.2)
Recovering/Resolving	4 (1.6)	2 (1.2)	0	1 (0.6)
Not recovered/Not resolved	27 (11.1)	19 (11.4)	5 (9.6)	2 (1.2)
Fatal	0	0	0	0
Action taken for treatment [6], n (%)				

Dose not changed	60 (24.6)	43 (25.7)	8 (15.4)	30 (18.4)
Dose reduced	13 (5.3)	11 (6.6)	1 (1.9)	1 (0.6)
Drug interrupted	32 (13.1)	24 (14.4)	6 (11.5)	4 (2.5)
Drug withdrawn	8 (3.3)	6 (3.6)	1 (1.9)	0
Not applicable	5 (2.0)	3 (1.8)	0	0
Unknown	0	0	0	0

[1] *AG881-C-004 Vorasidenib 40 mg without Crossover: includes data from subjects in Study AG881-C-004 who were randomized to and treated with vorasidenib 40 mg QD (or 50 mg QD uncoated).*
[2] *AG881-C-004 Vorasidenib 40 mg Post-crossover: includes post crossover data from subjects initially randomized to placebo and treated with vorasidenib 40 mg QD after crossover in Study AG881-C-004.*
[3] *AG881-C-004 Placebo: includes data from subjects whose actual treatment was placebo in Study AG881-C-004. For subjects that subsequently cross over to receive vorasidenib 40 mg QD, only data before crossover is included.*
[4] *Only the most serious event is counted - Seriousness: Serious > Nonserious.*
[5] *Only the most severe outcome is counted - Outcomes: Fatal > Not recovered/Not resolved > Recovering/Resolving > Recovered/Resolved with sequelae > Recovered/Resolved > Unknown.*
[6] Only the action taken associated with the worst toxicity grade is reported. If there were multiple actions taken for the worst grade AE, or multiple AEs of the same worst grade, each of the actions taken will be counted
Source: RMP Table 18.3.4.7.

In the overall glioma cohort treated with 40 mg QD (N=244) the majority of TEAEs within hepatotoxicity search strategy were presented by ALT and/or AST increased. These events were mostly Grade 1 or 2 and were reversible to Grade 1 or baseline with dose modifications, including dose reductions and interruptions, or drug discontinuations and supportive care, which included hospitalization for monitoring liver function and administration of symptom-directed treatments. Grade ≥ 3 TEAEs occurred in 24 (9.8%) subjects, and in 87 (35.7%) subjects hepatotoxicity TEAEs were reported as related by Investigator.



[redacted]

There were no fatal reports of hepatotoxicity.

Risk factors and risk groups:

Idiosyncratic drug-induced liver injury is the result of the interplay between the environment, drugs, and host (genetic, age, sex, immune factors, pre-existing diseases) (Yuan, 2013). The prevalence of DILI tends to be higher in hospitalized patients. Despite the lack of sufficient evidence that pre-existing chronic liver disease may increase the risk of DILI, DILI patients with preexisting liver diseases appear to be at increased risk for a more severe outcome (Li, 2022). Female sex may be associated with a greater risk of drug-induced acute liver failure (ALF). Similar to age, alcohol consumption is included as a risk factor in the CIOMS/RUCAM (Council for International Organizations of Medical Sciences/Roussel Uclaf Causality Assessment Method) causality assessment scale and gives an extra point to patients with a known history of alcohol consumption, although no specific level of consumption has been defined (EASL, 2019). It is also suggested that patients with fatty liver disease or components of metabolic syndrome are at increased risk of DILI. In patients with DILI Diabetes mellitus has been associated with increased risk of mortality, and dyslipidaemia was associated with increased risk of chronic liver injury. Although patients with chronic liver disease may not in general have an increased risk of developing DILI, the consequences of a DILI episode in these patients might be more severe. (CIOMS DILI 2020).

No specific risk factors or risk groups associated with use of vorasidenib or other IDH inhibitors are known.

Preventability:

The key to preventing clinically significant liver injury from DILI is early detection of the signal event before it becomes symptomatic or severe. (Fontana, 2023). A clinical picture resembling acute viral hepatitis with jaundice, malaise, anorexia, nausea and abdominal pain is the principal presentation of DILI and easily recognizable by the physicians.

Nevertheless, the majority of the hepatic events observed with vorasidenib in clinical development were asymptomatic.

Hepatotoxicity associated with vorasidenib cannot be prevented; however, the risk can be minimised through routine monitoring of hepatic enzymes. SmPC provides detailed guidance on the monitoring and management of hepatoxicity in SmPC sections 4.2, 4.4 and 4.8 and PL sections 2 and 4. Hepatic Event Query Form will be used to collect additional information on post-authorisation cases of hepatotoxicity.

Impact on the benefit-risk balance of the product:

Patients with glioma have a poor prognosis with a serious unmet medical need for safe and effective targeted therapies. The benefit of vorasidenib as an effective treatment of Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation outweighs the risk of hepatotoxicity. It can be managed in clinical practice through routine monitoring, dose modification, and dose interruption.

Public health impact:

As Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation is a rare

condition and the hepatic events observed with vorasidenib mostly consisted in the low-grade elevation of AST and ALT, the overall public health impact is expected to be low. In addition, there is no indication that the frequency or severity will be any different in the post-marketing setting.

Important Potential Risk: Impairment of Fertility

Potential mechanism:

The mechanism of vorasidenib‘s effects on reproductive organs is unclear.

Evidence source and strength of evidence:

Effects on reproductive organs were seen in male and female rats during repeat-dose toxicity studies. The effects mainly consisted of loss/alteration of estrous cyclicity and atrophy (ovaries, uterus, cervix, vagina) for females. In males, degeneration of seminiferous tubules, cellular debris in the epididymides, epithelial atrophy in the prostate and seminal vesicles were observed. However, there are currently no data to understand the potential implications in humans. No events of impaired fertility have been reported in vorasidenib clinical trials.

Characterisation of the risk:

No events of impaired fertility have been reported in vorasidenib clinical trials.

Risk factors and risk groups:

Given the relatively young age of patients with glioma, including a range of adolescence in their late teens in an otherwise healthy patient population, sexually active women of childbearing potential and male patients whose partners are women of childbearing potential are at risk of possible impairment of male and female reproductive function with potential infertility.

Preventability:

Prescribers and patients are informed of the potential impact on fertility and advised to seek reproductive counselling, as per the SmPC sections 4.4, 4.6 and PL section 2.

Impact on the benefit-risk balance of the product:

The benefit of vorasidenib as an effective treatment for Grade 2 astrocytoma or oligodendroglioma IDH1 or IDH2 mutation which has an unmet medical need for targeted therapies, outweighs the potential risk of impairment of fertility that can be managed by seek counseling and advice from their doctor on their options.

Public health impact:

As Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation is a rare condition and there were no events of impaired fertility observed with vorasidenib in clinical trials, the overall public health impact is expected to be low.

Important Potential Risk: Use during pregnancy (embryo-foetal development toxicity)

Potential mechanism:

The mechanism of vorasidenib induced embryo-foetal development toxicity is unclear. There are limited human data available regarding the potential effect of vorasidenib on development of the embryo or foetus.

Evidence source and strength of evidence:

In non-clinical embryo-foetal toxicity studies in rats or rabbits, vorasidenib was associated with maternal toxicity, early or late resorptions, lower foetal weights, delayed skeletal ossification and visceral malformations in rats (kidney and testis). There are no or limited amount of data from the use of vorasidenib in pregnant women. It is not known whether vorasidenib can cause foetal harm when administered to a pregnant woman.

Characterisation of the risk:

No embryo-foetal development toxicity was reported in the clinical development program as screenings for pregnancy were performed prior to and during treatment with vorasidenib.

Risk factors and risk groups:

Sexually active women of childbearing potential and male patients whose partners are women of childbearing potential not using effective contraception during treatment with vorasidenib and for at least 2 months after the last dose are at risk. Patients treated with hormonal contraceptives not using a barrier method of contraception are also at increased risk, as vorasidenib may decrease the effectiveness of hormonal contraceptives.

Preventability:

Vorasidenib could cause foetal harm when administered to a pregnant woman. Pregnancy testing is recommended in women of childbearing potential prior to starting treatment with vorasidenib. Women of childbearing potential and males with female partners of childbearing potential should use effective contraception during treatment and for at least 2 months after the last dose of vorasidenib. Since the effect of vorasidenib on the metabolism and efficacy of systemically acting hormonal contraceptives has not been investigated, barrier methods should be applied as a second form of contraception to avoid pregnancy. Guidance on the effective use of contraception is provided in SmPC sections 4.4, 4.5 and 4.6 and PL section 2. Pregnancy follow-up will be completed in case of pregnancy reports from post-marketing setting via routine pharmacovigilance activities.

Impact on the benefit-risk balance of the product:

The benefit of vorasidenib as an effective treatment of non-enhancing astrocytoma or oligodendroglioma with a susceptible IDH1 or IDH2 mutation, which has an unmet medical need for targeted therapies, outweighs the potential risk of use during pregnancy (embryo-foetal development toxicity) that can be managed by adhering to the use of effective contraception as described in the SmPC sections 4.4, 4.5, 4.6 and PL section 2.

Public health impact:

As Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation is a rare condition and no embryo-foetal development toxicities were reported in vorasidenib clinical trials, the overall public health impact is expected to be low.

Important Potential Risk: QT Prolongation

Potential mechanism:

No plausible mechanism of QT prolongation has been identified.

Evidence source and strength of evidence:

There is no non-clinical or clinical evidence indicating that vorasidenib could induce QT prolongation. Multiple studies have been conducted to address the potential cardiovascular effects of vorasidenib and the metabolite AGI-69460, including automated and manual patch clamp assays for potential inhibition against currents known to be associated with prolonged heart rate-corrected QT interval (QTc). An electrocardiogram (ECG) assessment was included in the 28-day and 13-week GLP (Good laboratory practice)-compliant cynomolgus monkey studies. These studies demonstrated that vorasidenib and AGI-69460 do not inhibit the rapidly activating delayed rectifier potassium current at the highest concentration tested (IC50 > 12.3 μM and > 30 μM, respectively). A marginal prolongation of the QTc of 32 msec was identified in 1 male monkey administered the non-tolerable vorasidenib dose of 40 mg/kg/day in the 28-day repeat-dose toxicology study. In the 13-week study, there were no vorasidenib-related abnormalities in frequency, rhythm, or waveform morphology, nor in conduction times. In addition, vorasidenib did not elicit any in vitro alert regarding human ether-à-go-go-related gene (hERG) or other cardiac ion channels. Therefore, this single minimal QTc prolongation was

considered an isolated finding in the non-clinical cardiovascular evaluation of vorasidenib.

The concentration-QTc modelling analysis was performed to model the relationship between vorasidenib plasma concentrations and ECG QTc data from the three Phase 1 studies (AG881-C-001, AG881-C-002, and AG120-881-C-001). Results from this analysis showed no relationship between the vorasidenib plasma concentrations and the change from baseline in QTcF over a wide dose range (10 mg to 1100 mg once daily [QD]), where neither the slope (0.0239 [95% Confidence Interval - 0.0639, 0.0161]) nor the intercept itself was significant ($p<0.05$), with a confidence interval upper bound of <1 msec at therapeutic and supratherapeutic doses. This analysis demonstrated no significant effect of vorasidenib plasma concentrations on QTcF prolongation.

Characterisation of the risk:

The analysis of QT prolongation was based on the broad SMQ Torsade de Pointes/QT prolongation, MedDRA v25.1, for subjects with glioma in Studies AG881-C-004, AG881-C-002 and AG120-881-C-001.

Table 12: QT prolongation

	Glioma (Safety Analysis Set)			
	Glioma Overall - Vorasidenib 40 mg [1] N = 244	**AG881-C-004 Vorasidenib 40 mg without Crossover [2] N = 167**	**AG881-C-004 Vorasidenib 40 mg Post-crossover [3] N = 52**	**AG881-C-004 Placebo [4] N = 163**
Subjects with TEAEs, n (%)	7 (2.9)	6 (3.6)	1 (1.9)	3 (1.8)
Total number of TEAEs	8	7	1	4
Incidence rate - # of subjects with TEAEs per 100 person-years [5]	2.71	3.25	4.17	1.88
95% CI for incidence rate [6]	1.29, 5.68	1.46, 7.23	0.59, 29.61	0.61, 5.83
Severity [7], n (%)				
Missing	0	0	0	0
Grade 1	4 (1.6)	3 (1.8)	1 (1.9)	2 (1.2)
Grade 2	0	0	0	0
Grade 3	3 (1.2)	3 (1.8)	0	1 (0.6)
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Seriousness [8], n (%)				
Serious	0	0	0	0
Nonserious	7 (2.9)	6 (3.6)	1 (1.9)	3 (1.8)
Relationship to treatment [9], n (%)				
Related	1 (0.4)	0	1 (1.9)	2 (1.2)
Not related	6 (2.5)	6 (3.6)	0	1 (0.6)
Outcomes [10], n (%)				
Unknown	0	0	0	0
Recovered/Resolved	7 (2.9)	6 (3.6)	1 (1.9)	3 (1.8)
Recovered/Resolved with sequelae	0	0	0	0
Recovering/Resolving	0	0	0	0
Not recovered/Not resolved	0	0	0	0
Fatal	0	0	0	0
Action taken for treatment [11], n (%)				
Dose not changed	7 (2.9)	6 (3.6)	1 (1.9)	3 (1.8)
Dose reduced	0	0	0	0
Drug interrupted	0	0	0	0
Drug withdrawn	0	0	0	0

Not applicable	0	0	0	0
Unknown	0	0	0	0

[1] Glioma Overall – Vorasidenib 40 mg: contains data from subjects with glioma treated with vorasidenib 40 mg QD (or 50 mg QD uncoated) in Study AG881-C-004, post crossover data from subjects initially randomized to placebo and treated with vorasidenib 40 mg QD after crossover in Study AG881-C-004, data from subjects treated with vorasidenib 50 mg QD in Study AG120-881-C-001, and data from subjects treated with vorasidenib 50 mg QD in Study AG881-C-002.
[2] AG881-C-004 Vorasidenib 40 mg without Crossover: includes data from subjects in Study AG881-C-004 who were randomized to and treated with vorasidenib 40 mg QD (or 50 mg QD uncoated).
[3] AG881-C-004 Vorasidenib 40 mg Post-crossover: includes post crossover data from subjects initially randomized to placebo and treated with vorasidenib 40 mg QD after crossover in Study AG881-C-004.
[4] AG881-C-004 Placebo: includes data from subjects whose actual treatment was placebo in Study AG881-C-004. For subjects that subsequently cross over to receive vorasidenib 40 mg QD, only data before crossover is included.
[5] Person-year: (Date of last dose – Date of first dose + 1)/365.25; for subjects who are still on treatment at data cut-off, the date of the last dose will be the last dosing date or a pre-specified data cut-off date, whichever is earlier. For AG120-881-C-001 subjects, person-year is the sum of pre-surgery person-time in years and post-surgery person-time in years.
[6] The estimate of incidence rate and the associated confidence interval is derived from Poisson Regression.
[7] Grading of TEAE severity used CTCAE v5.0 for Study AG881-C-004 and CTCAE v4.03 for Studies AG881-C-002 and AG120-881-C-001. Only the most severe event is counted - Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing.
[8] Only the most serious event is counted - Seriousness: Serious > Nonserious.
[9] An AE with relationship missing (unknown) is counted as Related. Only Related is counted if both Related and Not related are present.
[10] Only the most severe outcome is counted - Outcomes: Fatal > Not recovered/Not resolved > Recovering/Resolving > Recovered/Resolved with sequelae > Recovered/Resolved > Unknown.
[11] Only the action taken associated with the worst toxicity grade is reported. If there were multiple actions taken for the worst grade AE, or multiple AEs of the same worst grade, each of the actions taken will be counted.
Source: RMP Table 18.3.4.8.

In Glioma Overall – Vorasidenib 40 mg population, 7 (2.9%) subjects in the vorasidenib arm vs. 3 (1.8%) subjects in the placebo arm experienced non-serious TEAEs within the QT prolongation SMQ; no TEAEs of QT prolongation were serious. None of these events were associated with interruption or modification of the vorasidenib dose, and all were recovered/resolved without additional treatment.

Risk factors and risk groups:

Patients with a previous medical history of severe and/or uncontrolled ventricular arrhythmias, a QTc interval ≥ 450 ms, or who are taking medications that are known factors that increase the risk of QT prolongation or arrhythmic events (eg, heart failure, hypokalemia, family history of long QT interval syndrome). Additionally, the following may increase the risk of QT prolongation: advanced age (>60 years of age), being female and on heart medication, nutritional disorders such as anorexia, celiac disease, or other metabolic processing deficiencies.

No special population is at increased risk to develop QT/QTc interval prolongation with vorasidenib has been identified.

Preventability:

QT prolongation is a theoretical risk from non-clinical findings: there was a single and minimal QT prolongation isolated finding in the non-clinical cardiovascular evaluation of vorasidenib. Therefore, no specific measures to prevent QT prolongation are proposed at this stage. Nevertheless, a close monitoring of QT prolongation, as well as periodic cumulative analysis of such events will be performed in each PSUR to further characterize this potential risk.

Impact on the benefit-risk balance of the product:

Patients who experience QT prolongation may be at increased risk of ventricular arrhythmias and sudden cardiac death. All events of QT prolongation reported with vorasidenib were asymptomatic, low grade and self-limited and none was complicated by such conditions or required emergency treatment such as cardiopulmonary resuscitation, defibrillation, electrical/chemical cardioversion, or implantation

of cardioverter/defibrillator/ cardiac pacemaker.

The benefit of vorasidenib as an effective treatment of Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation, which has an unmet medical need for targeted therapies, outweighs the potential risk of QT prolongation.

Public health impact:

As Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation is a rare condition the overall public health impact is expected to be low.

Important Potential Risk: Carcinogenicity

Potential mechanism:

The mechanism by which vorasidenib could potentially induce carcinogenicity is unclear. There are limited non-clinical and clinical data available regarding the potential effect of vorasidenib on carcinogenic risk.

Evidence source and strength of evidence:

Kupffer cell hyperplasia was observed in monkeys during repeat-dose studies. No evidence of genotoxic potential for vorasidenib and its main metabolite, AGI-69460 were demonstrated during *in vitro* and *in vivo* genotoxicity studies. Carcinogenicity studies on vorasidenib are planned in rats and transgenic mice.

Characterisation of the risk:

The analysis of Carcinogenicity was based on the SMQ Malignant or unspecified tumours, MedDRA v25.1, for Glioma Overall – Vorasidenib 40 mg population.

Table 13: Carcinogenicity

Glioma (Safety Analysis Set)				
	Glioma Overall - Vorasidenib 40 mg [1] N = 244	**AG881-C-004 Vorasidenib 40 mg without Crossover [2] N = 167**	**AG881-C-004 Vorasidenib 40 mg Post-crossover [3] N = 52**	**AG881-C-004 Placebo [4] N = 163**
Subjects with TEAEs, n (%)	3 (1.2)	3 (1.8)	0	1 (0.6)
Total number of TEAEs	3	3	0	1
Incidence rate - # of subjects with TEAEs per 100 person-years [5]	1.16	1.62	NA	0.63
95% CI for incidence rate [6]	0.37, 3.60	0.52, 5.04	NA	0.09, 4.45
Severity [7], n (%)				
Missing	0	0	0	0
Grade 1	1 (0.4)	1 (0.6)	0	1 (0.6)
Grade 2	0	0	0	0
Grade 3	2 (0.8)	2 (1.2)	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Seriousness [8], n (%)				
Serious	1 (0.4)	1 (0.6)	0	0
Nonserious	2 (0.8)	2 (1.2)	0	1 (0.6)
Relationship to treatment [9], n (%)				
Related	0	0	0	0
Not related	3 (1.2)	3 (1.8)	0	1 (0.6)
Outcomes [10], n (%)				
Unknown	0	0	0	0
Recovered/Resolved	1 (0.4)	1 (0.6)	0	1 (0.6)

Recovered/Resolved with sequelae	1 (0.4)	1 (0.6)	0	0
Recovering/Resolving	1 (0.4)	1 (0.6)	0	0
Not recovered/Not resolved	0	0	0	0
Action taken for treatment [11], n (%)				
Dose reduced	0	0	0	0
Drug interrupted	1 (0.4)	1 (0.6)	0	0
Drug withdrawn	0	0	0	0
Not applicable	0	0	0	0
Unknown	0	0	0	0

[1] Glioma Overall – Vorasidenib 40 mg: contains data from subjects with glioma treated with vorasidenib 40 mg QD (or 50 mg QD uncoated) in Study AG881-C-004, post crossover data from subjects initially randomized to placebo and treated with vorasidenib 40 mg QD after crossover in Study AG881-C-004, data from subjects treated with vorasidenib 50 mg QD in Study AG120-881-C-001, and data from subjects treated with vorasidenib 50 mg QD in Study AG881-C-002.
[2] AG881-C-004 Vorasidenib 40 mg without Crossover: includes data from subjects in Study AG881-C-004 who were randomized to and treated with vorasidenib 40 mg QD (or 50 mg QD uncoated).
[3] AG881-C-004 Vorasidenib 40 mg Post-crossover: includes post crossover data from subjects initially randomized to placebo and treated with vorasidenib 40 mg QD after crossover in Study AG881-C-004.
[4] AG881-C-004 Placebo: includes data from subjects whose actual treatment was placebo in Study AG881-C-004. For subjects that subsequently cross over to receive vorasidenib 40 mg QD, only data before crossover is included.
[5] Person-year: (Date of last dose – Date of first dose + 1)/365.25; for subjects who are still on treatment at data cut-off, the date of the last dose will be the last dosing date or a pre-specified data cut-off date, whichever is earlier. For AG120-881-C-001 subjects, person-year is the sum of pre-surgery person-time in years and post-surgery person-time in years.
[6] The estimate of incidence rate and the associated confidence interval is derived from Poisson Regression.
[7] Grading of TEAE severity used CTCAE v5.0 for Study AG881-C-004 and CTCAE v4.03 for Studies AG881-C-002 and AG120 881 C 001. Only the most severe event is counted - Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing.
[8] Only the most serious event is counted - Seriousness: Serious > Nonserious.
[9] An AE with relationship missing (unknown) is counted as Related. Only Related is counted if both Related and Not related are present.
[10] Only the most severe outcome is counted - Outcomes: Fatal > Not recovered/Not resolved > Recovering/Resolving > Recovered/Resolved with sequelae > Recovered/Resolved > Unknown.
[11] Only the action taken associated with the worst toxicity grade is reported. If there were multiple actions taken for the worst grade AE, or multiple AEs of the same worst grade, each of the actions taken will be counted.
Source: RMP Table 18.3.4.9.

[redacted]

[redacted]

[redacted]

Risk factors and risk groups:

Environmental factors, including benzo[α] pyrene contained in tobacco smoke and ethyl alcohol, as well as genetic factors, including disorders in DNA repair genes and cell cycle genes, were identified as carcinogenic risk factors. (Saeki,2001).

Advanced age, familial history, exposures to toxines, and lifestyle, might increase the risk associated with cancer (Crosby, 2022).

Preventability:

As the mechanism of vorasidenib-induced carcinogenicity is not elucidated, it cannot be prevented, Nevertheless, the information about this potential risk is provided in SmPC.

Impact on the benefit-risk balance of the product:

Carcinogenicity is a theoretical risk from non-clinical findings. Very few events of malignancies have been reported across vorasidenib development program. The available data in subjects exposed to vorasidenib for >12 months and ≥24 months showed no unexpected trends in the safety profile of vorasidenib and occurrence of malignancies is not anticipated. Therefore, the benefit of vorasidenib as an effective treatment of Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation, which has an unmet medical need for targeted therapies, outweighs the potential risk of carcinogenicity.

Public health impact:

As Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation is a rare condition the overall public health impact is expected to be low.

SVII.3.2 Presentation of the missing information

Use during breastfeeding

Evidence source:

IDH-mutant diffuse gliomas are more commonly diagnosed in younger patients, including a range of adolescents in their late teens. It is anticipated that vorasidenib will be used in women of childbearing potential whilst the current understanding of safety in this population is limited. Therefore, use of vorasidenib during breastfeeding is considered as missing information in patients with glioma.

Population in need of further characterisation:

In case of pregnancy reports from post-marketing setting, the Applicant will ensure pregnancy follow up via routine pharmacovigilance practice.

Use in the paediatric population 12 years and older

Evidence source:

Efficacy in adolescents will be extrapolated from that observed in adults based on the assumption that an exposure range in adolescents that matches the exposure range in adults will be efficacious and tolerable, and that the exposure-efficacy relationship is the same in adults and adolescents whilst the current understanding of safety in this population is limited. Therefore, use of vorasidenib in the paediatric population 12 years and older is considered as missing information in patients with glioma.

Population in need of further characterisation:

The Applicant will perform a clinical trial in paediatric patients.

Long term safety > 12 months

Evidence source:

The available data in subjects exposed to vorasidenib for >12 months and ≥24 months, showed no unexpected trends in the incidence or severity of TEAEs, and considering that vorasidenib does not demonstrate accumulation with long-term exposure, the Applicant does not anticipate delayed toxicities or unexpected long-term safety concerns. Nevertheless, due to the lack of non-clinical characterisation of deschloro-methyl sulfone (AGI-69460), the main metabolite of vorasidenib and the potential treatment duration of several years, it was added as missing information in the list of safety concerns for vorasidenib.

Population in need of further characterisation:

Patients with potential treatment with vorasidenib duration of >12 months.

Part II: Module SVIII - Summary of the safety concerns

Table 14: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Hepatotoxicity
Important potential risks	Impairment of Fertility Use during pregnancy (embryo-foetal development toxicity) QT prolongation Carcinogenicity
Missing information	Use during breastfeeding Use in the paediatric population 12 years and older Long term safety > 12 months

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

III.1. Routine pharmacovigilance activities

Specific adverse reaction follow-up questionnaire for hepatotoxicity:
Specific follow-up form will be used as routine pharmacovigilance activities beyond adverse reactions reporting and signal detection to collect additional information on post-authorisation cases of hepatotoxicity (Annex 4).

Other forms of routine pharmacovigilance activities for QT prolongation:

Cumulative detailed analysis of QT prolongation in each PSUR.

III.2. Additional pharmacovigilance activities

III.2.1 Carcinogenicity

Two non-clinical studies will be conducted to further characterise the carcinogenic potential of vorasidenib and its main metabolite AGI-69460. Rats and mice will be dosed with vorasidenib and the plasma exposure to both vorasidenib and the metabolite will be determined. A summary of each study is presented below:

III.2.1.1 Study 1 Short Name and Title: A 26-Week Carcinogenicity Study of Vorasidenib Administered by Oral Gavage to CB6F1/TgrasH2 Hemizygous Mice

Study Rational and Objective(s):

Rational: Further assess vorasidenib carcinogenic potential.
Objective(s): To identify a tumorigenic potential in animals and to assess the relevant risk in humans.

Study design:

This study will be conducted in accordance with ICHS1 using a statistical analysis of mortality and tumor histomorphological data (spontaneous and induced) vs absolute controls and positive reference compound-dosed animals.

Milestones: Final report submission - 04/2027.

III.2.1.2 Study 2 Short Name and Title: A 2-Year Carcinogenicity Study of Vorasidenib Administered by Oral Gavage to the Wistar Rat

Study Rational and Objective(s):

Rational: To further assess vorasidenib carcinogenic potential.
Objectives: To identify a tumorigenic potential in animals and assess the relevant risk in humans.

Study design:

This study will be conducted in accordance with ICHS1 using a statistical analysis of mortality and tumor histomorphological data (spontaneous and induced) vs absolute control animals.

Milestones: Final report submission - 12/2028.

III.2.2 Long term safety (> 12 months)

To further characterise long term safety, a safety follow-up of all patients receiving vorasidenib from the ongoing pivotal phase 3 study AG881-C-004 (INDIGO) will be conducted.

III.2.2.1 Study Short Name and Title: AG881-C-004 (INDIGO) A Phase 3, Multicenter, Randomized, Double-blind, Placebo-Controlled Study of AG-881 in Subjects with Residual or Recurrent Grade 2 Glioma with an IDH1 or IDH2 Mutation

Study Rationale and Objective(s):

Rational: Further characterise the long term safety in patients receiving vorasidenib. These subjects continue to be assessed for safety according to the study protocol, which is anticipated to continue until 5 years after the last subject is enrolled.
Objective(s): To evaluate safety of long term vorasidenib treatment.

Study design:

A randomized, double-blind, placebo-controlled study designed to demonstrate the efficacy and safety of vorasidenib in subjects with an IDH1 or IDH2 gene-mutated Grade 2 oligodendroglioma or astrocytoma who had surgery as their only treatment compared with placebo.

Study population:

Patients with Grade 2 astrocytoma or oligodenderogliomas receiving vorasidenib.

Milestones: Final Report Submission - 04/2029.

III.2.3 Use in Paediatric Population

To further characterize the use of vorasidenib in the intended paediatric population, a clinical trial enrolling paediatric patients 12 years of age and older will be conducted to adequately characterise baseline risk factors and safety outcomes, following exposure to vorasidenib.

III.2.3.1 Study Short Name and Title: Safety evaluation of vorasidenib in Paediatric patients 12 years of age and older

Study Rationale and Objective(s):

Rational: To characterise the use of vorasidenib in paediatric population.
Objective(s): To assess safety outcomes in paediatric patients following treatment with vorasidenib.

Study design: Interventional, open-label, single-arm clinical trial.

Study population: Patients 12 through 18 years of age with Grade 2 oligodendroglioma or astrocytoma and histology confirmed IDH1 or IDH2 gene mutation status.

Milestones:
Final protocol as approved by the FDA: Q4/2025.
Interim report submission: Q4 2029,
Final Report Submission - 12/2033.

III.3. Summary Table of additional Pharmacovigilance activities

Table 15: Summary Table of 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 authorisation **None**				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances **None**				
Category 3 - Required additional pharmacovigilance activities				
Pivotal phase 3 Study AG881-C-004 (INDIGO) Ongoing	To provide further long-term safety data in patients remaining on treatment with vorasidenib	Long term safety > 12 months	Final report	04/2029
A clinical trial in paediatric patients following exposure to vorasidenib Planned	To assess the safety of vorasidenib in paediatric patients	Use in paediatric population 12 years of age and older	Final protocol as approved by the FDA Interim report Final report	Q4/2025 Q4/2029 12/2033
26-Week Carcinogenicity Study of Vorasidenib Administered by Oral Gavage to CB6F1/TgrasH2 Hemizygous Mice Planned	Identify a tumorigenic potential in animals and assess the relevant risk in humans: statistical analysis of mortality and tumor histomorphological data (spontaneous and induced) vs absolute controls and positive reference compound-dosed animals	Carcinogenic potential	Final report	04/2027
2-Year Carcinogenicity Study of Vorasidenib Administered by Oral Gavage to the Wistar Rat Planned	Identify a tumorigenic potential in animals and assess the relevant risk in humans: statistical analysis of mortality and tumor histomorphological data (spontaneous and induced) vs absolute control animals	Carcinogenic potential	Final report	12/2028

Part IV: Plans for post-authorisation efficacy studies

Not applicable, since no post-authorisation efficacy studies are proposed.

Part V: Risk minimisation measures (including the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table 16: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Hepatotoxicity (Important identified risk)	Routine risk communication: SmPC section 4.2 "Posology and method of administration" SmPC section 4.4 "Special warnings and precautions for use" SmPC section 4.8 "Undesirable effects" PL sections 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for liver enzymes monitoring are included in SmPC sections 4.2, 4.4 and in the corresponding section of the PL. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine. Treatment to be initiated by experienced oncologist.
Impairment of Fertility (Important potential risk)	Routine risk communication: SmPC section 4.4 "Special warnings and precautions for use". SmPC section 4.6 "Fertility, pregnancy and lactation" PL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: Patients advised to seek reproductive counselling as per SmPC sections 4.4, 4.6 and PL section 2. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine. Treatment to be initiated by experienced oncologist.
Use during pregnancy (embryo-foetal development toxicity) (Important potential risk)	Routine risk communication: SmPC section 4.4 "Special warnings and precautions for use". SmPC section 4.5 "Interaction with other medicinal products and other forms of interaction". SmPC section 4.6 "Fertility, pregnancy and lactation" PL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for pregnancy and contraception are included in SmPC sections 4.4, 4.5 and 4.6 and in the corresponding sections of the PL. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine. Treatment to be initiated by experienced oncologist.
QT prolongation (Important potential risk)	Routine risk communication: None Other routine risk minimization measures beyond the Product Information: Legal status: Prescription only medicine.

	Treatment to be initiated by experienced oncologist.
Carcinogenicity (Important potential risk)	Routine risk communication: SmPC section 4.4.
Use during breastfeeding (Missing information)	Routine risk communication: SmPC section 4.6 “Fertility, pregnancy and lactation” PL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for breastfeeding are included in SmPC section 4.6 and in the corresponding section of the PL. Other routine risk minimization measures beyond the Product Information: Legal status: Prescription only medicine. Treatment to be initiated by experienced oncologist.
Use in the paediatric population 12 years and older (Missing information)	Routine risk communication: SmPC section 5.1 “Pharmacodynamic properties”. SmPC section 5.2 “Pharmacokinetic properties”. Other routine risk minimization measures beyond the Product Information: Legal status: Prescription only medicine. Treatment to be initiated by experienced oncologist.
Long term safety > 12 months (Missing information)	Routine risk communication: SmPC section 4.4. Other routine risk minimization measures beyond the Product Information: Legal status: Prescription only medicine. Treatment to be initiated by experienced oncologist.

V.2. Additional Risk Minimisation Measures

None.

V.3 Summary of risk minimisation measures

Table 17: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hepatotoxicity (Important identified risk)	Routine risk minimisation measures: SmPC sections 4.2, 4.4 and 4.8 and PL sections 2 and 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Hepatic Event Query Form
Impairment of Fertility (Important potential risk)	Routine risk minimisation measures: SmPC sections 4.4, 4.6 and PL section 2	None
Use during pregnancy (embryo-foetal development toxicity) (Important potential risk)	Routine risk minimisation measures: SmPC sections 4.4, 4.5, 4.6 and PL section 2	None

QT prolongation (Important potential risk)	No routine risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Cumulative summary of QT prolongation adverse events in PSUR
Carcinogenicity (Important potential risk)	Routine risk minimisation measures: SmPC section 4.4	Additional pharmacovigilance activities: Non-clinical carcinogenicity studies
Use during breastfeeding (Missing information)	Routine risk minimisation measures: SmPC section 4.6 and PL section 2	None
Use in the paediatric population 12 years and older (Missing information)	Routine risk minimisation measures: SmPC sections 5.1, 5.2	Additional pharmacovigilance activities: clinical trial in paediatric patients following exposure to vorasidenib Interim report submission: Q4/2029. final report 12/2033
Long term safety > 12 months (missing information)	Routine risk minimisation measures: SmPC section 4.4	Additional pharmacovigilance activities: Pivotal phase 3 Study AG881-C-004 (INDIGO) final report 04/2029

Part VI: Summary of the risk management plan

This is a summary of the risk management plan (RMP) for vorasidenib. The RMP details important risks of Voranigo, how these risks can be minimised, and how more information will be obtained about Voranigo risks and uncertainties (missing information).

Voranigo's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Voranigo should be used.

This summary of the RMP for Voranigo 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 Voranigo's RMP.

I. The medicine and what it is used for

Voranigo is authorized for the treatment of predominantly non-enhancing Grade 2 astrocytoma or oligodendroglioma with an IDH1 R132 or IDH2 R172 mutation in adults and paediatric patients aged 12 years and older and weighing at least 40 kg who only had surgical intervention and who are not in immediate need of radiotherapy or chemotherapy. It contains vorasidenib as the active substance and it is given by oral route.

Further information about the evaluation of Voranigo's benefits can be found in Voranigo's EPAR, including in its plain-language summary, available on the European Medicines Agency website under the medicine's webpage http://www.ema.europa.eu.

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

Important risks of Voranigo, together with measures to minimize such risks for learning more about Voranigo's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals,
- Important advice on the medicine's packaging,
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly,
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report 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 Voranigo is not yet available, it is listed under 'missing information' below.

IIA. List of important risks and missing information

Important risks of Voranigo are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Voranigo. 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 collected (e.g. on the long term use of the medicine).

Table 18: List of important risks and missing information

List of important risks and missing information	
Important identified risks	Hepatotoxicity
Important potential risks	Impairment of Fertility Use during pregnancy (embryo-foetal development toxicity) QT prolongation Carcinogenicity
Missing information	Use during breastfeeding Use in the paediatric population 12 years and older Long term safety > 12 months

II.B. Summary of important risks

Table 19: Summary of important risks

Important identified risks: Hepatotoxicity	
Evidence for linking the risk to medicine	Liver findings suggestive of hepatic enzyme induction have been observed in the pre-clinical setting. Liver enzyme elevations (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) was added as an important identified risk of vorasidenib during the Phase 1 studies in subjects with hematologic malignancies and solid tumours including glioma. Liver enzyme elevations are among the most common adverse events reported in clinical studies, including the pivotal study. Evidence from these sources is considered to be a reliable predictor of how subjects will respond to treatment in clinical practice, by convention.
Risk factors and risk	Idiosyncratic drug-induced liver injury is the result of the interplay between the

groups	environment, drugs, and host (genetic, age, sex, immune factors, pre-existing diseases) (Yuan, 2013). The prevalence of DILI tends to be higher in hospitalized patients. Despite the lack of sufficient evidence that pre-existing chronic liver disease may increase the risk of DILI, DILI patients with preexisting liver diseases appear to be at increased risk for a more severe outcome (Li, 2022). Female sex may be associated with a greater risk of drug- induced acute liver failure (ALF). Similar to age, alcohol consumption is included as a risk factor in the CIOMS/RUCAM causality assessment scale and gives an extra point to patients with a known history of alcohol consumption, although no specific level of consumption has been defined (EASL, 2019). It is also suggested that patients with fatty liver disease or components of metabolic syndrome are at increased risk of DILI. In patients with DILI Diabetes mellitus has been associated with increased risk of mortality, and dyslipidaemia was associated with increased risk of chronic liver injury. Although patients with chronic liver disease may not in general have an increased risk of developing DILI, the consequences of a DILI episode in these patients might be more severe. (CIOMS DILI 2020) No specific risk factors or risk groups associated with use of vorasidenib or other IDH inhibitors are known.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4 and 4.8 and PL sections 2 and 4.
Important potential risks: Impairment of Fertility	
Evidence for linking the risk to medicine	Effects on reproductive organs were seen in male and female rats during repeat-dose toxicity studies. The effects mainly consisted of loss/alteration of estrous cyclicity and atrophy (ovaries, uterus, cervix, vagina) for females. In males, degeneration of seminiferous tubules, cellular debris in the epididymides, epithelial atrophy in the prostate and seminal vesicles were observed. However, there are currently no data to understand the potential implications in human. No events of impaired fertility have been reported in vorasidenib clinical trials.
Risk factors and risk groups	Given the relatively young age of patients with glioma, including a range of adolescence in their late teens in an otherwise healthy patient population, sexually active women of childbearing potential and male patients whose partners are women of childbearing potential are at risk of possible impairment of male and female reproductive function with potential infertility.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4, 4.6 and PL section 2.
Important potential risk: Use during pregnancy (embryo-foetal development toxicity)	
Evidence for linking the risk to medicine	In non-clinical embryo-foetal toxicity studies in rats or rabbits, vorasidenib was associated with maternal toxicity, early or late resorptions, lower foetal weights, delayed skeletal ossification and visceral malformations in rats (kidney and testis). There are no or limited amount of data from the use of vorasidenib in pregnant women. It is not known whether vorasidenib can cause foetal harm when administered to a pregnant woman.
Risk factors and risk groups	Sexually active women of childbearing potential and male patients whose partners are women of childbearing potential not using effective contraception during treatment with vorasidenib and for at least 2 months after the last dose are at risk. Patients treated with hormonal contraceptives not using a barrier method of contraception are also at increased risk, as vorasidenib may decrease the effectiveness of hormonal contraceptives.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4, 4.5, 4.6 and PL section 2.
Important potential risk: QT prolongation	
Evidence for linking the risk to medicine	QT prolongation was initially considered an important potential risk of vorasidenib based on non-clinical findings of marginal QTc prolongation of 32 msec in a single high-dose-group (40 mg/kg/day) male monkey in the 28-day toxicity study. A

	detailed review of clinical data across Studies AG881-C-001, AG881-C-002, AG120-881-001, and AG881-C-004 of the preferred term (PT) Electrocardiogram QT prolonged, as well as analysis of treatment-emergent adverse events (TEAEs) within the broad standard Medical Dictionary of Regulatory Activities (MedDRA) Query (SMQ) Torsade de Pointes/QT prolongation, showed no concerning findings regarding predisposition, including the underlying disease or relevant cardiac comorbidities. Review of these data led the Applicant to no longer consider QT prolongation to be an important potential risk or potential risk of vorasidenib. However, given the potential class effect of IDH1/2 inhibitors, the modest hERG blockade, and the relatively limited sample size of the pivotal study. QT prolongation is still considered as important potential risk.
Risk factors and risk groups	Patients with a previous medical history of severe and/or uncontrolled ventricular arrhythmias, a QTc interval ≥ 450 ms, or who are taking medications that are known factors that increase the risk of QT prolongation or arrhythmic events (e.g., heart failure, hypokalemia, family history of long QT interval syndrome). No special population at increased risk to develop QT/QTc interval prolongation has been identified.
Pharmacovigilance activities	Routine pharmacovigilance measures: a cumulative summary of QT prolongation adverse events within PSUR.
Important potential risk: Carcinogenicity	
Evidence for linking the risk to medicine	Kupffer cell hyperplasia was observed in monkey during repeat-dose studies. No evidence of genotoxic potential for vorasidenib and its main metabolite, AGI-69460 were demonstrated during in vitro and in vivo genotoxicity studies. No other results of carcinogenicity studies are available yet and long-term clinical safety data are insufficient to characterise this risk. Further carcinogenicity studies are planned
Risk factors and risk groups	Environmental factors, including benzo[α] pyrene contained in tobacco smoke and ethyl alcohol, as well as genetic factors, including disorders in DNA repair genes and cell cycle genes, were identified as carcinogenic risk factors. Advanced age, familial history, exposures to toxins, and lifestyle, might increase the risk associated with cancer.
Risk minimisation measures	Routine risk minimization measures: SmPC section 4.4.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Non-clinical carcinogenicity studies See section II.C of this summary for an overview of the post-authorisation development plan.
Missing information: Use during breastfeeding	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6 and PL section 2.
Missing information: Use in the paediatric population 12 years and older	
Risk minimisation measures	Routine risk minimization measures: SmPC sections 5.1 and 5.2.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: A clinical trial in paediatric patients following exposure to vorasidenib. See section II.C of this summary for an overview of the post-authorisation development plan.
Missing information: Long term safety > 12 months	
Risk minimisation measures	Routine risk minimization measures: SmPC section 4.4.
Additional	Additional pharmacovigilance activities:

pharmacovigilance activities	Pivotal phase 3 Study AG881-C-004 (INDIGO). See section II.C of this summary for an overview of the post-authorisation development plan.

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 Voranigo.

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

Table 20: Other on-going and planned studies in post-authorisation development plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Pivotal phase 3 Study AG881-C-004 (INDIGO) Ongoing	To provide further long term safety data in patients remaining on treatment with vorasidenib	Long term safety > 12 months	Final report	04/2029
A clinical trial in paediatric patients following exposure to vorasidenib Planned	To assess the safety of vorasidenib in paediatric patients	Use in paediatric population 12 years of age and older	Final protocol as approved by the FDA Interim report Final report	Q4/2025 Q4/2029 12/2033
26-Week Carcinogenicity Study of Vorasidenib Administered by Oral Gavage to CB6F1/TgrasH2 Hemizygous Mice Planned	Identify a tumorigenic potential in animals and assess the relevant risk in humans: statistical analysis of mortality and tumor histomorphological data (spontaneous and induced) vs absolute controls and positive reference compound-dosed animals	Carcinogenic potential	Final report	04/2027
2-Year Carcinogenicity Study of Vorasidenib Administered by Oral Gavage to the Wistar Rat Planned	Identify a tumorigenic potential in animals and assess the relevant risk in humans: statistical analysis of mortality and tumor histomorphological data (spontaneous and induced) vs absolute control animals	Carcinogenic potential	Final report	12/2028

Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms
Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Annex 4 - Specific adverse drug reaction follow-up forms

Hepatic Event Query Form.

Hepatic Event Query Form

PART 1: Case Details

This part is for internal Servier use only (to be completed by Servier staff)	
Email address:	
Servier Case ID:	
Patient ID:	Date of Birth: ____/____/_____
Servier Awareness Date (DD/MM/YYYY): ____/____/_____	Country:
Suspect Product(s): Vorasidenib	

PART 2: Event Information

Event(s), Diagnosis(es)	**Date of Onset of Symptoms or Lab Abnormality (DD/MM/YYYY)**
*If confirmed diagnosis is not available, please include lab abnormalities for the Hepatic Events	

Signs and Symptoms (Check all that apply)

☐ Anorexia ☐ Fatigue ☐ Nausea ☐ Vomiting ☐ Dark Urine ☐ Pruritus

☐ Fever ☐ Abdominal pain ☐ Confusion ☐ Tremor ☐ Coma ☐ Jaunice/Icterus

☐ Other: _____

Additional Event Information

Did the event involve any of the following?

☐ Hospitalization: Admission Date: ____/____/_____ Discharge Date: ____/____/_____
Admitting Diagnosis: _____

☐ Medically Significant ☐ Disability ☐ Life-threatening ☐ Death

Event outcome:	
☐ Recovered	☐ Recovered with Sequelae: _____
☐ Recovering/Resolving	
☐ Not recovered	
☐ Fatal	☐ Not reported
☐ Unknown	

►Return ALL pages to Local affiliate (Local affiliate please indicate return E-mail/ Fax/Postal address)

Additional event comments:				
Did the event(s) improve after the stopping or after reducing the dose of the therapeutic agent? (positive dechallenge)	☐ Yes	☐ No	☐ Unknown	☐ N/A
Did the event(s) occur again after re-exposure to the therapeutic agent? (positive rechallenge)	☐ Yes	☐ No	☐ Unknown	☐ N/A

PART 3: Relevant Lab Data

Test Name	Date	Result	Normal Range
Standard Liver Function Tests			
Alanine aminotransferase (ALT)			
Aspartate aminotransferase (AST)			
Alkaline phosphatase (ALP)			
Gamma-glutamyl transferase (GGT)			
Bilirubin (total, direct, indirect)			
Albumin			
International normalized ratio (INR)			
Priority Core Viral Serologies			
HAV serology (IgM, IgA, IgG)			
HBV serology (HBsAg, IlBsAb, HBcAb [titers], HBeAg)			
HCV serology (IgG, if present, HCV RNA load [quantitative])			
HDV serology (IgG, IgM)			
HEV serology (IgM, IgA, IgG)			
Other Relevant Tests			
Herpes simplex virus serology (IgM, IgG)			
CMV (Cytomegalovirus) serology (IgM, IgA, IgG)			
EBV (Epstein-Barr virus) serology (EA, EBNA, VCA)			
Parvo virus serology, Virus load (quantitative)			
Toxoplasma serology (IgM, IgA, IgG)			
Varicella virus serology (IgM, IgA, IgG			
Autoimmune antibodies (e.g., ANA, SMA, ant - LKM)			

►Return ALL pages to Local affiliate (Local affiliate please indicate return E-mail/ Fax/Postal address)

PART 4: Concomitant Medications and Prior History / Risk Factors (Include the dates)

Concomitant Medications (Including Herbal Supplements/Medications)

☐ Not reported ☐ None ☐ Unknown

Trade Name or Active Substance	Indication	Dose/Frequency/Route of Administration	Start Date	Stop Date	Ongoing
					☐
					☐
					☐
					☐
					☐
					☐
					☐

History / Risk Factors	Yes	No	Unknown	Additional Information
Alcoholism (dependency)	☐	☐	☐	
Hepatitis	☐	☐	☐	
Cholelithiasis (gall stones)	☐	☐	☐	
Prone to bleeding or bruising	☐	☐	☐	
Hepatitis infections (e.g. hepatitis A, B, C, D, E)	☐	☐	☐	
Autoimmune disease	☐	☐	☐	
Blood transfusion	☐	☐	☐	
Injection drug use (IDU)	☐	☐	☐	
Anabolic steroid use	☐	☐	☐	
Recent tattoos	☐	☐	☐	
Other liver disease	☐	☐	☐	

PART 5: Additional Relevant History

Additional Relevant History	Yes	No	Additional Information
Travel to areas endemic for hepatitis? Countries visited in the last 2 years?	☐	☐	Countries visited:
Evidence of immune suppression?	☐	☐	
Quantitative alcohol consumption history? Number of alcoholic drinks per week? If so, amount consumed preceding the event?	☐	☐	
Fever, leukocytosis, abdominal pain, hepatomegaly	☐	☐	
Biliary tract disease, including gallstones (with ultrasound)	☐	☐	
Non-alcoholic steatohepatitis (NASH), splenic enlargement, hyperlipoproteinemia (Fatty liver disease)	☐	☐	
Evidence of transient liver ischemia (including those due to hypotension, right ventricular failure, rigorous/extraneous exercise, etc)	☐	☐	
Provide all available past liver enzyme test results	☐	☐	

PART 6: Diagnostic Procedures and Test

Were Any Diagnostic Tests Performed?	☐ **Yes**	☐ **No**	☐ **Unknown**
(Ultrasound and/or CT are priorities. MRI, ERCP, liver biopsy, others as applicable [provide a copy of report when available])			
Details of diagnostic procedures and tests:			

►Return ALL pages to Local affiliate (Local affiliate please indicate return E-mail/ Fax/Postal address)

PART 7: Additional comments/details:

Form Completed by:

Name: _____ Signature: Date: ____/____/_____

Address: _____

Contact Number: _____ Email: _____

►Return ALL pages to Local affiliate (Local affiliate please indicate return E-mail/ Fax/Postal address)

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

Not Applicable