24 July 2025
EMA/271829/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Voranigo

International non-proprietary name: vorasidenib

Procedure No. EMEA/H/C/006284/0000

Note

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

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List of abbreviations

Abbreviation	Definition
2-HG	2-hydroxyglutarate
ADME	Absorption, Distribution, Metabolism, and Excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
AUC	area under the concentration versus time curve
AUC0-inf	area under the plasma concentration-time curve from 0 hours to infinity
AUC0-t	area under the plasma concentration-time curve from 0 to time of last measurable concentration
AUCavg	area under the plasma concentration-time curve at steady state based on the actual average dose up to the time of an event, up to the end of treatment or up to the study data cutoff in case a subject did not experience an event
AUCeot	area under the plasma concentration-time curve at steady state based on the actual average dose across the treatment duration until end of treatment
AUCss	area under the plasma concentration-time curve at steady state
BCRP	Breast Cancer Resistance Protein
BIRC	Blinded Independent Review Committee
BOR	best overall response
BrCS	brain cancer subscale
CHMP	Committee for Human Medicinal Products
CI	confidence interval
Cmax,avg	maximum plasma concentration at steady state based on the actual average dose
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CRO	contract research organization
CSR	clinical study report
CV	coefficient of variation
CxDy	Cycle x, Day x (where x is the cycle number and y is the day number)
CYP	cytochrome P450
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DoR	duration of response
DS	drug substance
EANO	European Association of Neuro-Oncology

ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EOT	end of treatment
EU	European Union
EWB	emotional well-being
F1	early phase formulation (uncoated) (Formulation 1)
F2	intended commercial formulation (film-coated) (Formulation 2)
FA	final analysis
FACT-Br	Functional Assessment of Cancer Therapy – Brain
FACT-G	Functional Assessment of Cancer Therapy – General
FAS	Full Analysis Set
FDA	United States Food and Drug Administration
FWB	functional well-being
GBS	Guillain-Barré syndrome
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMR	geometric mean AUC ratio
HR	hazard ratio
HRQoL	health-related quality of life
IA2	interim analysis 2
ICF	informed consent form
ICH	International Council for Harmonisation
IDH	isocitrate dehydrogenase
IDH1	isocitrate dehydrogenase 1
IDH2	isocitrate dehydrogenase 2
IDMC	independent data monitoring committee
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IWRS	interactive web response system
KPS	Karnofsky Performance Scale
LGG	low-grade glioma
LPPS	Lansky Play-Performance Scale
LVEF	left ventricular ejection fraction
MAA	Marketing Authorization Application
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed models for repeated measures
mR	minor response
MRI	magnetic resonance imaging
NADPH	Reduced nicotinamide adenine dinucleotide phosphate
NE	not evaluable

NTI	narrow therapeutic index
OR	objective response
ORR	objective response rate
OS	overall survival
PCV	procarbazine/lomustine/vincristine
PD	progressive disease
PDF	probability distribution function
PFS	progression-free survival
PGI	patient global impression
PGI-C	Patient Global Impression of Change
PGI-F	Patient Global Impression of Frequency
PGI-S	Patient Global Impression of Severity
P-gp	p-glycoprotein
PH	proportional hazards
PI	Principal Investigator
PIP	Paediatric Investigation Plan
PK	pharmacokinetic
PPS	Per Protocol Set
PR	partial response
PRO	patient-reported outcome
Pop PK	population PK
PT	preferred term
PWB	physical well-being
QD	once daily
QTcB	QT interval corrected for heart rate using Bazett formula
QTcF	QT interval corrected for heart rate using Fridericia formula
RANO-LGG	Response Assessment in Neuro-oncology for Low-grade Gliomas
RI	renal impairment
RT	radiation therapy
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Safety Analysis Set
SD	stable disease
SEM	standard error of measurement
SMQ	Standard MedDRA Query
SOC	system organ class
StD	standard deviation
SWB	social/family well-being
TEAE	treatment-emergent adverse event
TGR	tumor growth rate
TOI	trial outcome index
TTNI	time to next intervention
TTR	time to response

ULN	upper limit of normal
US	United States
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Les Laboratoires Servier submitted on 4 January 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Voranigo, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 January 2023.

Voranigo was designated as an orphan medicinal product EU/3/22/2737 on 13 January 2023 in the following condition: treatment of glioma.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Voranigo as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Voranigo.

The applicant applied for the following indication:

Voranigo as monotherapy is indicated for the treatment of predominantly non-enhancing astrocytoma or oligodendroglioma with a susceptible isocitrate dehydrogenase-1 (IDH1) R132 mutation or isocitrate dehydrogenase-2 (IDH2) R172 mutation in adult and adolescent patients 12 years and older following surgical intervention.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

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

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0007/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0007/2022 was completed.

The PDCO issued an opinion on compliance for the PIP P/0007/2022.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's request(s) for consideration

1.5.1. Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

1.5.2. New active substance status

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

1.6. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
25 July 2019	EMEA/H/SA/4161/1/2019/III	*Ms Blanca García-Ochoa Martín and Prof. Brigitte Blöchl-Daum*
23 February 2023	EMA/SA/0000121022	*Dina Apele-Freimane and Anna Vikerfors*

The applicant received Scientific Advice on the development of vorasidenib hemicitric acid hemihydrate for the treatment of residual or recurrent grade 2 glioma with mutations in IDH1 or IDH2 from the CHMP on 25 July 2019 (EMEA/H/SA/4161/1/2019/III). The Scientific Advice pertained to the following pre-clinical development and clinical aspects:

Pre-clinical

On the appropriateness of the toxicology evidence package.

Clinical

On the unmet medical need status of LGG that harbours an IDH1/2 mutation and on the proposed phase III study including:

- The proposed study patient population,
- PFS as a primary endpoint,
- Tumour growth rate as assessed by volume as the key secondary endpoint,
- Statistical assumptions and the methodology,
- ORR, TTR, DoR as assessed by BIRC and the Investigator; PFS as assessed by the Investigator; OS; and HRQoL using the FACT-G as additional secondary endpoints,
- The choice of comparator (placebo) and the allowance of crossover from placebo to active treatment at the time of radiographic progression by BIRC
- The safety monitoring plan
- The selected 50 mg QD dose
- The PRO and PerfO strategies.

The applicant received Scientific Advice on the development of vorasidenib hemicitric acid hemihydrate for the adjuvant treatment of residual or recurrent WHO grade 2 oligodendroglioma or astrocytoma with mutations in IDH1 or IDH2 from the CHMP on 23/02/2023 (EMA/SA/0000121022). The Scientific

Advice pertained to the following Quality aspects:

Stability package to support the proposed shelf life for the commercial finished product; decoupling active substance and finished process validation.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Alexandre Moreau Co-Rapporteur: Peter Mol

The application was received by the EMA on	4 January 2024
Accelerated Assessment procedure was agreed-upon by CHMP on	9 November 2023
The procedure started on	25 January 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	27 March 2024
The CHMP Co-Rapporteur's assessment was circulated to all CHMP and PRAC members on	5 April 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	2 April 2024
In accordance with Article 6(3) of Regulation (EC) No 726/2004, the CHMP Rapporteur declared that they had completed their assessment report in less than 80 days	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 April 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on The procedure was reverted back from accelerated to standard assessment timelines on	23 April 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	24 May 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	2 July 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 July 2024
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	25 July 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	19 August 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues	4 September 2024

to all CHMP and PRAC members on	
The CHMP agreed on a second list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	19 September 2024
The applicant submitted the responses to the second CHMP List of Outstanding Issues on	21 December 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the second List of Outstanding Issues to all CHMP and PRAC members on	16 January 2025
The CHMP agreed on a third list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	30 January 2025
The applicant submitted the responses to the third CHMP List of Outstanding Issues on	23 June 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the third List of Outstanding Issues to all CHMP and PRAC members on	9 July 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Voranigo on	24 July 2025
The CHMP adopted a report on similarity of Voranigo with Finlee and Spexotras on	24 July 2025
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	24 July 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The proposed indication is:

Voranigo as monotherapy is indicated for the treatment of predominantly non-enhancing astrocytoma or oligodendroglioma with a susceptible isocitrate dehydrogenase-1 (IDH1) R132 mutation or isocitrate dehydrogenase-2 (IDH2) R172 mutation in adult and adolescent patients 12 years and older following surgical intervention.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Gliomas are rare tumours, defined as neuroepithelial tumours that originate from glial cells in the central nervous system (CNS) and are the most common form of primary malignant brain tumours. They are either astrocytic, oligodendrocytic, or ependymal, and are typically malignant (National Brain Tumour Society, 2022).

IDH1 mutations are the most frequent genetic events in Grade 2 and 3 diffuse gliomas, occurring in approximately 80% of cases, while IDH2 mutations occur in approximately 4% (Cohen et al. 2013). More than 90% of the observed IDH1 mutations are IDH1 R132H, which is usually detected using immunohistochemical testing, while non-canonical IDH1 (R132C/G/L/S) and IDH2 (R172K/W/G) are much rarer (Hartmann et al. 2009).

Although adult-type diffuse gliomas occur in paediatric patients and adolescents, they are distinct from paediatric-type diffuse gliomas as per the 2021 WHO classification of CNS tumours (Louis et al. 2021). Adult-type diffuse gliomas can arise during the early adolescent years or manifest during adulthood; regardless of when they are diagnosed, these gliomas have similar behaviour. IDH-mutant oligodendroglioma and astrocytoma that occur in adolescents (≥12 to <18 years) resemble the disease in the adult population, with similar clinical path (indolent growth and favourable prognosis) (Packer et al. 2017; Ryall et al. 2017; Sturm et al. 2017).

The incidence of adult-type diffuse gliomas harboring an IDH mutation is rare in paediatric and older adolescent patients. In a multi-institutional study, 76 out of 851 patients were aged 10 to 21 years (median 16.8) and had IDH-mutant gliomas (majority of which were Grade 1 or 2). Out of these 76 patients, a total of 68 (89.5%) and 8 (10.5%) had IDH1 mutations and IDH2 mutations, respectively. The incidence of IDH-mutant gliomas in paediatric patients younger than 10 years of age is extremely rare (Yeo et al. 2023).

2.1.3. Aetiology and pathogenesis

IDH mutations occur early in tumorigenesis and are disease defining characteristics of diffuse gliomas (Cohen et al. 2013). IDH mutations confer neomorphic enzymatic activity resulting in the reduction of alpha-ketoglutarate (α-KG) to form 2-hydroxyglutarate (2-HG), which consumes reduced nicotinamide adenine dinucleotide phosphate (NADPH) and renders the cell vulnerable to oxidative stress (Dang et al. 2009). IDH mutations lead to accumulation of the oncometabolite, 2-HG, resulting in a broad range of changes to the deoxyribonucleic acid (DNA) hydroxymethylation, gene expression, cellular differentiation, and the tumour immune microenvironment (Bunse et al. 2018; Turcan et al. 2012).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

IDH-mutant diffuse gliomas are most commonly diagnosed in young patients. The median age of diagnosis is 45 years for patients with oligodendrogliomas and 38 years for patients with astrocytomas (Cancer Genome Atlas Research Network, 2015). These young patients do not usually suffer from significant non-glioma-related comorbidities. 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. Many of these symptoms worsen over time due to diffuse infiltrative glioma growth or because of adverse effects from treatments such as surgery, radiation therapy (RT), chemotherapy, and antiepileptic medications (Dietrich and Wen et al. 2022; van den Bent and Loeffler et al. 2022).

In gliomas, contrast enhancement on MRI is associated with a worse prognosis and lower survival rates. Most IDH-mutant gliomas initially present as non-enhancing on MRI (Leu et al. 2017); in a subset of these non-enhancing gliomas, minimal, diffuse, non-progressive, non-nodular enhancement are seen, but are not indicative of more aggressive tumour behaviour. As such, these tumours are referred to as predominantly non-enhancing tumours (NCCN, 2023).

Although patients with non-enhancing IDH-mutant gliomas are considered to have a better prognosis and higher survival rates compared with patients with enhancing gliomas, all non-enhancing gliomas eventually progress, develop contrast enhancement, and transform to a more aggressive form (Claus et al. 2015).

2.1.5. Management

There are no approved therapies for Grade 2 IDH-mutant diffuse gliomas, and most treatments used are adopted from the higher-grade setting (Dietrich and Wen et al. 2022; van den Bent et al. 2021). The current treatment approach for IDH-mutant diffuse gliomas at the time of initial diagnosis includes maximal safe resection of the tumour followed by either RT and/or chemotherapy or an alternative active observation approach with serial magnetic resonance imaging (MRI) (NCCN, 2021; Weller et al. 2021).

Post-operative active observation is a standard of care option for patients with Grade 2 IDH-mutant gliomas who are not in immediate need of chemoradiotherapy. The goal of this approach is to defer the need for more toxic regimens (e.g. RT and chemotherapy) until there is evidence of progression and/or evidence of clinical deterioration.

There is an unmet need for alternative therapies that target IDH-mutant gliomas early in their development. As IDH mutations are early genetic drivers of the disease, a targeted approach suppressing the mutant enzyme may offer an opportunity to intervene early (before radiotherapy or chemotherapy) in the disease course, delaying disease progression, the development of contrast enhancement, and the malignant transformation and therefore the need for more aggressive therapies.

2.2. About the product

Vorasidenib (also known and mentioned in the text as AG 881, S95032) 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 the oncogenic metabolite 2-hydroxyglutarate (2-HG), resulting in impaired cellular differentiation and increased cellular proliferation 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.

For this initial marketing application, the initially proposed indication for vorasidenib was:

Voranigo as monotherapy is indicated for the treatment of predominantly non-enhancing astrocytoma or oligodendroglioma with a susceptible isocitrate dehydrogenase-1 (IDH1) R132 mutation or isocitrate dehydrogenase-2 (IDH2) R172 mutation in adult and adolescent patients 12 years and older following surgical intervention.

And the final approved one is:

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 are not in immediate need of radiotherapy or chemotherapy.

In the SmPC, the recommended dose of vorasidenib in adults and adolescents 12 years of age and older is:

- 40 mg taken orally once daily for patients weighing at least 40 kg

No dose recommendation can be made in patients weighing less than 40 kg because of the lack of clinical data in this population.

Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. Relevant instruction on dose adjustment in case of adverse reactions can be found in the Summary of product characteristics.

Vorasidenib should be taken after at least 2 hours of fasting, and food intake should be avoided for at least 1 hour after taking vorasidenib.

2.3. Type of application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. Vorasidenib was thus expected to fulfil the unmet medical need by providing a significant delay in tumour progression and being likely to delay the time to next intervention in the younger patient's population with chemoradiotherapy. Indeed, there are lot of concerns about the toxicities of these aggressive therapies including long-term effects particularly neurocognitive effect of the radiation leading to memory loss and functional decline in young patients otherwise in good general condition.

However, following the assessment of the dossier submitted by the applicant, the CHMP identified several critical issues resulting in major objections (MO) being raised. In light of these raised major objections, the CHMP concluded that it is no longer appropriate to maintain an accelerated assessment.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film-coated tablets containing 10 mg or 40 mg of vorasidenib. The product contains the vorasidenib hemicitric acid, hemihydrate form of the active substance.

Other ingredients are:

Tablet core - Microcrystalline cellulose (E460), croscarmellose sodium, silicified microcrystalline cellulose (contains microcrystalline cellulose and silica colloidal anhydrous), magnesium stearate (E470b), sodium lauryl sulfate (E487).

Tablet film-coating – Hypromellose, titanium dioxide (E171), lactose monohydrate, macrogol (E1521).

Printing ink - Black iron oxide (E172), propylene glycol (E1520), hypromellose (E464).

The product is available in a white high density polyethylene (HDPE) bottle with a polypropylene (PP) child-resistant closure and polyethylene (PE) faced induction heat seal liner, three HDPE silica gel desiccant cannisters are present as described in section 6.5 of the SmPC.

2.4.2. Active substance

2.4.2.1. General information

The chemical name of vorasidenib (as hemicitric acid, hemihydrate) is 6-(6-chloropyridin-2-yl)-N2,N4-bis[(2R)-1,1,1-trifluoropropan-2-yl]-1,3,5-triazine-2,4-diamine, 2-hydroxypropane-1,2,3-tricarboxylic acid, hydrate (2:1:1) corresponding to the molecular formula $C_{14}H_{13}ClF_6N_6 \cdot 1/2\ C_6H_8O_7 \cdot 1/2\ H_2O$. It has a relative molecular mass of 519.8 g/mol and the following structure:

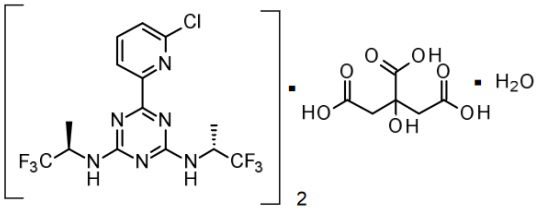


Figure 1. active substance structure

The chemical structure was elucidated by a combination of IR spectroscopy, ^{1}H & ^{13}C NMR, LC/MS & UV spectroscopy. The solid state properties of the active substance were measured by XRPD.

The active substance is a white to off-white solid powder, it is practically insoluble in water.

Vorasidenib exhibits stereoisomerism due to the presence of two chiral centres, both have an R-configuration. These stereocentres originate from one of the starting materials. Correct stereochemistry is adequately controlled in the specification of the starting material and the specification of the active substance.

Polymorphism has been observed for the active substance, the potential polymorphic landscape of the various hydrates and the free base form was investigated. The manufactured form is consistently manufactured via the proposed synthetic route and is stable as demonstrated by the stability studies.

2.4.2.2. Manufacture, characterisation and process controls

Vorasidenib (as hemicitric acid, hemihydrate) is synthesized in several steps using well defined starting materials with acceptable specifications. The manufacturing process is conducted at one proposed manufacturing site.

One of the initially proposed starting materials was not considered acceptable, as it is introduced late into the synthetic process and the applicant was requested to redefine this material as an intermediate. This was raised as a major objection (MO). To resolve this MO, the applicant provided justification that the starting material had been considered in line with the principles of ICH Q11 and steps prior to its inclusion do not impact the impurity profile of the active substance. In addition to this, materials upstream of this material are highly volatile which make characterisation and processing

a challenge. The further justification provided for the use of this material was considered sufficient and the MO was considered resolved.

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

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

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. During development the final drug substance manufacturing process (A3) was used in the clinical studies, earlier processes referred to as A1 & A2 were also used in some of the studies. Changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process. The applicant developed the active substance manufacturing process on the basis of univariate experiments, nevertheless the dossier initially claimed a degree of flexibility via claimed proven acceptable ranges for the manufacturing process, these went beyond the experiments performed. As the potential impact of such manufacturing process variation was unknown an MO was raised on this aspect. To resolve this MO, the applicant included an explanatory statement indicating no multivariate flexibility is claimed.

The active substance is packaged in low-density double polyethylene (LDPE) bags which comply with Commission Regulation (EU) 10/2011, as amended. The LDPE bags are placed in an aluminium foil bag with desiccant and then placed into a HDPE container.

2.4.2.3. Specification

The active substance specification includes tests for: appearance (visual), identity (IR, HPLC, XRPD), assay (HPLC), related substances (HPLC), water content (KF), residual solvents (GC), residual benzene (GC), sulfated ash (Ph. Eur.), citric acid (potentiometry), particle size (laser light diffraction), microbiological quality (Ph. Eur.).

1Overall, the test parameters and limits proposed for the active substance specification are sufficient to ensure the active substance quality and are in line with relevant guidelines.

One impurity is present at higher than the qualification threshold according to ICH Q3A, this impurity is qualified by toxicological studies and appropriate specifications have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from 12 commercial scale batches of the active substance using the proposed commercial route of synthesis are provided. The results are within the specifications and consistent from batch to batch.

2.4.2.4. Stability

Stability data from 3 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was performed on one

commercial scale batch. Results on stress conditions of increased light, heat, humidity, acid & basic hydrolysis, oxidation and exposure to metal ions were also provide on one batch.

The following parameters were tested: appearance (visual), identity (XRPD), assay (HPLC), related substances (HPLC), water content (KF), citric acid (potentiometry), and microbiological quality (Ph. Eur.).

At long term and accelerated conditions, all tested parameters were within the specifications and no significant changes or trends were observed. The photostability results identified an increase in an unidentified impurity not observed in the long term studies, for this reason the active substance should be stored in the light protective packaging of the commercial container closure.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months with the instruction to store in the container closure system to protect from light.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is presented in two strengths which are a 10 mg and 40 mg film-coated tablets, which have the following appearance:

10 mg: White to off white, round tablets with a 6 mm diameter, imprinted with '10' on one side.

40 mg: White to off white, oblong tablets with a length of 14.8 mm and width of 6.3 mm, imprinted with '40' on one side.

2The aim of development was to enable an immediate release formulation which would be acceptable for the intended population of adult and paediatric patients from 12 years old.

The active substance possesses low aqueous solubility and high permeability, it is regarded as a BCS class II active substance. The physical characteristics of the active substance that could impact the performance of the finished product are controlled in the active substance specifications. A suitable specification for the particle size distribution and the solid state form of the active substance are included.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. The excipients are considered suitable in line with the intended paediatric population.

Different finished product formulations were used during the early clinical studies, during the phase 3 studies a change from formulation F1 to formulation F2 took place. This F2 formulation is the formulation proposed for commercial use. A bioavailability study was performed to determine the appropriateness of the F2 formulation, this formulation showed a higher exposure as compared to the F1 formulation. For this reason 40 mg of the active substance in the F2 formulation was shown as equivalent to 50 mg in the F1 formulation. For details of the bioequivalence study performed please refer to the clinical sections of the report.

The discriminatory power of the dissolution method has been demonstrated, the method was shown to be discriminatory with respect to quantitative changes in excipient amounts and differing tablet hardness. The proposed QC method is considered appropriate. The manufacturing process of the active substance and the finished product was developed in conjunction with the clinical program. The

provided dissolution comparisons to support the link between the pivotal and commercial manufacturing processes were initially not acceptable, as insufficient information was provided on the dissolution profiles and values used to support comparability of profiles. An MO was raised concerning this, and to resolve this MO the applicant provided sufficient information concerning dissolution results and in-vitro comparisons. Individual drug release values were presented with relevant mean and RSD values for the three pH conditions used for the comparisons, information was also provided concerning calculations performed to support the dissolution profile comparisons. Following this, the comparability of dissolution profiles between the pivotal clinical and final commercial processes was acceptable from a Quality perspective.

The primary packaging is a white HDPE bottle with a polypropylene (PP) child resistant closure and polyethylene (PE) faced induction heat seal liner including three silica gel desiccants in HDPE canisters. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The manufacturing process consists of several steps: blending, lubrication, compression, coating, imprinting and packaging. The process is considered to be a standard manufacturing process, and is conducted at one proposed manufacturing site.

The manufacturing process is considered to be standard, and the applicant has presented a prospective process validation scheme to be conducted on three consecutive commercial scale batches prior to marketing. The proposed process validation scheme is acceptable.

The proposed in process controls were clearly presented and are acceptable. The proposed bulk product holding time has been validated with stability studies.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form appearance (visual), identification (LC-UV, LC-UV-DAD), assay (LC), degradation products (LC-UV), dissolution (Ph. Eur.), uniformity of dosage units (Ph. Eur.).

The finished product specifications are based on results obtained with clinical and registration batches manufactured to date and according to ICH requirements for film-coated tablets. Overall the proposed specification parameters and limits are considered adequate for the type of dosage form. Degradation products are controlled in line with ICH Q3B requirements and there are no degradation products present above the relevant qualification threshold.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 3 commercial scale batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

The initially provided nitrosamine impurities risk assessment could not be accepted, as it was not clear whether the applicant had taken into account all potential root causes as described in the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products"

(EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). The applicant was asked to update their nitrosamine impurity assessment and to further justify the absence of potential nitrosamine impurities related to known impurities. The applicant was also requested to provide detail of the validation for methods used to screen for potential nitrosamine impurities. An MO was raised on these aspects. The first response provided partially resolved this MO, the risk evaluation was updated and information was provided concerning the validation of methods used to screen for potential nitrosamine impurities. However, the applicant's response indicated that certain nitrosamines of impurities could theoretically form under certain experimental conditions, the MO was therefore maintained and testing data was requested for these potential nitrosamines. To resolve this aspect of the MO the applicant provided justification that these impurities cannot form during the manufacturing process of the active substance or finished product. The applicant outlined that the experimental data to synthesize such impurities required specific additives which would promote and catalyse such reactions, the data provided also showed that such impurities do not form in conditions where these additives are not present. The justification was accepted as the additives in question are not present or relevant to the manufacturing process for the active substance or finished product. Following resolution of this MO it was accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided more than three commercial scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from three commercial scale batches of each strength of the finished product stored for up to eighteen months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance (visual), assay (LC), solid state form (XRPD), degradation products (LC-UV), dissolution (Ph. Eur.), water content (KF), microbiological quality (Ph. Eur.). The analytical procedures used are stability indicating. At both long term and accelerated conditions the product is stable, all results remain within specifications and no significant trends are observed.

With respect to ongoing stability programs: In accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

In addition, one commercial batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results indicate that the product is not sensitive to light.

Based on available stability data, the proposed shelf-life of 30 months without any specific storage conditions as stated in the SmPC are acceptable.

2.4.3.5. Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on the development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

In the course of the procedure four MOs related to quality aspects were raised. For the active substance these concerned the multivariate flexibility proposed for the manufacturing process, and the initially provided justification for one of the starting materials. For the finished product the first objection encompassed the dissolution data provided initially to support the link between the proposed commercial manufacturing process and the clinical manufacturing process. The finished product nitrosamines risk assessment was also initially not sufficiently comprehensive to support the proposed no risk conclusion.

To resolve the MOs connected to the active substance process, the applicant updated the dossier to outline that the flexibility for the manufacturing process will not go beyond the univariate studies performed during development. With regards to the starting material in question the applicant provided acceptable further justification that the selection of the starting material was within the principles of ICH Q11 and steps upstream of its introduction do not impact the active substance. For the finished product, the applicant provided detailed information on the dissolution comparisons used to support the link between the clinical and commercial manufacturing processes. The nitrosamines risk assessment was updated to account for all known and suspected route causes for nitrosamine impurities and following detailed justification supported by experimental data it was accepted that there was no risk of nitrosamine impurities. The MOs connected to the finished product were therefore also resolved.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.4.6. Recommendation(s) for future quality development

Not applicable

2.5. Non-clinical aspects

2.5.1. Introduction

The non-clinical dossier has been developed by the applicant based on the ICH S9 guideline. GLP for the studies provided has been followed only for a part of them. No GLP inspection has been considered necessary.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In the clinical population participating to the clinical trials, the vast majority of the treated patients in the intended indication presented IDH1 mutant isoforms (95%) and IDH2 mutant form (for only for 5%). IDH1R132H is the most common IDH1 mutation (85.8% frequency) then IDH1R132C (4.5% frequency) and few patients are bearing IDH1 R132L/S/G mutant isoforms. For IDH2 mutant isoforms, IDH2R172K mutant isoforms were present in the patient population as well as R172G/W (with a very limited number of patients) (no IDH2R140Q isoforms). Binding affinity of vorasidenib was studied in IDH biochemical system. Vorasidenib is a potent inhibitor against IDH1 mutant isoforms (R132H/C/G/L/S, IC_{50} = 6-34 nM) and IDH1WT (IC_{50} = 190 nM at 1h). When incubation was prolonged (1 to 16h), the affinity towards IDH1WT markedly increased (190 nM after 1h vs 4 nM after 16h) unlike the affinity towards IDHR132H which is not time-dependent. Vorasidenib is also a potent time-dependent inhibitor against IDH2 mutant isoforms (heterodimer forms). Vorasidenib is also a potent time-dependent inhibitor against IDH2WT isoform (IC_{50}= 374 nM at 1h vs 31 nM at 16h). Vorasidenib also inhibited the/an heterodimer enzyme in a time-dependent manner IDH1 WT/R132H, IDH2 WT/R140Q and IDH2 WT/R172K (IC_{50} at nanomolar levels).

It appears evident that vorasidenib could rapidly inhibit the IDH1 R132H enzyme (and other IDH1 mutated isoforms) and the IDH2 mutant isoforms as well as IDH1/2 WT isoforms.

Cellular assays confirmed that vorasidenib inhibited 2-HG production in cells expressing IDH1 and IDH2 mutant forms at low nanomolar level. A lower potency to inhibit 2-HG by vorasidenib was confirmed in cells expressing IDH2R172K vs IDH1 mutant forms.

Vorasidenib induced differentiation in cells where such process was pathologically halted. The restoration of erythroid and myeloid differentiation markers observed after vorasidenib treatment is indicative of the potential of vorasidenib to correct the differentiation blockade. Such effects were demonstrated by the increased expression of hemoglobin and Kruppel-like factor 1 (KLF1) in erythroleukemia cell lines and the presence of cell surface markers CD15 and CD24 in primary acute myeloid leukemia (AML) samples. The development of possible drug resistance process after long-term treatment with vorasidenib was not studied.

The applicant submitted an array of three similar *in vivo* studies investigating the effect of oral vorasidenib administration on 2-HG levels in blood and tumour tissue in mice bearing xenograft tumours formed from subcutaneously injected human chondrosarcoma/fibrosarcoma HT1080 cells (IDH1R132C mutation) or glioblastoma U87 cells (IDH2R140Q) and the third xenograft mice model was based on mice bearing xenograft tumours formed from injected (intra-cranial) human glioma TS603 cells (IDH1R132H). These studies evaluated the inhibition of 2-HG; however, the biological consequences of this suppression were not investigated (e.g. decrease of tumour size). Therefore, it could be considered

that the non-clinical proof-of-concept is limited but in view of the clinical information is not further pursued.

In a HT1080 chondrosarcoma/fibrosarcoma xenograft mice model with an endogenous IDH1R132C mutation (SC inoculation), vorasidenib significantly dose-dependently reduced 2-HG level up to 96.7% at the maximum dose tested of 30 mg/kg (3 oral doses, 12h intervals). The estimated vorasidenib plasma exposure (AUC0-12h) to obtain a 97% decrease of 2-HG in the tumour was 22400 ng.h/mL. In a U87 (IDH2R140Q) glioblastoma xenograft mice model (similar design applied), vorasidenib significantly dose-dependently reduced 2-HG level up to 98.5% at the maximum dose tested of 150 mg/kg (3 oral doses, 12h intervals). The estimated vorasidenib plasma exposure ($AUC_{0\text{-}12h}$) to obtain a 97% decrease of 2-HG in the tumour was very similar than the one observed in the previous model (22600 ng.h/mL).

In an orthotopic TS603 (IDH1R132H) glioma tumour xenograft model (intracranial inoculation), vorasidenib significantly dose-dependently reduced 2-HG level up to 99.98% at the maximum dose tested of 10 mg/kg (6 oral doses, 12h intervals). Vorasidenib was well distributed in the brain tissue and reached the brain tumour with relevant levels to allow an almost complete decrease of 2-HG level. The estimated vorasidenib plasma exposure ($AUC_{0\text{-}12h}$) to obtain a 97% decrease of 2-HG in the tumour was 753 ng.h/mL. This value is 30-fold lower than those obtained in the HT1080 and U97 xenograft models however the study design slightly differed from the two other models.

Vorasidenib is expected to reduce 2-HG by at least 50% in tumours harbouring the IDH1 R132C or IDH2 R140Q mutation, and by greater than 90% in tumours harbouring the most common mutation, IDH1 R132H; therefore, the clinical efficacy could differ depending on the mutation presented by the patient. The activity of vorasidenib and of metabolite AGI-69460 on wild-type IDH1/2 is limited at clinical concentrations.

No patient-derived xenograft model was performed.

Additional PD assays were performed to study the PD activity of AGI-69460. AGI-69460 exhibited nanomolar potency against IDH1 R132H (2-HG inhibition, IC_{50} = 6.709 nM) and IDH1 R132C (2-HG inhibition, IC_{50} = 264 nM) as well as a potency against wild-type IDH isoforms. Vorasidenib was a more potent inhibitor of 2-HG production than metabolite AGI-69460; however, AGI-69460 presented a 4- to 9-fold higher plasma unbound trough concentration compared to vorasidenib and a similar total plasma trough concentration at steady state. The metabolite AGI-69460 is considered as an active metabolite but its participation to overall target engagement is considered limited (see section Clinical Pharmacology).

The pharmacodynamic activity of metabolite AGI-69460 was not tested *in vivo*.

2.5.2.2. Secondary pharmacodynamic studies

In vitro receptor binding assays in a panel of 89 targets demonstrated 92% inhibition of adenosine A3 receptor at 1 µM (vorasidenib) (percent binding inhibition ≥50%). In follow up assays, vorasidenib was assessed for its selectivity to bind adenosine receptors and the transporter, as well as functional activity in GTPγS (guanosine 5'-O-triphosphate) assays. Vorasidenib was shown to bind the adenosine A3 receptor and act as a functional antagonist with an IC_{50} of 1.50 µM. The achieved concentrations systemically and in the brain are approximately 300-fold and 150-fold less, respectively, than the concentration of vorasidenib required to inhibit the adenosine A3 receptor by 50%. Furthermore, in light of the favourable clinical safety data available so far it appears unlikely that binding of vorasidenib to the adenosine A3 receptor is of relevance.

In vitro receptor binding assays in a panel of 89 targets demonstrated 75% inhibition of adenosine A3 receptor at 1 µM (AGI-69460). The achieved unbound metabolite AGI-69460 concentrations systemically

and in the brain are approximately 35-fold and 5-fold less, respectively, than the concentrations of AGI-69460 required to inhibit the adenosine A3 receptor by 72%. No IC50 was determined, and the margins of safety are quite limited in the brain. However, no clinical signs related to central nervous system effects were observed in toxicology studies conducted in rats (including the Irwin test) or monkeys.

2.5.2.3. Safety pharmacology programme

The cardiovascular system was assessed *in vitro* and *in vivo* in monkeys in the pivotal 28-day and 13-week studies. A preliminary hERG study (non-GLP study) demonstrated that vorasidenib inhibited hERG current in dose dependent manner up to 35% at 30 µM. The test was repeated according to GLP requirements and only 2 concentrations were tested (3.1 and 12.3 µM) due to the solubility limit. Similarly, vorasidenib inhibited hERG in dose-dependent manner up to 10 % at 12.3 µM. Based on the results from clinical study AG881-C-004, an IC_{50} value of > 30 µM for vorasidenib for hERG current inhibition is > 3500-fold greater than the unbound human steady-state Cmax at the proposed therapeutic dose of 40 mg daily of vorasidenib (Cmax = 133 ng/ml). AGI-69460 was tested on the hERG channel current to assess potential inhibition of the rapidly activating delayed rectifier potassium current (IKr, GLP study). Results demonstrated a dose dependent inhibition of the hERG current up to 36% at 30 µM. IC_{50} was not calculated but was estimated to be greater than 30 µM. The mean plasma unbound trough concentration prior to the next dose of AGI-69460 at steady state was 27.7 nM on Day 1 of Cycle 10. Given that the IC50 of AGI-69460 was estimated to be greater than 30 µM, the ratio between the human ether-á-go-go related gene (hERG) current inhibitory concentration and the circulating free fraction of the metabolite AGI-69460 will be more than 1000 fold.

ECGs were recorded in 28-day and 13-week toxicity studies in monkeys (GLP studies). An effect on ECG was not observed in the 13-week study up to 20 mg/kg/day. However, in the 28-day study, a marginal but statistically significant QTc prolongation of 32 msec that was noted in a single high-dose (40 mg/kg/day group) male that corresponded to the highest study day 27 Cmax (total Cmax 22 100 ng/ml) which corresponds to330-fold the free C_{max} at the human intended dose.

The CNS system was assessed in a modified Irwin test which was performed in the 28-day study in rat. No test article-related observations or effects on body temperature were noted during this study at day 0 or 27 of the Irwin assessment up to 100 mg/kg/day (> 175-fold the total $AUC_{0\text{-}24h}$ at the human recommended dose).

Only sporadic effects on respiratory function were observed.

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic assessments were conducted during the conduct of the drug-drug interaction PK studies.

2.5.3. Pharmacokinetics

The PK/toxicokinetic (TK) data was collected from BALB/c mice, Sprague-Dawley rats, beagle dogs, New Zealand White rabbits and cynomolgus monkeys studies as well as from *in vitro* studies with relevant human cell types. The *in vivo* administration routes were IV and oral, when the planned administration route in humans is oral.

The PK of vorasidenib was assessed after single-dose administration in mice, rat, dog and monkeys (IV and PO routes). Vorasidenib undergoes rapid oral absorption consistent with high in vitro permeability observed in Caco-2 cells. Oral bioavailability ranged from 6.42% (free base, dog) to 109% (spray-dried

dispersion (SDD) form, monkey). Vorasidenib exposure to plasma in the fed monkeys was higher than that in the fasted monkeys. However, due to poor solubility of the compound and differences in water intake, high variability in absorption and exposure was observed between the individual animal values in the respective studies which makes the results interpretation less reliable. A low total body plasma clearance was observed in mice, rats, and monkeys and a high clearance in dogs as well as a high volume of distribution at steady-state in mice, rats, dogs, and monkeys.

Vorasidenib mean elimination half-life ($t_{½}$) values ranged from 6.4 hours in dogs to 24 hours in monkeys after IV dosing. Vorasidenib mean elimination half-life ($t_{½}$) values ranged from 9.4 hours in mice to 31 hours in monkeys after PO dosing.

PK/TK data was collected for up to 13-weeks (7-day, 28-day, and 13-weeks repeat-dose studies) in rats and monkeys after once daily oral dosing. In rats, no gender differences were observed, accumulation ratios measured up to 4.41 in the 28-day study. Accumulation increased with the doses in the 28-day study and inversely decreased with the doses in the 13-week study (up to 8.53 in males and 6.52 in females at the lowest doses). In monkeys, accumulation ratios were observed up to 4.89 in 13-week study as well as a slight higher exposure was observed in female monkeys (1.89 based on AUC_{0-24}). In the 13-week study in rats, vorasidenib exposure after last dose was dose proportional at 5 and 15 mg/kg/day but increased in less than a dose proportional manner in rats at 50 mg/kg/day dose level. In the 13-week study in monkeys, vorasidenib exposure after the last day of dosing was dose proportional at 2 and 6 mg/kg/day dose, but greater than dose proportional at 20 mg/kg/day dose. The highest dose tested represented in rats 160-fold the human exposure and in monkeys 66-fold the human exposure (based on AUC_{0-24}).

Two PK studies completed the assessment of vorasidenib's brain penetration. In non-tumour bearing animals, brain-to-plasma ratios ranging from 0.624 to 0.720 in mice after a single administration and 1.11 to 1.42 in rats after a single administration. Similar ratios were observed after a 5-day administration in the same animal model. In tumour bearing mice, brain-to-plasma ratios were 0.95 to 1.96 (PD xenograft mice model). In monkey toxicity studies, brain-to-plasma ratios were observed up to 2.43 after 28-day administration and 2.12 and after 13-week of dosing. The tissue distribution study in male rats after a single PO administration of [^{14}C]vorasidenib confirmed a rapid brain penetration at similar plasma/blood level.

Vorasidenib had a mean plasma protein binding of >94% in all species and did not show any notable interspecies differences or non-linearity in binding. After identification of human metabolite AGI-69460, additional protein binding assays were performed in human plasma. The unbound fraction in human plasma for AGI-69460 is largely higher (13%) than the unbound fraction of vorasidenib (2.66%). The unbound fraction of AGI-69460 in the five tested animal species was higher than the one for vorasidenib, as observed in humans. The highest unbound fraction of AGI-69460 was observed in monkeys (20-28%).

Red blood cell (RBC) partitioning coefficient values of vorasidenib were 0.23, 0.15, 0.13, 0.22, and 0.22 in human, monkey, dog, rat, and mouse, respectively.

The tissue distribution study in male rats after a single PO administration of [^{14}C]vorasidenib showed that the drug-derived radioactivity was quickly absorbed and distributed to tissues and eliminated slowly from the body. Approximately 63% of the assessed tissues were above the lower limit of quantification at 504 hours post-dose. Vorasidenib was largely distributed to tissues; in particular vorasidenib distributed in fat (ratio tissue/plasma up to 32), in the gastrointestinal tract especially in large intestine (up to 12), in adrenal cortex/gland (up to 10) and in the bile. No distribution study was performed in female rats.

Distribution of metabolite AGI-69460 into the tissues was not studied. Although the free concentration of AGI-69460 is higher than vorasidenib in plasma, vorasidenib and its metabolite AGI-69460 were present in the brain tumour at equimolar concentration (see section 2.6.2. Clinical Pharmacology)

The metabolism of vorasidenib was investigated in several *in vitro* studies and one *in vivo* rat study. Additionally, plasma samples obtained from toxicity studies in mouse, rats and monkeys were also tested. *In vitro*, a low turnover of vorasidenib was observed in liver microsomes and hepatocytes from multiple species, including humans. *In vitro* metabolites identification study revealed a species' difference in the metabolism of vorasidenib.

In addition, the human metabolite M458 (AGI-69460) was firstly identified later during the clinical development (study AG881-C-005). In human plasma, metabolite AGI-69460 accounted for 9.10% and 43.9% of the total radioactivity for pooled $AUC_{0\text{-}72hr}$ and $AUC_{96\text{-}336hr}$ plasma (study AG881-C-005). The geometric mean metabolite to parent molar ratio of trough concentrations at steady state levels was 1.17. The observed Cthrough in patients was 128 +/- 71.8 ng/ml. The activity of vorasidenib and AGI-69460 on wild-type IDH1/2 is limited at clinical concentrations. AGI-69460 is likely a downstream metabolite of the deschloro GSH conjugate of vorasidenib that undergoes hydrolysis to thiol, subsequent methylation and oxidation to deschloro-methyl sulfone likely via a combination of hepatic and extrahepatic pathways. Two dedicated PK studies were performed in rats and in monkeys. Vorasidenib was administrated to male rats at 30 mg/kg and to male monkeys at 20 mg/kg for 7 days, and vorasidenib and its metabolite AGI-69460 were measured at D1 and D7. Results demonstrated that AGI-69460 was detected in both species. AGI-69460 was late forming as observed in human. It was present only at maximum 0.32% in rat and 4.5% in monkeys (comparison metabolite/parent based on $AUC_{0\text{-}last}$). The observed $T_{1/2}$ of AGI-69460 was very long (113h in the rat and 102h in the monkey versus vorasidenib rat: 30h and 23h in monkey). AGI-69460 was measured in the animal study performed after its identification: micronucleus in rat and embryofetal development (EFD) studies in the rat and in the rabbit. In the micronucleus study in the rat (2 administrations separated from 24h), AGI-69460 was also observed at very low levels (up to a maximum of 0.15% based on $AUC_{0\text{-}24}$). Finally, AGI-69460 was measured in EFD studies. Exposures to AGI-69460 was also very low compared to the parent maximum 1% in rats and up to 30% in rabbits on GD19 (based on $AUC_{0\text{-}24}$). Accumulation was observed with the metabolite AGI-69460 up to 38% in the rabbit, probably explained by the long half-life observed and/or distribution of the metabolite.

Additional experiments indicated that rats, monkeys and rabbits presented low exposures to AGI-69460 when compared to the parent. However, after 7-day exposure, monkeys were exposed to the metabolite AGI-69460 at a similar range than those observed after clinical exposure at the intended dose. Given the accumulation observed in monkeys, the metabolite AGI-69460 was qualified in the 13-week study in monkeys. In rats, the exposure to the metabolite after 7 days of dosing (at a lower dose than used in the 13-week study), is only 0.2-fold the human exposure. In the EFD rat study after 17 days of dosing the exposure was 0.6-fold the human exposure. This was reached at a higher dose (75 mg/kg/day) than used in the 13-week study (50 mg/kg/day). However, it can be assumed that after accumulation of the metabolite after 1 week of dosing >0.5-fold exposure compared to human is reached, which is in line with the requirements of the ICH M3 guideline.

In the bile excretion study, at least 62.7% of the compound appears to have been systemically absorbed (61.0%±11.7% of radioactivity identified in the bile, 1.77±0.31% in urine). This is higher than the reported bioavailability of 53.8±2.23% in rats. The difference in bioavailability observed in the two rat studies is probably caused by the use of different formulations (free base in 10% VE-TPGS, 1% HPMC-AS, and 0.1% simethicone in water, versus free base in 0.5% methylcellulose with 0.2% Tween 80 in water), which causes a difference in solubility and thus absorption.

2.5.4. Toxicology

The non-clinical toxicology program has been designed according to the ICH S9 guideline recommendations. The non-clinical toxicity studies were conducted via oral gavage in rats and monkeys as the intended route of administration in patients. Rat and cynomolgus monkey were selected as standard species and due to their metabolite profiles to assess the safety profile of vorasidenib. The safety evaluation included 28-day and 13-week repeat-dose toxicity studies in Sprague-Dawley rats and cynomolgus monkeys, a complete genotoxicity assessment through *in vitro* bacterial reverse mutation assay, human peripheral blood lymphocyte micronucleus assay and *in vivo* micronucleus assay. Dose range-finding (DRF) and definitive embryo/foetal development studies in Sprague-Dawley rats and New Zealand White rabbits were also performed. An ototoxicity study to assess both functional and morphological effects on the auditory system as well as phototoxicity was also carried out. Evaluation of two impurities (AGI-29365 and AGI-64635) and metabolite AGI-69460 were also performed. During the *in vivo* nonclinical toxicology program, vorasidenib was administered by oral route supporting the therapeutic mode of administration in patients.

2.5.4.1. Single dose toxicity

No single toxicity study was performed in rats and monkeys. Indeed, one TK study (non-GLP) was performed to evaluate the TK profile in monkeys after single administration (2M+2F/group). Only physical administration and body weight were examined in this study. Vorasidenib was well tolerated after single dose administration up to 80 mg/kg in monkeys. General acute toxicity information can be obtained from the GLP repeat-dose toxicity studies in rats as well as monkeys.

2.5.4.2. Repeat dose toxicity

Non-pivotal studies in rats (7-day studies)

Three preliminary studies in rats were performed by oral administration for 7 days.

Firstly, vorasidenib was administrated twice a day in rats at dose of 0.1, 1, and 5 mg/kg/dose equivalent to 0.2, 2, and 10 mg/kg/day. No adverse findings were observed up to 10 mg/kg/day.

A second 7-day repeat-dose study in rats was performed to test higher doses following a similar administration scheme (BID, 12h apart): 2×15, 2×50, 2×150, and 2×500 mg/kg/dose equivalent to 30, 100, 300, and 1000 mg/kg/day. The maximum tolerated dose (MTD) was determined to be at 30 mg/kg/day. Indeed, dose levels ≥100 mg/kg/day exceeded the MTD, leading to mortality, severe clinical observations, clinical pathology related alterations and effects on body and organ weights as well as food consumption.

A third 7-day repeat-dose study in rats was performed to study single daily administration in two different vehicles: vehicle 1: 0.5% MC/1% HPMC-AS/0.1% simethicone in deionized water and vehicle 2: 10% vitamin E TPGS/1% HPMC-AS/0.1% simethicone in deionized water. Vorasidenib was administrated at 50, 100, 200 mg/kg/d (formulated with vehicle 1). The choice of the tested doses is not clearly understood as the MTD determined in the previous study was 30 mg/kg/day. However, rats treated with vorasidenib formulated in the vehicle 1 was well tolerated. Indeed, at dose levels of 50 and 100 mg/kg/day for 6 days, animals presented no findings and animals treated at 200 mg/kg/day (vehicle 1) presented non-adverse test article-related effects on clinical observations, body weights, and food consumption. However, a 5-day treatment with vorasidenib formulated in vehicle 2 was not tolerated and resulted in moribundity at 200 and 400 mg/kg/day in females and 400 mg/kg/day in males. No explanation regarding the difference in resulting toxic findings between the two vehicles tested at 200 mg/kg/d was provided and no TK analysis was performed.

Pivotal studies in rats (28-day and 13-week studies)

The toxicity profile of vorasidenib was first determined in a 28 days GLP study in rats (with 14-day recovery period). Vorasidenib was administrated once a day in rats at doses of 3, 10, 30 and 100 mg/kg/day. Vorasidenib was supplied as vorasidenib/HPMC-AS (1:1 w:w) in the vehicle (10% vitamin E TPGS/1% HPMC-AS/0.1% simethicone in deionized water). Test article-related morbidity/mortality and significant toxic clinical signs were noted at 100 mg/kg/day (cause of death: body weight loss and gastrointestinal (GI) tract toxicity). This dose of 100 mg/kg/day was identified as the severely toxic dose that resulted in 10% lethality (STD_{10}).

Both the test article and excipient produced local irritation in the stomach. Excipient-related changes were evidenced as higher incidences and/or severities of mixed cell inflammation in the glandular stomach compared to the vehicle control group. Test article-related changes were erosion, submucosal oedema, and exacerbation of mixed cell inflammation of the glandular stomach; erosions, neutrophilic infiltrates, and mucosal hyperplasia in the duodenum adjacent to the pylorus; and higher incidences of ulcers, erosions, squamous epithelial degeneration, limiting ridge hyperplasia, and subacute inflammation in the non-glandular stomach compared to the vehicle control and control article-treated groups. GI tract toxicity was observed in all test article-treated groups at doses (≥ 3 mg/kg/d, 7-fold over the human exposure), the analysis at the end of the 14-day recovery period showed only partial recovery. Test article-related changes in the middle ear were minimal to mild neutrophilic infiltrates in all test article treated groups at primary necropsy. Minimal vacuolated macrophages and luminal inflammatory exudates in all the test article-treated groups and in control article-treated group males were considered excipient effects. The neutrophilic infiltrates were consistently present at or adjacent to the opening of the Eustachian tube, consistent with irritation ascending from the oropharynx. These histological findings of the middle ear inflammation were similar to those previously reported. No ear findings were reported in at the end of the recovery period. In a previous rat DRF study, minimal, multifocal necrosis of the granular cells of the main olfactory bulb of the brain was noted at 100 mg/kg/day. A similar change was observed in the control article-treated and test article-treated animals in the current study, and was determined to be an artefact. Hepatocellular hypertrophy was observed at dose levels ≥10 mg/kg/day, an analysis at the end of 14-day recovery period showed only partial recovery. Epidermal hyperplasia and sebaceous gland hypertrophy were observed only at the highest dose of 100 mg/kg/day and were not observed at the end of the recovery period. Vorasidenib impaired male and female reproductive tracts. In males, tubular degeneration in the testis and luminal cellular debris in the epididymis at 100 mg/kg/day, epithelial atrophy in the prostate at ≥30 mg/kg/day and in the seminal vesicles at ≥10 mg/kg/day were observed. In females, loss of oestrous cyclicity was observed at ≥3 mg/kg/day and at doses ≥100 mg/kg/day, decreased corpora lutea in the ovaries, atrophy of the uterus, cervix and vagina, and mucification of the cervix and the vagina were observed. All other excipient-related and test article-related microscopic and microscopic observations and organ weight changes were no longer apparent. To conclude, the target organs of vorasidenib's toxicity identified in the 28-day rat study were GI tract, middle ear, male and female reproductive organs and skin. No NOAEL was determined.

A 13-week repeat-dose toxicity study was conducted in male and female Sprague-Dawley rats treated with vorasidenib to confirm the toxicity profile determine in the 28-day study. Dose levels were 5, 15 and 50 mg/kg/day, a recovery period of 4 weeks was added. Vorasidenib supplied as vorasidenib/HPMC-AS (1:1 w:w) in the vehicle (10% vitamin E TPGS/1% HPMC-AS/0.1% simethicone in deionized water) was administered once daily via oral gavage. Administration of 50 mg/kg/day vorasidenib was not tolerated with early termination of 9 animals between Days 49 and 90. A definitive cause of moribundity was not determined; however, vorasidenib-related findings such as body weight loss, skeletal muscle atrophy, and/or renal tubular degeneration were considered to have contributed to the deteriorating conditions. Mid-dose level of 15 mg/kg/day was considered as the MTD. Vorasidenib related microscopic

observations were noted in the liver, kidney, skeletal muscle, skin, mammary gland and male and female reproductive tracts at ≥ 5 mg/kg/day, in the urinary bladder in females at 50 mg/kg/day. Several isolated findings were observed at 50 mg/kg/day in single animals and were possibly related to vorasidenib treatment: erosion/ulcer in the glandular stomach in one male, mild degeneration/necrosis of the wall of a coronary artery in an early death male, and cardiomyocyte vacuolation in one high dose female.

The recovery of the observed toxic findings was assessed after a 4-week treatment-free period. At recovery necropsy, no toxicity was observed in urinary bladder indicating a full recovery. Only partial recovery was observed for atrophy of the skeletal muscle, atrophy of the mammary gland in male rats, centrilobular hepatocyte hypertrophy, mammary gland and male and female reproductive organs. At the end of the recovery period, microscopic changes observed in the kidney were still observed in females with similar incidence and/or severity, thus not considered reversible.

No NOAEL was set as vorasidenib related findings were observed at all dose levels.

A chronic study was not performed and AGI-69460 was not measured in pivotal rats studies.

Non-pivotal study in monkeys (7-day study)

One preliminary study in monkeys was performed by oral administration for 7 or 10 days. Vorasidenib was administrated once daily in monkeys at dose of 0, 1, 10, 50 and 100 mg/kg/day. The highest tested dose of 100 mg/kg/day was not tolerated. The dose of 50 mg/kg/day was tolerated over a 10-day dosing period and clinical observations were limited to slight tremors. The NOAEL was determined at 50 mg/kg/day by the applicant. Even this dose was tolerated, it could not be set as a NOAEL given the observed adverse effects. In fact, 50 mg/kg/d was considered as the MTD.

Pivotal studies in monkeys (28-day and 13-week studies)

Two pivotal repeated-dose toxicity studies were conducted in cynomolgus monkeys with vorasidenib (GLP studies). The dosing schemes were 0, 3, 10 and 40 mg/kg/day in a 4-week study and 0, 2, 6 and 20 mg/kg/day in a 13-week study. No chronic study was performed. TK analysis were conducted for all the repeat-dose studies at all dose levels. The NOAEL could be set at 3 mg/kg/day in the 4-week study and at 2 mg/kg/day in the 13-week study.

The target organs of vorasidenib's toxicity identified in monkeys were the liver, adrenal cortex, bone marrow and thymus. Indeed, liver toxicity was identified from both pivotal toxicity studies in monkeys (28-day and 13-week studies). A minimal to mild hepatocellular hypertrophy correlated to an increase in hepatic enzymes and an increase of liver weight were observed from 6 mg/kg/day after a 13-week administration, which were fully reversible. A minimal Kupffer cell hyperplasia was observed at 20 mg/kg/day at the primary necropsy (3/4M+3/4F). After 4-week of recovery, this finding did not reverse. Indeed, minimal Kupffer cell hyperplasia was observed in one female at 6 mg/kg/day, 2 males and 1 female at 20 mg/kg/day and a mild Kupffer cell hyperplasia was observed in one female at 20 mg/kg/day. These findings were observed at 8-fold the clinical exposure, worsened during the recovery period and could be of particular interest for identifying carcinogenic potential. The mechanism of this toxicity seems not known.

A mild to moderate decrease in zona fasciculata vacuolation in the adrenal cortex was observed in the 10 and 40 mg/kg/day males and females after 28-day administration. The recovery at 40 mg/kg/day is difficult to interpret given that only one female was left in the recovery group at 40 mg/kg/day which was treated only for 14 days; however, no toxic finding persisted in the 10 mg/kg/day group and at similar exposure or above this finding was not observed after a 13-week exposure. A minimal bone marrow depletion (sternum bone marrow) was in a single 40 mg/kg/day female and was not observed in the 13-week study. Thymic lymphoid depletion was observed in all males at the high dose and still

observed at the end of the recovery period in only one female (40 mg/kg/day, 30-fold the clinical exposure) but was not observed after longer duration treatment.

A NOAEL was set at 2 mg/kg/day in the 13-week study. The safety margins obtained were around 2.

2.5.4.3. Genotoxicity

A standard test battery was performed according to ICH S2 guideline. Vorasidenib was tested in gene mutation in bacteria and chromosome/genome mutation in mammalian cells and male Sprague Dawley rats. Vorasidenib was detected in the plasma but bone marrow exposure was not confirmed in this study; in a biodistribution study vorasidenib was distributed in the bone marrow. Standard tests with vorasidenib did not show any evidence for a relevant genotoxic potential. Vorasidenib exposure in the plasma of rats at the lowest dose was >100-fold (Cmax or AUC0-24) the human exposure at the intended recommended human dose.

Metabolite AGI-96460 was negative in the Ames test up to the maximum recommended dose in the current ICH S2 guideline (5000 µg/plate). AGI-69460 was measured in rat plasma in the in vivo micronucleus test. AGI-69460's concentrations in the rat micronucleus study were lower than the concentration detected at steady state in human (max 0.2-fold the human Cthrough at steady state). Therefore, AGI-69460's exposures detected in the micronucleus study in rats with vorasidenib administration were insufficient to consider the assessment of AGI-69460's genotoxicity potential as relevant. The genotoxicity potential of AGI-69460 was further characterized in dedicated studies (see below).

2.5.4.4. Carcinogenicity

Two-year carcinogenicity in rats and 26-week in transgenic mice studies were not conducted.

2.5.4.5. Reproductive and developmental toxicity

Embryo-foetal development studies were performed in Sprague-Dawley rats and New Zealand White rabbits. In rats, developmental toxicity consisted in drug-related visceral malformations (malpositioned kidneys and testis) and embryo-foetal lethality at 75 mg/kg. At this dose, AUC-levels determined on GD6 and GD17 were 39- to 108-fold higher than those in humans, respectively. In addition, foetal weight decreases greater than 10% vs. concurrent controls associated with delayed ossification were noted from the dose of 25 mg/kg, and considered adverse. A dose-related increased incidence of short 13th ribs was also reported in all treated groups and considered as non-adverse. Overall, the developmental NOAEL was set at 10 mg/kg/day which corresponds to a safety margin ranging from 8.0 to 28.5 based on AUC values determined on GD6 and GD17, respectively.

In rabbits, embryo-foetal lethality was reported at the high maternal-toxic dose level of 18 mg/kg corresponding to 3.8- to 10.9-fold AUC levels in humans on GD6 and GD19, respectively. Decreased foetal weights with related delayed ossification were noted from 6 mg/kg. These effects were considered related to effects on maternal animals, although no significant maternal toxicity was observed at 2 and 6 mg/kg. At these dose levels, foetal weights were decreased by <5% vs. controls (2.9% and 4.4% at 2 and 6 mg/kg, respectively, sexes combined) whereas the effect was more pronounced at 18 mg/kg (8.1%). In addition, there was no significant treatment-related effect on gravid uterus weight. Therefore, the developmental NOAEL of 6 mg/kg/day is endorsed. At this dose level, exposure ratios ranged from 1.1 to 4.9 based on AUC levels measured on GD6 and GD19, respectively, leaving a low safety margin.

The exposure ratios at the NOAEL for embryo-foetal development in rats and rabbits were 1.6 and 0.4, respectively.

2.5.4.6. Toxicokinetic data

See section 2.5.4.2 Repeat-dose toxicity.

2.5.4.7. Local tolerance

The intended route of administration is oral. The gastrointestinal tract was evaluated in all repeat-dose toxicology studies in Sprague-Dawley rats and cynomolgus monkeys. No dedicated local tolerance testing was conducted. A severe GI tract toxicity was observed in the 28-day rat study.

2.5.4.8. Other toxicity studies

Metabolite AGI-69460

AGI-69460 was not detected in previous *in vitro* and *in vivo* PK studies and was not measured in pivotal toxicity studies, since these non-clinical studies were already performed. Therefore, after 2020, the non-clinical package was completed with dedicated non-clinical studies with AGI-96460 (PD and PK studies (see data above), Ames test and hERG assay) and AGI-69460 was measured in micronucleus in rats and in EFD studies in rats and in rabbits.

hERG assay: AGI-69460 was tested on the hERG channel current to assess potential inhibition of the rapidly activating delayed rectifier potassium current (IKr, GLP study). Results demonstrated a dose dependent inhibition of the hERG current up to 36% at 30 µM. IC_{50} was not calculated but was estimated to be greater than 30 µM. A margin of safety based on unbound Cmax of AGI-69460 needs to be specified when human AGI-69460 Cmax will be available.

Genotoxicity: AGI-96460 was negative in the Ames test up to the maximum recommended dose in the current ICH M7 guideline (5000 µg/plate). Two additional studies were performed to complete the standard genotoxicity battery according to ICH S2. An in vitro micronucleus test was performed and submitted, negative results were obtained. In addition, the additional data (QSARs prediction for the parent and its metabolite AGI-69460) indicated the absence of mutagenicity which is already known as a negative AMES test was submitted earlier. A combined in vivo micronucleus test and Comet assay (liver) was conducted in rats according to GLP requirements. AGI-69460 (batch) was administrated at 250 (low dose (LD)), 500, 750 and 1000 (high dose (HD)) mg/kg/day once daily for 3 days by oral gavage to SD rats (6/sex/main group +3/sex/TK group). Negative and positive control groups were added. A TK analysis was performed (all doses except LD group). This study could be considered as GLP compliant. No mortality was observed during the study. Clinical signs were observed (hunched posture, eyes partly closed, decrease activity) more pronounced in females than males (higher exposure in females). A decrease in body weight gain was observed in all AGI-69460 treated groups, up to -16.1% in males and -13.3% in females at 750 mg/kg/day. AGI-69460 was measured in blood and bone marrow samples confirming the systemic exposure to AGI-69460 and in the target organ (bone marrow). AGI-69460 was not cytotoxic in the bone marrow. Negative genotoxic results were observed in the bone marrow and in the liver. The exposure at the highest dose tested 1000 mg/kg/day were 1385 µg.h/ml (AUC24) and 66 650 ng/ml (Cmax). Only limited preliminary human PK parameters are available (Cthrough in patients was 171 ng/ml, study AG881-C-004). The highest dose in rats represents 390-fold the human exposure. Therefore, it could be concluded that AGI-69460 was confirmed to be non-genotoxic at concentrations largely higher than the clinical exposure.

Carcinogenicity: no carcinogenicity study with AGI-96460 has been performed.

Impurities

The following 4 specified impurities were identified in the drug substance: AGI-28998, AGI-29361, AGI-29360, and AGI-23089. These 4 impurities were present in pivotal toxicity studies in rats and monkeys at 0.13%, 0.10%, 0.16% and 0.56% respectively. NOEALs were determined only in monkeys. After a 28-day administration, the observed NOAEL was determined at 3 mg/kg/day; therefore the 4 mentioned impurities could be considered qualified at HED = 0.0012 mg/kg/d for AGI-28998, 0.001 mg/kg/d for AGI-29361, 0.0015 mg/kg/day for AGI-29360 and at 0.0054 mg/kg/d for AGI-23089. The 4 following impurities could be considered qualified at 0.15% for AGI-29361 and AGI-29360, AGI-23089 at NMT 0.5%, and AGI-28998 is now controlled under the unspecified impurities at 0.10%. Two Ames tests were conducted since alert structure was detected for the two following impurities: AGI-29365 and AGI-64635. No mutagenicity potential was observed in both test results.

Phototoxicity

Vorasidenib showed some light absorption with maximum absorption at a wavelength of 215 nm and 281 nm but does not bind to melanin. The phototoxic potential of vorasidenib was examined in BALB/c 3T3 mouse fibroblasts. All OECD 432-recommended cell survival and OD540 criteria and promethazine cytotoxicity and phototoxicity criteria were met, indicating that the assays were valid. Vorasidenib demonstrated no phototoxic potential in the in vitro neutral red uptake (NRU) phototoxicity test with BALB/c 3T3 mouse fibroblasts.

Ototoxicity

In 7-day DRF study in rat, acute inflammation of the middle ear was observed at 30 and 100 mg/kg/day (only these two doses were assessed in histopathology) as minimal neutrophilic infiltrates in the tympanic cavity.

A dedicated 28-day ototoxicity study was performed in male rats in parallel to the 28-day pivotal rat study (same administration dates, same doses administrated, same vehicle, 2 different CRO, only males tested in the ototoxicity study). Vorasidenib was administrated at doses levels of 3, 10, 30 and 100 mg/kg/day. A 14-day recovery period was added. Vorasidenib was administered in the vehicle (10% vitamin E TPGS/1% HPMC-As/0.1% simethicone in deionized water) once daily.

Vorasidenib administered at 30 and 100 mg/kg/day (62- and 174-fold the clinical exposure range) resulted in potential test article-related macroscopic findings of brown foci in the temporal bone, foreign material in the oval window, and oedema in the tympanic cavity. These findings were without microscopic correlate. Vorasidenib administered at 10, 30, and 100 mg/kg/day (27-, 62- and 174-fold the clinical exposure range) produced a reversible non-adverse microscopic finding of minimal neutrophil infiltration of the epithelial lining of the middle ear and Eustachian tube (otitis media). There were no vorasidenib-related effects on ABRs, otoscopic examinations, cytocochleograms, utricle hair cell density, or macroscopic or microscopic pathologies of the brain, cochlear nerve, or spiral ganglion.

Ear findings observed in parallel in a 28-day study were limited to the observation of neutrophilic infiltrates in the mucosa/submucosa at all dose groups which were not observed at recovery necropsy. No ear findings were observed in 13-week in rats and in repeated-dose monkeys' studies. Only 2 otitis were observed amongst 244 treated patients.

The toxicological significance of the ear findings observed in the rat preliminary study and 28-day rat study was ruled out.

2.5.5. Ecotoxicity/environmental risk assessment

Table 6. Summary of main study results

Substance (INN/Invented Name): vorasidenib			
CAS-number (if available): 2316810-02-1			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 123	t.b.d.	t.b.d.
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{sw,refined}$	0.0052	µg/L	≥ 0.01 threshold: N
Other concerns (e.g. chemical class)			N

2.5.6. Discussion on non-clinical aspects

Pharmacodynamics

Vorasidenib at the clinical intended dose could inhibit IDH1 and IDH2 mutant forms. Vorasidenib inhibited 2-HG production in cells expressing IDH1R132C, R132G, R132H and R132S mutations as well as IDH2R140Q. The development of a possible drug resistance process after long-term treatment with vorasidenib was not studied. AGI-69460 is an active metabolite but its participation to the overall target engagement is limited.

In vivo experiments confirmed that vorasidenib caused an inhibition of 2-HG production in vivo, however, inhibition of the tumor growth was not studied. This lack is mentioned in SmPC section 5.1. In vivo studies in xenografted mice model suggested that the clinical efficacy could differ based on the mutation presented by the patient.

Furthermore, in light of the favourable clinical safety data, so far it appears unlikely that binding of vorasidenib to the adenosine A3 receptor, as putatively detected in secondary pharmacology studies, is of relevance.

A low potential for QT prolongation was predicted after vorasidenib's administration although a dose dependent inhibition in the hERG assay and one male animal presenting an QTc prolongation were observed. A low potential for QT prolongation was predicted for AGI-69460.

Respiratory function assessment in the pivotal toxicity studies demonstrated only sporadic incidents. The lack of a dedicated study could be considered acceptable given the current significant clinical experience.

Pharmacokinetics

The methods of analysis described in the dossier were considered adequate and suitable for the purpose.

The tissue distribution study was performed only in male rats after a single PO administration of [14C]vorasidenib. Rat and monkey could be considered as relevant species for toxicity studies even the bias in determining it.

The in vitro study showing the difference in metabolite profile within different species was performed after the in vivo study which identified the metabolites profiles of vorasidenib in plasma samples of mouse, rat, and monkey were collected for the ongoing toxicity study. Therefore, the performance of this in vitro study is not completely understood. The toxicity program was already ongoing (pivotal 28-day in rats and dogs report signed in 2015) when metabolites identification was studied. The choice of the animal species for the pivotal studies was therefore not determined based on metabolism profile. The monkey shows more extensive metabolism of vorasidenib than the mouse and the rat. The

justification that the monkey species was chosen based on the similar metabolic profiling is not considered acceptable. However, dogs demonstrated to be not a better relevant model based on PK profile comparison (animal vs human). Therefore, the use of monkeys could be understood. The primary pathway of vorasidenib's metabolic clearance in humans could be considered to be covered by rats; therefore, the choice of the rat as a metabolic relevant species could be understood. CYP1A2 appears as the primary contributor to the human metabolism but no data in the rat was submitted.

The human metabolite M458 (AGI-69460) was firstly identified later during the clinical development (study AG881-C-005). AGI-69460 was not detected in previous in vitro and in vivo PK studies and was not measured in pivotal toxicity studies, as already performed. Only limited PK results are available. AGI-69460 is likely a downstream metabolite of the deschloro GSH conjugate of vorasidenib that undergoes hydrolysis to thiol, subsequent methylation and oxidation to deschloro-methyl sulfone likely via a combination of hepatic and extrahepatic pathways. The observed T1/2 of AGI-69460 was very long (113h in rat and 102h in monkey versus vorasidenib rat: 30h and 23h in monkey). Accumulation was observed with the metabolite AGI-69460 up to 38% in rabbits, probably explained by the long half-life observed and/or distribution of the metabolite.

It can be assumed that after accumulation of the metabolite after 1 week of dosing >0.5-fold exposure compared to human is reached, which is in line with the requirements of the ICH M3 guideline.

The biliary route was the major route of excretion; urinary excretion was a minor excretion pathway.

Toxicology

The applicant has submitted a non-clinical package according to the recommendations mentioned in the ICH guideline S9; however, given the long-life expectancy of the patients the claimed indication does not fall under the scope of the ICH S9 guideline. Since the current clinical experience (more than 136 patients are treated for more than 12 months of which 79 are treated for more than 24 months) could be considered sufficient and in accordance with the 3R's principles, no chronic toxicity studies will be requested.

The human metabolite AGI-69460 was firstly identified later during the clinical development and was not measured in pivotal animal studies AGI-69460 is an active metabolite contributing to the overall target engagement, but its participation is limited (up to 10%). It can be concluded that exposure was sufficient in the 13-week toxicity studies in rats (0.5-fold) and monkeys (slightly higher than clinical exposure).

The main target toxicities identified during repeat dose toxicity studies concern liver, gastrointestinal tract, skin, kidney, skeletal muscle, reproductive organs and mammary gland.

No NOAEL was set as vorasidenib related findings were observed at all dose levels. Therefore, all toxic effects observed at the lowest tested dose (5 mg/kg/day corresponding animal-to-human exposure ratio of 26-fold) could be considered of particular interest. Indeed, no threshold for these observed toxic effects could be determined and therefore these finding could be considered as clinically relevant. The mechanisms involved in these toxicities were not investigated or discussed therefore a description of these effects are reported in the RMP as clinically relevant as well as in section 5.3 of the SmPC.

The toxicity observed though the toxicity studies performed in monkeys (7-days, 28 days and 13-week studies) was coherent. Liver was the primary target organ identified. A NOAEL was set at 2 mg/kg/day in the 13-week study. The safety margins obtained was around 2. In this 13-week study, a concern is raised by the observation of Kupffer cell hyperplasia which is not reversible and even worsened in the recovery group, this concern is mentioned in the sections 4.4 and 5.3 of the SmPC.

GI tract is a target organ of vorasidenib but the exact mechanism of action for IDH1-related gastrointestinal toxicity is not clear. Gastrointestinal toxicity is commonly described in patients treated with IDH inhibitors and is reflected in the RMP (non-clinical part).

Skin toxicity (epidermal hyperplasia and sebaceous gland hypertrophy) was observed at high doses. Conclusion regarding the reversibility of epidermal hyperplasia could not be clearly drawn from the available data. It is acknowledged that skin toxicity secondary to treatment with IDH inhibitors have been described in the literature. As mentioned in the clinical part, skin toxicity is not considered as a particular concern from clinical experience to date. No effect was observed in treated cynomolgus monkeys.

Effects on reproductive organs were seen in male and female rats during repeat-dose toxicity studies. Reversibility was not demonstrated, and no safety margin could be derived for these effects since they were observed already from the low dose level. Risk minimization measures have been implemented in sections 4.4 and 4.6 of the SmPC consisting notably in cryopreservation of sperm of patients planning to conceive a child prior to initiation of treatment. This is viewed as acceptable for male patients considering the testicular toxicity (tubular degeneration) shown in male rats without proven reversibility and safety margin. This concern is mentioned in section 4.6 of the SmPC.

Minimal and mild atrophy of mammary gland was observed in male and female rats treated with vorasidenib. The toxic findings in mammary gland were restricted in males at doses $\geq$ 15 mg/kg/day. This finding seems reversible in females, nevertheless, atrophy was observed in low dose male group (5 mg/kg/day) at recovery necropsy. The high incidence of this finding in the control group is misleading the dose dependant effect observed in males and in females and has conducted to not study the finding in low and mid-dose groups in females. A test article related effect could not be ruled out. This target organ has therefore been added in section 5.3 of the SmPC in the list of target organs; the clinical relevance has been included in the RMP. No effect was observed in treated cynomolgus monkeys.

In the 13-week toxicity study in rats, skeletal muscle atrophy consistent with a neurogenic origin was observed from 5 mg/kg/day dose level. 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. 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. As no NOAEL was determined in this study, no threshold could be determined for this toxicity. The mechanism of the toxicity is not discussed. This is reflected in the RMP. No effect was observed in treated cynomolgus monkeys.

Vorasidenib led to hepatic effects at the lowest or tolerated doses tested in rats and monkeys during repeat-dose toxicity studies. These effects appear in monkeys at 8-fold the human exposure associated with liver enzyme elevation, whereas no threshold was determined in rats as no NOAEL was determined. The effects were reported as restricted to signs suggestive of hepatic enzyme induction (higher liver weights and hepatocellular hypertrophy) without hepatocellular degeneration or necrosis. However, in the 13-week monkey study, a minimal Kupffer cell hyperplasia was observed at 20 mg/kg/day at the primary necropsy (3/3M+3/4F). After 4-week of recovery, this finding did not reverse. These findings were observed at 8-fold the clinical exposure. The exact mechanism is not known, and the issue has not been further discussed. These findings are reported in the SmPC section 5.3.

The lack of longer term toxicity data for metabolite AGI-69460 is not considered acceptable considering that the claimed indication does not fall under the ICH S9 guideline. Formation and accumulation of AGI-69460 is slow in humans, and therefore significant long-term exposure is limited. Since no safety concern was detected in significant clinical experience (more than 136 patients were treated for more than 12 months of which 79 were treated for more than 24 months), dedicated chronic toxicity studies of AGI-69460 are not considered required.

Vorasidenib was not genotoxic in the standard battery of tests. AGI-69460 concentrations detected after vorasidenib administration were far lower than the AGI-69460 concentration detected in human; therefore, AGI-69460 genotoxic potential was further characterized. AGI-69460 was not mutagenic. The in vitro micronucleus test with the metabolite AGI-69460 showed negative results. A combined in vivo

MN test and Comet assay (liver) was conducted with the metabolite AGI-69460 in rats according to GLP requirements and negative genotoxic results are confirmed up to 1000 mg/kg/day (390-fold the human exposure calculated based on preliminary clinical PK data of AGI-69460).

As described in the ICH S1B guideline, a 6-month study is required to adequately address the potential for pre-neoplastic findings such as hyperplasia. Interestingly, in both rats and monkeys, hepatocellular hypertrophy was observed even after 13 weeks, and liver toxicity is also an important identified risk in the clinical trials. In addition, in the 13-week study in monkeys, Kupffer cell hyperplasia were observed at primary necropsy and worsened after recovery period at 8-fold the clinical exposure. Therefore, a risk for liver tumour formation cannot be excluded. Furthermore, in 13-week study in rats, the squamous metaplasia and hypertrophy of the uterine epithelium and hyperplasia of the vaginal and/or cervical epithelium were observed, as indication of carcinogenic risk. In addition, findings from rat toxicity studies suggested hormonal perturbation. Such findings may be suggestive of potential carcinogenic risk. Moreover, a chronic toxicity study of 6-month duration might reveal other findings that are not apparent yet from the 13-week study. Finally, publicly available data reveals that no chronic or carcinogenicity studies were performed for other marketed IDH inhibitors, therefore no experience could be gained for molecules with the same mechanism of action. Carcinogenicity studies in mice and rats and pre- and post-natal development studies will be conducted and submitted as post-approval measures (MEAs) with submission of the final study report by April 2027, December 2028 and May 2026, respectively. These studies will be performed with vorasidenib and AGI-69460 concentrations will be followed through these studies. In the meantime, as a carcinogenicity risk in humans could not be excluded, this concern is mentioned in section 4.4 of the SmPC. It should be noted that the rat carcinogenicity study with vorasidenib should also cover AGI-69460 at sufficient levels (greater than 0.5-fold of the human AUC). In this case, a separate study on AGI-69460 is not required.

Vorasidenib induced embryo-foetal toxicity in rats and rabbits consisting in embryo-foetal lethality in both species and visceral malformations in rats (malpositioned kidneys and testis). The developmental NOAEL were set at 10 mg/kg/day in rats and 6 mg/kg/day in rabbits, corresponding to exposure multiples of 8.0-28.5 and 1.1-4.9, respectively. The claimed indication being out of the scope of the ICH S9 guideline, therefore waiving the conduct of other developmental and reproduction toxicity studies is not considered justified on this sole basis. Further justification has not been provided apart from a discussion on fertility, which is a different issue, and a statement that dedicated developmental and reproductive (DART) studies would not likely provide additional information. This is not agreed, as the endpoints measured in a pre- and postnatal development (PPND) study such as learning and memory effects on the offspring, are not covered by any other study. Since the patient population also includes women of childbearing potential who might have a wish to become pregnant due to the relatively long life-expectancy, the applicant has committed to perform and submit a PPND study in rats post-approval with submission of the final study report by Q2 2026. In addition, as the impact of vorasidenib treatment on the development of the foetus is unknown, the level of recommendation for use during pregnancy has been upgraded from "is not recommended" to "should not be used" in section 4.6 of the SmPC.

As regards fertility, a dedicated study would not add significant additional information based on the results of repeat-dose toxicity studies showing treatment-related effects on reproductive organs in rats.

The applicant was also requested to assess any risk for human development which may be related to major human metabolite AGI-69460. It was shown by the applicant that exposure to AGI-69460 was sufficient in the rabbit EFD study. Although exposure margins are low, this is agreed. In the rat EFD study, the exposure was low, but still >0.5-fold the human exposure. Taken together, it can be agreed that EFD is sufficiently covered. For fertility, a risk has already been identified for the parent compound, and therefore no further studies are required. For PPND, no data is available, but it is anticipated that the rat PPND study with vorasidenib which should be performed will also cover AGI-69460 in sufficient amounts (>0.5-fold human AUC). Therefore, a separate PPND study on AGI-69460 is not required.

Vorasidenib demonstrated no phototoxic potential. The toxicological significance of the ear findings observed in rat preliminary study and 28-day rat study was ruled out by a dedicated 28-day ototoxicity.

Ecotoxicity/environmental risk assessment

$PEC_{surfacewater}$ for vorasidenib is below the action limit of 0.01 µg/L. An OECD 123 (slow stirring) test to determine the log Kow will be performed by the applicant as a post-authorisation measure (REC). A final conclusion on potential risk of vorasidenib to the environment cannot be drawn.

Assessment of paediatric data on non-clinical aspects

The absence of any juvenile toxicity study is acceptable in line with the agreed PIP.

2.5.7. Conclusion on the non-clinical aspects

The main target toxicities identified during repeat-dose toxicity studies concern liver, gastrointestinal tract, skin, kidney, skeletal muscle, reproductive organs and mammary gland.

Vorasidenib was not genotoxic in the in vitro bacterial reverse mutation (Ames) assay, in vitro human lymphocyte micronucleus and in vivo rat bone marrow micronucleus assays. AGI 69460, its major circulating metabolite, was not genotoxic in the Ames assay, the in vitro human lymphocyte micronucleus assay, and the in vivo rat bone marrow micronucleus and Comet assays.

In the 13-week study in monkeys, Kupffer cell hyperplasia were observed at primary necropsy and worsened after recovery period at 8-fold the clinical exposure. In addition, findings from rat toxicity studies suggested hormonal perturbation. Such findings may be suggestive of potential carcinogenic risk. Carcinogenicity studies have not been conducted yet with vorasidenib but will be provided in the post authorisation setting.

Effects on reproductive organs were noted during repeat-dose toxicity studies after administration of vorasidenib in rats. Adverse effects in female reproductive organs included atrophy of the ovaries, uterus, cervix and vagina and oestrous and cycle variations. In male rats, effects were noted on the epididymis (cellular debris), seminal vesicle/prostate (atrophy), and testis (weights, tubular degeneration). These findings were observed at the lowest tested dose of 5 mg/kg/day in the 13-week rat study, resulting in an exposure level 26-fold higher than the human exposure at 50 mg daily dose.

Vorasidenib caused embryo foetal toxicity in pregnant rats and rabbits (higher incidence of resorptions, delayed ossification, visceral malformations for kidney and testes in rats). These effects occurred at doses that were higher compared to patients receiving the therapeutic daily dose. The exposure ratios at the NOAEL for embryo foetal development in rats and rabbits were 8.0 to 28.5 and 1.1 to 4.9, respectively, on gestation days 6 and 17 for rat and 6 and 19 for rabbit.

In conclusion, considering the risk minimisation included in the SmPC regarding the non-clinical findings, and based on the review of the totality of submitted non-clinical data, the application for Voranigo in 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 are not in immediate need of radiotherapy or chemotherapy, is approvable.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

Study Number/Status	**Study Title or Description**
Clinical Studies	
AG881-C-004	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
AG881-C-002	A Phase 1, Multicenter, Open-Label, Dose-Escalation and Expansion, Safety, Pharmacokinetic, Pharmacodynamic, and Clinical Activity Study of Orally Administered AG-881 in Patients with Advanced Solid Tumors, Including Gliomas, with an IDH1 and/or IDH2 Mutation
AG120-881-C-001	A Phase 1, Multicenter, Randomized, Controlled, Open- label, Perioperative Study of AG-120 and AG-881 in Subjects with Recurrent, Non-enhancing, IDH1 Mutant, Low-grade Glioma
AG881-C-001	Phase 1, Open-label, Dose-escalation Study in Subjects with Hematologic Malignancies

2.6.2. Clinical pharmacology

During the clinical development two different formulations (F1 (uncoated tablets) and F2) of Voranigo were used. The proposed commercial formulation (F2) is a film coated tablet supplied at two strengths: 10 and 40 mg. F2 was used as part of the ongoing pivotal phase 3 study AG881-C-004, as well as in completed phase 1 studies PKH-95032-008, PKH-95032-009, AG881-C-007, AG881-C-008.

The clinical development program for vorasidenib presented in, encompasses 7 completed clinical studies as well as two ongoing phase 1 (AG120-881-C-001 and AG881-C-002) and one ongoing phase 3 (AG881-C-004).

Table 73. Clinical Pharmacology studies

Study ID/ Status (Location)	Title	Formulation / Vorasidenib Dose Regimen	No. of Subjects Planned /Dosed / PK Evaluable[a]
Clinical Pharmacology Studies in Healthy Subjects			
Excretion Balance and Metabolic Profile			
AG881-C-005/ Completed (US)	A Phase I, Open-label Study to Evaluate the Absorption, Distribution, Metabolism, and Excretion, and to Assess the Absolute Bioavailability of AG-881 in Healthy Male Subjects Following Administration of a Single Oral Dose of [^{14}C]AG-881 and Concomitant Intravenous Microdose of [$^{13}C_3{}^{15}N_3$]AG-881	Powder-in-capsule Single oral dose of approximately 50 mg [^{14}C]vorasidenib (free form) containing approximately 100 µCi of radiocarbon Solution for injection Single IV microdose of approximately 100 µg [$^{13}C_3{}^{15}N_3$]vorasidenib	5/5/5
Extrinsic Factors			
AG881-C-007/ Completed (US)	A Phase 1, Open-Label Study to Compare the Relative Bioavailability of Two AG-881 Formulations and to Evaluate the Effect of High Fat Meal and Multiple-Dose Omeprazole on the Pharmacokinetics of a Single Dose of AG-881 in Healthy Adult Subjects	Treatment A: single dose of 50 mg vorasidenib F1 (2 × 25 mg tablets) administered PO at Hour 0 on Day 1 (fasted). Treatment B: single dose of 50 mg vorasidenib F2 (1 × 50 mg tablet) administered PO at Hour 0 on Day 1 (fasted) Treatment C: single dose of 50 mg vorasidenib F2 (1 × 50 mg tablet) administered PO at Hour 0 on Day 1 (fed, high fat meal) Treatment D: 40 mg omeprazole (1 × 40 mg capsule) administered PO approximately every 24 hours at Hour -1 for 3 consecutive days (Day 1 to Day 3 [prior to breakfast]) and on Day 4 of Period 4 (Hour -1, fasted) (daily dosing ± 1 hour of the dosing time on Day 1) with a single dose of 50 mg vorasidenib F2 (1 × 50 mg tablet) administered PO at Hour 0 on Day 4 of Period 4 (fasted)	36/36/36
PKH-95032-009/ Completed (US)	A Phase 1, Open-Label Study to Evaluate the Effect of a Low-Fat Meal and Multiple Doses of Ciprofloxacin on the Pharmacokinetics of Vorasidenib in Healthy Subjects	F2 Substudy A: Treatment A: Single oral dose of 40 mg (1 × 40 mg) vorasidenib tablet under fasted conditions Treatment B: Single oral dose of 40 mg vorasidenib following a low-fat meal. Substudy B: Treatment A: Single oral dose of	Substudy A: 36/36/34 Substudy B: 28/28/28

Study ID/ Status (Location)	Title	Formulation / Vorasidenib Dose Regimen	No. of Subjects Planned /Dosed / PK Evaluable[a]
		vorasidenib 2 × 10 mg tablets administered on Day 1. Treatment B: Single oral dose of vorasidenib 2 × 10 mg tablets administered on Day 1 and BID oral doses of ciprofloxacin 1 × 500 mg tablet on Days 1 – 14	
Intrinsic Factors			
AG881-C-008/ Completed (US)	A Phase 1, Open-label, Single Ascending Dose Study to Evaluate AG-881 in Healthy Japanese and Non-Asian Subjects	F2 Vorasidenib PO with 8 oz (240 mL) water following an overnight fast as follows: Period 1: 10 mg vorasidenib as 1 tablet Period 2: 50 mg vorasidenib as 1 tablet.	32/32/28
PKH-95032-008[d]/ Completed (US)	A Phase 1, Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of a 20-mg Dose of Vorasidenib in Subjects with Moderate or Mild Hepatic Impairment and Matched Subjects with Normal Hepatic Function	F2 Single oral dose of 20 mg (2 × 10 mg) vorasidenib	40/20/20
Effect of vorasidenib on the PK of other drugs			
AG881-C-006/ Completed (US)	A Phase 1, Open-label Study to Evaluate the Effect of AG-881 on the Pharmacokinetics of a Single Dose of Lamotrigine in Healthy Adult Subjects	F1 50 mg vorasidenib (2 × 25 mg tablets), PO QD (Day 1 to Day 15). Reference: single dose of 50 mg lamotrigine (2 × 25 mg tablets) was co-administered PO on Day 1 of Period 1 and on Day 14 of Period	22/22/22
Clinical Studies in Subject Populations			
AG881-C-001/ Completed (US and France)	A Phase 1, Multicenter, Open-Label, Dose-Escalation, Safety, Pharmacokinetic, Pharmacodynamic, and Clinical Activity Study of Orally Administered AG-881 in Subjects with Advanced Hematologic Malignancies with an IDH1 and/or IDH2 Mutation	F1 Vorasidenib 25mg QD starting dose, 50mg, 100mg, 200mg, 400mg, 600mg, or 1100 mg QD in a 28-day cycle.	46/46/46
AG881-C-002/ Ongoing (US)	A Phase 1, Multicenter, Open-Label, Dose-Escalation and Expansion, Safety, Pharmacokinetic, Pharmacodynamic, and Clinical Activity Study of Orally Administered AG-881 in Subjects	F1 Vorasidenib 25 mg QD up to 400 mg QD PO and 200 mg BID PO were tested in subjects with non-glioma solid tumors and doses of 10mg, 25mg, 50mg, 100mg, 200mg, or 300 mg QD PO in subjects with gliomas	139/93/91

Study ID/ Status (Location)	Title	Formulation / Vorasidenib Dose Regimen	No. of Subjects Planned /Dosed / PK Evaluable[a]
	with Advanced Solid Tumors, Including Gliomas, with an IDH1 and/or IDH2 Mutation		
AG120-881-C-001/ Ongoing (US)	A Phase 1, Multicenter, Randomized, Controlled, Open-label, Perioperative Study of AG-120 and AG-881 in Subjects with Recurrent, Non-enhancing, IDH1 Mutant, Low-grade Glioma	F1 Vorasidenib 50 mg PO QD or 10 mg PO QD. Ivosidenib 500 mg PO QD or 250 mg PO BID	45/49/45
AG881-C-004/ Ongoing (US, Canada, France, Germany, Israel, Italy, Netherlands, Spain, Switzerland, UK)	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	F1: Vorasidenib 50 mg QD[b] or placebo[c] (clinical formulation replaced by commercial formulation) F2: Vorasidenib 40 mg QD or placebo orally from Day 1 to Day 28	340/331[d]/162[e]

Note: F1 = uncoated tablets (early phase formulation) (Formulation 1); F2 = film-coated tablets (intended commercial formulation) (Formulation 2).

A Population PK analysis was developed (Report AG881-C-004-PPK) from which predicted exposure metrics were used as input for two exposure-response (ER) analysis (Report AG881-C-004-ER). A physiologically based pharmacokinetic (PBPK) model was developed and applied to a series of simulations to assess both perpetrator and victim drug-drug interactions (DDI) effects of vorasidenib (Report AG881-C-META-PBPK).

2.6.2.1. Pharmacokinetics

Methods

The pharmacokinetics of vorasidenib have been characterised in patients with low grade glioma with an IDH1 or IDH2 mutation and in healthy subjects.

PK data were analysed using non-compartmental analysis (NCA) and population PK modelling (PPK).

For single or multiple-dose studies, PK parameters evaluated in plasma include Cmax, Cmin, Tmax, AUCs (AUC0-t, AUC0-24, AUCtau, AUC0-∞), CL and Vss, CL/F and Vz/F, AUC%extra, AI (accumulation index), T1/2. In addition, unbound drug post-dose was measured.

Standard non-compartmental (model-independent) pharmacokinetic methods were used to calculate PK parameters using Phoenix WinNonlin v8.3 or later. PPK was developed using NONMEM (version 7.3, ICON Development Solutions, Hanover, MD).

Absorption

Across the clinical studies after single or multiple dose administration in healthy volunteers or patients, vorasidenib absorption was rapid with a median Tmax ranging from 2 to 3h.

At a 40 mg single dose with the commercial formulation, in healthy volunteers, geometric mean Cmax was 75.4 ng/mL and AUC0-inf 2860 ng.h/mL. In patients, geometric mean Cmax was 71.7 ng/mL and AUC0-4h 146.7 ng.h/mL.

At a 40 mg multiple dose with the commercial formulation, in patients, geometric mean Cmax was 132.8 ng/mL and AUC0-tau was 1988 ng/h/mL.

In most patients, a second plasma concentration peak occurred within 24 hours after drug administration but was lower than the observed Cmax at 2 hours post-dose.

Accumulation ratios were approximately 3.8 for C_{max} and 4.4 for AUC. Steady-state plasma levels were reached after 2 to 3 weeks of once- daily- dosing.

Absolute bioavailability

Although absolute bioavailability has not been directly determined, the absorption of vorasidenib is estimated to be moderate to high for the 40 mg film-coated tablets.

BCS Classification

Vorasidenib can be classified as a BCS class 4 compound (low solubility/low permeability).

Relative bioavailability/Bioequivalence

Two oral formulations of vorasidenib were developed and evaluated during the clinical development program. An uncoated tablet supplied at three strengths: 5, 25 and 100 mg (F1, clinical formulation), was used earlier in patients, and a film-coated tablet supplied at three strengths: 10, 40 and 50 mg (F2, intended commercial formulation), used in the pivotal study AG881-C-004 and mainly during the phase 1 studies in healthy volunteers. In addition, three drug substance (DS) process development were considered (A1, A2 and A3).

The commercial formulation is a film coated tablet (F2-A3) supplied at two strengths: 10 mg and 40 mg.

One relative bioavailability (rBA) study was performed to bridge the PK between the F1-A1 and F2-A1 formulation. Results from the rBA study AG881-C-007 indicate the F2 formulation was associated to an increased Cmax and AUCinf by 64% and 35% respectively compared to the F1 formulation.

Influence of food

The effect of food on the PK of vorasidenib was assessed with a high-fat meal and a low-fat meal compared with fasted condition. A food effect on vorasidenib PK was demonstrated. The mean C_{max} and AUC of vorasidenib increased by 3.1-fold and 1.4-fold, respectively, when vorasidenib was administered with a high-fat meal. Administration of vorasidenib with a low-fat meal resulted in increases in vorasidenib C_{max} and AUC of 2.3- and 1.4-fold, respectively

Influence of gastric modifier

Co-administration of omeprazole did not significantly change the extent of exposure of vorasidenib (study AG881-C-007), although a decreased Cmax by 29.4% is observed.

Distribution

Vorasidenib has a mean apparent volume of distribution of 3,930 L (CV%: 40). The vorasidenib volume of distribution following a single 0.1 mg IV microdose is 1,110 L. The bound plasma protein fraction for vorasidenib and AGI-69460 was 97% and 87%, respectively. Both vorasidenib and AGI-69460 exhibit preferential binding to serum albumin over alpha-1 acid glycoprotein. The unbound fraction of vorasidenib and AGI-69460 was not affected in moderate hepatic impairment subjects.

Vorasidenib blood to plasma ratio is 0.87, AGI-69460 blood to plasma ratio is 1.38, and vorasidenib brain tumour to plasma concentration ratio is 1.6.

Elimination

Across the clinical studies in healthy volunteers, after single dose of vorasidenib as a film-coated tablet F2-A3, mean half-life ranged from 229 to 442 hours. At a 40 mg dose as F2-A3, mean half-life was 238h (CV%: 57) and CL/F was 14 L/h (CV%: 56).

Based on the mass balance study AG881-C-005, the main elimination route was hepatobiliary. Vorasidenib is moderately metabolised, with 21% of orally administered [14C] AG-881 eliminated as metabolite in urine (3%) and feces (18%). Unchanged vorasidenib was not detected in urine and accounted for 55% of the dose in feces. Vorasidenib seems to undergo an enterohepatic recirculation.

- Mass balance

The excretion and biotransformation of [14C]-vorasidenib was investigated in 5 healthy subjects following a single oral dose of 50 mg vorasidenib (powder-in-capsule formulation with an absolute bioavailability of <34%) incorporating approximately 100 µCi [^{14}C]-vorasidenib.

The total recovery of radioactivity was reasonable (≈90%) with approximately 89.2% of the dose recovered and this is considered sufficient. Approximately 4.52% and 84.7% of the dose was recovered in urine and feces respectively, unchanged vorasidenib accounted for 55.5% in feces. Given the estimated half-life of both whole blood TRA and plasma TRA, 491 h and 298 h, compared to plasma AG-881, circulating metabolites with a prolonged half-life is plausible.

- Metabolism

Vorasidenib is primarily metabolised by CYP1A2 with negligible to minor contributions from CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5. Non CYP pathways may contribute up to 30% of vorasidenib liver metabolic clearance. Metabolite profiling was performed and approximately 11 metabolites were identified. In plasma, the unchanged parent vorasidenib was the most prominent drug related component and accounted for 66.2% and 29.4% of TRA for pooled AUC0-72h and AUC96-336h, respectively. AGI-69460 (M458), a late metabolite of vorasidenib accounted for 9.1% and 43.9% of TRA for pooled AUC0-72h and AUC96-336h, respectively. No other metabolites were detected in plasma.

AGI-69460 was not detected as part of the pre-clinical investigation and was further partially characterized after the ADME study AG881-C-005. AGI-69460 is an active metabolite.

In faeces, vorasidenib was the main component excreted with 55.5% of the dose, which can be attributed to pre-systemic elimination given its solubility limited absorption. M515, M516, M460 -1, and M472/M476 accounted for less than 6%. More than 86% of the dose excreted in faeces was identified.

In urine, unchanged vorasidenib was not found. M266 was the main component excreted with 2.54% of the dose. M266 was formed by N-dealkylation of AGI-69460. Less than 80% of the dose excreted in urine was identified (75%).

- Interconversion

The drug substance has two chiral centres. Both have an R-configuration. The drug substance is considered stable after manufacturing (refer to the Quality assessment). No in vivo inter-conversion is expected.

- Pharmacokinetic of metabolites

AGI-69460 identified as a main metabolite, was first discover as part of the mass balance study **AG881-C-005**. AGI-69460, a downstream metabolite of the deschloro glutathione conjugate of vorasidenib, is likely formed via a combination of hepatic and extra hepatic metabolism pathways.

After a single 40 mg vorasidenib oral dose, the observed Tmax for metabolite AGI 69460 was 336 hours, the observed geometric mean Cmax was 3.32 ng/mL (CV%: 55.6), and the geometric mean AUC0-t was 1,172 hr*ng/mL (CV%: 61). At steady state, geometric mean AGI 69460 Cmin,ss was 111 ng/mL (CV%: 58) and geometric mean AUC0-4 at cycle 2 day 1 was 190 hr*ng/mL (CV%: 90).

AGI-69460 is a pharmacological active metabolite with IC50 values for 2-HG inhibition in representative cell-lines (TS603 for IDH1R132H and HT1080 for IDH1R132C mutation) of 6.71 nM and 264 nM respectively, compared to 0.117 nM and 47 nM for vorasidenib respectively. The IC50 of AGI-69460 values were 57.3 and 5.62-fold higher than those of vorasidenib respectively.

For IDH1R132H, the most common IDH1 mutation (85.8% frequency) in the study population, the potential contribution of AGI-69460 to overall target engagement was therefore assessed as less than 10% on average across all cycles (range 6.75% to 13.8%). For the less common IDH1R132C mutation (4.5% frequency), the estimated potential contribution of AGI-69460 to overall target engagement was 52.4% on average across all cycles (range 42.5% to 62.0%) (Report RB-23-095032-014-DHMB).

AGI-69460 is not a substrate of P-gp, BCRP or OATP1B1/B3, but is an inhibitor of OATP1B3.

Dose proportionality and time dependencies

Vorasidenib dose proportionality was demonstrated between 10 mg to 40 mg. Steady state plasma levels were reached after 2 to 3 weeks of once-daily dosing. Accumulation ratios were approximately 3.8 for Cmax and 4.4 for AUC.

Intra-and inter-individual variability

The inter-subject variability in exposure of vorasidenib in healthy subjects across studies was moderate to high with range from 37.5 to 49.5 % for Cmax and 40.3 to 84.6 %for AUCt.

In patients with glioma after a single dose, the intersubject variability for vorasidenib PK was high for both Cmax and AUC0-4 with geoCV% of 76.6 and 73.1%, respectively, and remain high after multiple dose.

The intra-subject variability of vorasidenib based on CV% from crossover studies was moderate and range from 11.6 to 32.5% for Cmax and 7.6 to 29.1% for AUC0-t.

Pharmacokinetics in the target population

Studies have investigated vorasidenib PK in patient with advanced malignancies or glioma.

Study **AG881-C-002** was a phase 1, multi-center, open-label, dose escalation and expansion, safety, PK, PD, and clinical activity study of orally administered AG-881 in patients with advances solid tumours, including glioma with an IDH1 and/or IDH2 mutation. This FIH study was conducted to determine the MTD and RP2D of vorasidenib in subjects with glioma and assess the safety and tolerability of multiple dose of vorasidenib.

Subjects were administered vorasidenib dose at 10, 25, 50, 100, 200, 300 and 400 mg QD, or 200 mg BID (F1-A1). Mean concentration time profiles of vorasidenib is presented in Figure 2 and associated PK parameters after single dose in Table 8 and after multiple dose in Table 9.

Figure 2. Mean (±SD) plasma concentrations-time profile after single oral dose of vorasidenib (Day -3).

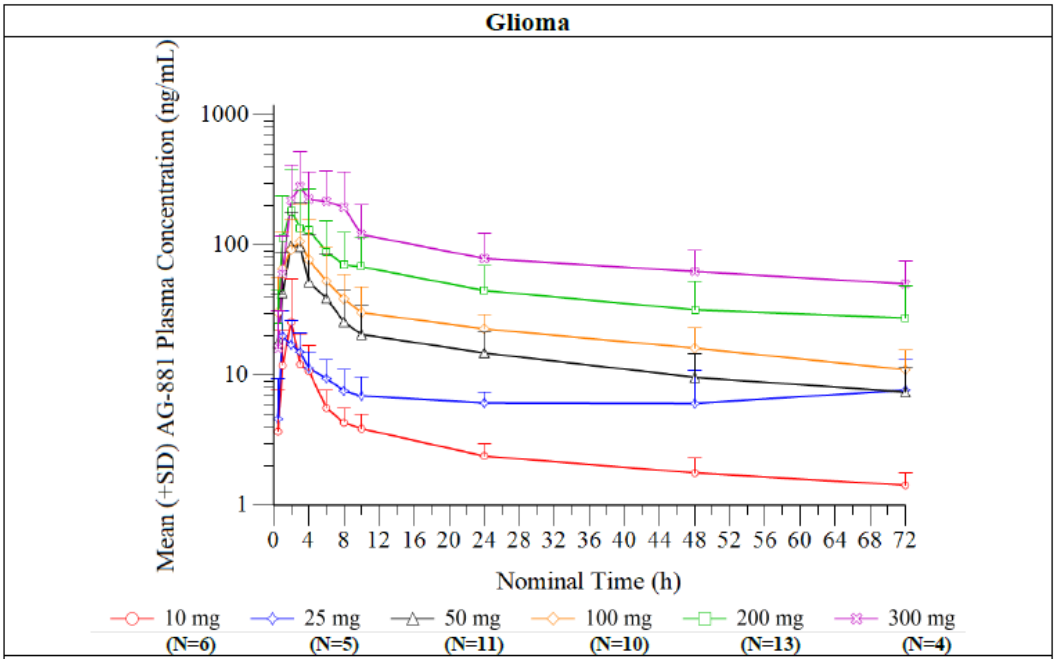


Table 84: PK parameter estimates of vorasidenib after a single dose (Day-3)

Disease Type	PK Parameter[a]	AG-881 Dose						
Glioma		10 mg (N=6)	25 mg (N=5)	50 mg (N=11)	100 mg (N=10)	200 mg (N=13)	300 mg (N=4)	400 mg (N=0)
	AUC_{0-10} (h*ng/mL)	84.1 (38.5);6	101.5 (21.2);5	373.5 (94.1);10	490.6 (71.9);10	803.7 (71.2);13	1530.1 (94.7);4	NA
	AUC_{0-24} (h*ng/mL)	129 (32.0);6	193 (21.8);5	610 (72.7);10	881 (53.0);10	1487 (64.3);13	2634 (98.7);4	NA
	AUC_{0-72} (h*ng/mL)	216 (27.0);6	458 (43.0);5	1083 (60.4);10	1671 (43.6);10	2909 (63.2);13	5348 (82.6);4	NA
	AUC_{0-t} (h*ng/mL)	217 (27.5);6	446 (46.3);5	661 (436.2);11	1720 (57.3);10	2930 (63.4);13	5120 (76.6);4	NA
	AUC_{inf} (h*ng/mL)	NC	381	1500 (77.0);5	1450 (8.2);3	3420 (110.0);5	NC	NA
	C_{max} (ng/mL)	26.7 (64.3);6	21.8 (38.2);5	63.3 (300.7);11	104 (70.5);10	178 (88.3);13	302 (104.0);4	NA
	T_{max}[b] (h)	2.07 (1.00 - 4.15);6	2.00 (1.00 - 71.92);5	2.00 (0.98 - 3.00);11	2.12 (0.50 - 9.85);10	2.08 (1.00 - 6.00);13	2.50 (2.00 - 8.00);4	NA
	$t_{1/2}$ (h)	66.3 (26.7);6	60.2 (94.5);3	48.7 (41.9);8	53.4 (70.2);8	44.1 (51.8);11	34.8 (34.3);2	NA
	CL/F (L/h)	NC	65.6	33.2 (77.0);5	68.8 (8.2);3	58.5 (110.0);5	NC	NA
	Vz/F (h)	NC	2310	1850 (57.8);5	2780 (27.8);3	2510 (87.1);5	NC	NA

Table 95: Summary of plasma PK parameters of AG-881 after multiple dose (C1D15-C2D1)

	C1D15						C2D1					
PK Parameter[a]	10 mg QD (N=6)	25 mg QD (N=5)	50 mg QD (N=11)	100 mg QD (N=9)	200 mg QD (N=10)	300 mg QD (N=3)	10 mg QD (N=6)	25 mg QD (N=5)	50 mg QD (N=9)	100 mg QD (N=7)	200 mg QD (N=10)	300 mg QD (N=3)
$AUC_{0\text{-}10}$ (h*ng/mL)	230.3 (36.8);6	425.3 (34.1);5	1027.4 (49.0);10	1356.4 (42.8);8	2766 (53.7);10	4133.8 (79.4);3	276.6 (38.9);5	505.6 (29.2);4	1581.2 (48.4);8	1474.9 (60.8);5	2844.6 (86.8);9	3984.1 (48.3);3
$AUC_{0\text{-}tau}$ (h*ng/mL)	462 (30.7);6	895 (33.2);5	2146 (48.8);11	2874 (34.8);9	5840 (65.9);10	8604 (77.0);3	559 (50.3);5	1105 (27.1);5	3144 (54.3);9	3414 (52.5);7	6317 (84.2);10	9074 (57.0);3
$AUC_{0\text{-}t}$ (h*ng/mL)	230 (36.8);6	425 (34.1);5	1020 (46.3);11	1310 (41.6);9	2770 (53.7);10	4140 (79.9);3	277 (38.9);5	441 (41.0);5	1270 (93.8);9	1470 (48.3);7	2840 (80.4);10	3980 (48.3);3
C_{max} (ng/mL)	38.9 (49.8);6	63.5 (36.8);5	155 (47.5);11	194 (52.5);9	394 (40.8);10	526 (86.3);3	45.7 (39.1);5	66.5 (25.2);5	206 (59.7);9	233 (43.8);7	361 (75.2);10	493 (56.3);3
T_{max}[b] (h)	3.04 (0.85–10.00);6	1.00 (0.67 – 6.00);5	2.00 (0.50–3.02);11	2.00 (0.53 – 4.00);9	2.08 (0.50–8.00);10	2.03 (2.00 - 2.95);3	2.08 (1.00 – 3.00);5	2.17 (1.00 – 3.00);5	3.00 (1.00 - 4.23);9	2.15 (0.95 – 6.00);7	2.53 (0.92 – 8.08);10	1.02 (0.50 – 2.03);3
C_{trough} (ng/mL)	14.4 (41.5);6	31.3 (44.8);5	72.8 (61.4);11	97.8 (32.5);9	188 (94.3);10	314 (75.1);3	17.7 (56.2);5	40.8 (36.9);5	111 (66.4);9	125 (54.5);7	219 (100.5);10	360 (73.3);3
$t_{1/2\_eff}$ (h)	50.3 (38.9);6	68.0 (37.6);5	44.0 (65.5);10	43.8 (35.1);9	42.8 (123.1);10	45.9 (76.3);3	60.7 (50.4);5	86.2 (37.7);5	63.2 (75.1);8	52.5 (54.3);7	61.4 (85.4);9	48.5 (98.3);3
CL_{ss}/F (L/h)	21.7 (30.7);6	27.9 (33.2);5	23.3 (48.8);11	34.8 (34.8);9	34.2 (65.9);10	34.9 (77.0);3	17.9 (50.3);5	22.6 (27.1);5	15.9 (54.3);9	29.3 (52.5);7	31.7 (84.2);10	33.1 (57.0);3
LI	NC	2.66	1.29 (52.6);5	1.51 (26.5);2	0.998 (71.6);4	NC	NC	2.86	1.49 (53.5);4	1.64 (74.1);2	1.09 (98.4);4	NC
Racc(AUC)	3.58 (31.8);6	4.64 (32.2);5	3.27 (49.8);10	3.19 (29.3);9	3.38 (80.2);10	3.38 (58.9);3	4.22 (43.6);5	5.73 (33.2);5	4.43 (61.5);8	3.73 (46.3);7	3.65 (97.0);10	3.56 (76.7);3
Racc(C_{max})	1.46 (84.2);6	2.91 (55.3);5	2.45 (378.9);11	1.87 (21.9);9	1.89 (87.8);10	1.84 (91.2);3	1.65 (69.7);5	3.05 (25.7);5	3.83 (496.9);9	2.31 (39.6);7	1.73 (106.8);10	1.73 (97.8);3

Study AG881-C-004 (pivotal study) was a phase 3, multicentre, randomized, double blind, placebo controlled study of AG-881 in subjects with residual or recurrent Grade 2 glioma with an IDH1 or IDH2 mutation.

Initially 9 subjects (5 randomized to receive vorasidenib and 4 randomized to receive placebo) received 50 mg vorasidenib QD (2 × 25 mg tablets of F1). Upon availability of F2, and implementation of a protocol amendment to modify the dose to 40 mg, all of the initial subjects and all subsequently enrolled subjects received 40 mg vorasidenib QD (4 × 10 mg tablets of F2).

The dose of 40 mg QD of F2 was initially introduced as 4 × 10 mg tablets, and subsequently, vorasidenib formulation and tablet strength have been administered as 1 × 40 mg tablets (F2).

Mean (+SD) plasma concentration-time profiles of vorasidenib following the first dose and multiple once daily oral administrations of AG-881 are presented in Figure 3 for C1D1 and C2D1. Table 10 presented the estimated PK parameters per formulation.

Figure 3: Mean (±SD) plasma vorasidenib concentration vs time after multiple oral administrations of 40 mg QD AG-881 at C1D1(left) and C2D1 (right).

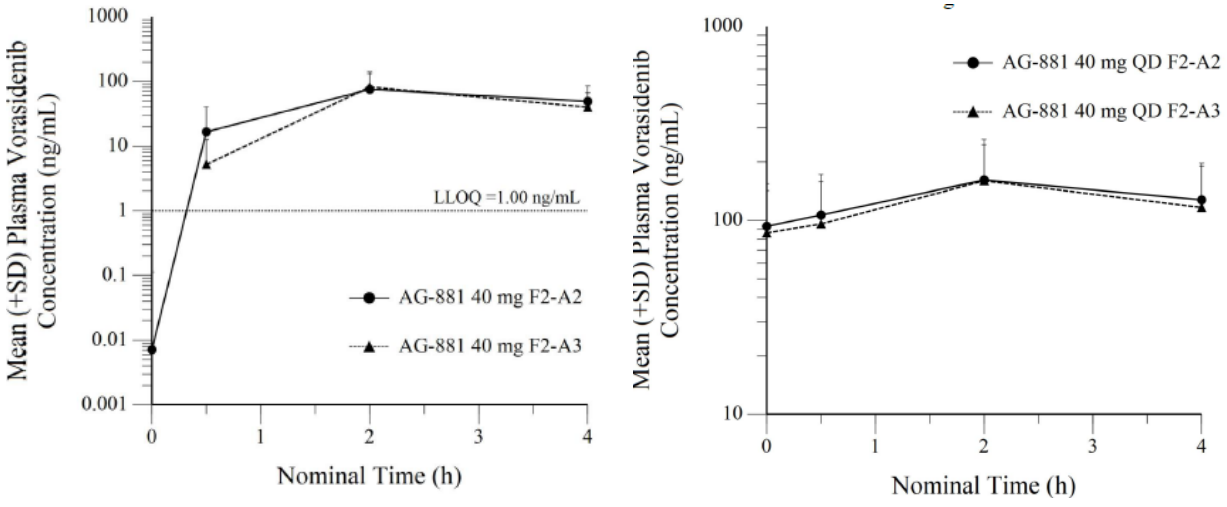


Table 106: Geometric mean (CV%) plasma vorasidenib PK parameters after single and multiple oral administrations of 40 mg QD.

Visit	PK Parameters	40 mg QD AG-881 (F2-A2)			40 mg QD AG-881 (F2-A3)		
		N	Geometric Mean	GeoCV%	N	Geometric Mean	GeoCV%
C1D1 (Single Dose)	AUC_{0-4} (h*ng/mL)	204	160.1	61.4	22	146.7	73.1
	C_{max} (ng/mL)	210	68.42	67.0	23	71.74	76.6
	T_{max} (h)[a]	210	2.04	(0.38, 4.07)	23	2.05	(1.87, 3.87)
C2D1 (Multiple Dose)	AUC_{0-4} (h*ng/mL)	179	465.2	59.5	24	405.9	75.9
	AUC_{0-tau} (h*ng/mL)	189	2309	64.5	22	1988	94.6
	$C_{max,ss}$ (ng/mL)	197	146.8	57.7	25	132.8	73.4
	$T_{max,ss}$ (h)[a]	197	2.03	(0.38, 4.50)	25	2.07	(0.50, 4.17)
C10D1	M:P Molar Ratio	142	1.173	55.7	NA	NA	NA

Population Pharmacokinetic analysis (PPK)

One population pharmacokinetic analysis (PPK, Report AG881-C-004-PPK) aiming to characterize the PK of vorasidenib in the target population and identifying/quantifying source of variability was developed. From this analysis, predicted exposure metrics were used as input of subsequent exposure-response (ER) and a modelling and simulation exercise was performed to predict the vorasidenib exposure in adolescent in order to provide a dosing recommendation for subjects with a body weight (BW) < 40kg (studied does of 20 mg/Kg QD).

The PPK of vorasidenib was based on PK results pooling 6 clinical studies including healthy volunteers (AG881-C-006/007/008) and patients (AG881-C-002/004 and AG120-881-C-001). The concentration-time data of vorasidenib was modelled using a compartmental approach. Covariates of interest in vorasidenib trials were baseline demographic covariates (age, body size, gender, race/ethnicity), formulation (strength) and dose, hepatic function measure (albumin, bilirubin, alanine and aspartate amino transferase), renal function measure (CrCL, eGFR), disease state and concomitant medications.

PPK was built using nonlinear mixed effects model with the first order conditional with interaction (FOCEI) for parameter estimation implemented in NONMEM (version 7.3, ICON Development Solutions, Hanover, MD). Covariate effects were first explored graphically, then testing of the covariate effects was performed using a stepwise covariate modelling (SCM) building strategy (single addition, forward inclusion and backward elimination) implemented in Perl-speaks-NONMEM (PsN) with $p<0.01$ for inclusion and $p<0.001$ for exclusion. Time varying covariates were considered. The decision to keep or remove covariates that did not lead to at least a 5% reduction in interindividual variability (IIV) on the respective parameter was made on a case-by-case basis. The PPK model was evaluated using standard diagnostic plots, visual predictive check and bootstrap.

Overall, 333 subjects with 7316 PK observations were included. N=197 below limit of quantification (BLQ) (2.46%) and N=504 flagged observations were excluded.

The final PPK model consisted of a three compartments PK model parameterized with first order absorption and lag time and linear elimination, in terms of Ka, Tlag, CL/Fs and Vd/Fs. IIV was considered on F, Ka, CL/F, V2/F and Q4/F. RUV was modelled using a proportional error. Dose non-linearity for the F1 formulation and its effect on F (relative bioavailability) were considered.

Overall all PK parameters were estimated with a good precision (relative standard error (RSE) <30% for the fixed <50 % for the random effects). Eta-shrinkage was generally low for all PK parameters (<25%) except for V2/F (48.8%). The condition number was 33.7 indicating that the model was stable.

For a typical subject (male not Hispanic nor latino, receiving formulation F2 at 40 mg), Ka, Tlag, CL/F, V2/F, Q3/F, Q4/F, V3/F and V4/F were 1.09 h^{-1}, 0.377 h, 17.8 L/h, 371 L, 12.1 L/h, 108 L/h, 2160 L and 1450 L, respectively. IIV for Ka, CL/F and Q4/ was high, 105%, 61.7% and 73.5%, IIV for F and V2/F was moderate, 38.2% and 38.8% respectively. F was reduced by 33.4% with F1 compared to F2. The covariate effects on the final model were decrease of CL/F and V2/F in female by 33.7 and 33.1% respectively and decreased CL/F in Hispanic subjects by 28.8%.

The GOF plot did not show any trend, suggesting that the model describes adequately the PK data. The final pop PK model was able to predict the observed median, 10^{th} and 90^{th} percentile vorasidenib concentrations at steady state with good accuracy for both the formulations (F1 and F2). The model sightly underpredicted plasma concentrations following the 1^{st} dose of vorasidenib formulation 1.

Special populations

Renal impairment

No formal PK study investigating the effect of renal impairment on both vorasidenib and AGI-69460 PK was performed. Based on NCA PK parameters from study **AG881-C004**, stratified in 4 different categories of baseline eGFR a limited effect of renal function is observed that is not clinically meaningful. The pharmacokinetics of vorasidenib in patients with eGFR ≤ 40 mL/min/1.73 m2 or renal impairment requiring dialysis are unknown.

Hepatic impairment

A formal PK study investigating the effect of moderate or mild hepatic impairment on both vorasidenib and AGI-69460 PK was performed. Results of this analysis indicated that following a 20 mg single dose, vorasidenib Cmax was unaffected but AUC0-t increased by 26%. For both compounds Fu% was not affected. The pharmacokinetics of vorasidenib and AGI 69460 in patients with severe hepatic impairment (Child Pugh class C) are unknown.

Ethnicity

A formal PK study investigating the effect of two single oral doses of vorasidenib of 10 mg and 50 mg in Japanese and non-Asians subjects was performed. Results from this analysis indicated that vorasidenib PK was not affected in both populations.

Age, weight,

No formal PK investigations with regard to age and weight have been performed. Based on NCA PK parameters from study AG881-C004, a limited effect of age or body weight was observed that is not clinically meaningful.

Gender

No formal PK investigations with regard to gender has been performed. Female patients were observed to have a 1.6 fold higher vorasidenib exposure as compared to male patients.

Paediatric 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.

Exposure-response analysis

Two ER analysis were performed using predicted PK metrics from the PPK analysis of vorasidenib. No relationship were identified between vorasidenib predicted exposure (AUCeot or AUCss) and any of the efficacy (PFS, TTNI, OR, CR+PR) nor any of the safety endpoints. A flat ER is observed.

Pharmacokinetic interaction studies

Vorasidenib as a victim drug:

Vorasidenib undergoes a metabolism through one main enzyme CYP1A2 (with contribution of 53% to 90%) Other minor pathways involved CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and/or CYP3A4/5, in a lesser extent.

One major, late forming, pharmacologically active metabolite has been identified: AGI-69460.

The findings from in vitro studies suggest that neither vorasidenib nor its metabolite (AGI- 69460) are substrates of P-gp, BCRP, OATP1B1 and OATP1B3. Therefore, the likelihood of drug-drug interactions between P-gp, BCRP, OATP1B1, OATP1B3 modulators, and both vorasidenib and AGI-69460 (a metabolite of vorasidenib) as a substrate is not expected.

The impact of co-administration of vorasidenib with a potent CYP1A2 inhibitor was evaluated in a clinical study using ciprofloxacin in 28 healthy adult subjects. Results showed a 1.29- and 2.53-fold increase in vorasidenib Cmax and AUC0-inf, respectively. Further investigations were carried out using the PBPK model to assess the potential of clinical DDI as a CYP1A2 substrate, evaluating DDI with potent CYP1A2 inhibitors (fluvoxamine and ciprofloxacin) and moderate CYP1A2 inducers (phenytoin and rifampicin). With strong CYP1A2 inhibitors, geometric mean ratios (GMRs) ranged from 1.78 to 7.18 times AUCtau and from 1.60 to 5.70 times Cmax. In addition, moderate CYP1A2 inducers reduced steady-state vorasidenib Cmax and AUC by around 30% and 40% respectively.

The PK of a single oral dose of 50 mg vorasidenib was assessed when co-administered with the proton pump inhibitor omeprazole (40 mg QD) (study AG881-C-007) to evaluate if changes in gastric pH could potentially alter the PK of vorasidenib. Multiple-dose administration of omeprazole (40 mg QD) did not affect plasma vorasidenib AUC and lowered vorasidenib Cmax (28%). Based on the ER relationship, the slight decrease in exposure is not expected to have an adverse impact on safety or efficacy

Vorasidenib as a perpetrator drug:

Several PBPK modelling simulations were carried out to assess the potential for clinical DDI with sensitive substrates of CYP2B6 (bupropion), CYP2C8 (repaglinide), CYP2C9 (S-warfarin), CYP2C19 (S-mephenytoin), CYP3A4 (midazolam), P-gp (digoxin) and BCRP (rosuvastatin). Results showed that multiple-dose administration of vorasidenib should result in weak induction ($0.5 <$ GMR AUC or GMR Cmax ≤ 0.8) with sensitive substrates of CYP2B6 (bupropion) and CYP2C19 (S-mephenytoin), leading to a 21% decrease in AUC for bupropion and S-mephenytoin, and a 35% decrease for mephenytoin. A strong interaction is observed with the CYP3A4 substrate (midazolam), resulting in an 82% decrease in AUC and a 79% decrease in Cmax. However, the impact on the pharmacokinetics of P-gp substrate (digoxin), BCRP substrate (rosuvastatin), CYP2C8 substrate (repaglinide, by interaction with CYP2C8 only) and CYP2C9 substrate (warfarin S) is negligible (AUC GMR or Cmax GMR ≤ 0.2). After conducting a sensitivity analysis, worst-case DDI simulations revealed that Vorasidenib strongly induced CYP3A4, moderately induced CYP2C19 (AUC and Cmax GMRs of 0.318 and 0.415) and CYP2C9 (AUC and Cmax GMRs of 0.445 and 0.911) while weakly inducing CYP2B6, CYP2C8,

with AUC and Cmax GMRs decreasing to 0.530 and 0.60, 0.71 and 0.80 respectively. BCRP substrate (rosuvastatin) showed increased AUC to 1.24-fold (with a 90% CI of 1.21 – 1.27) and Cmax to 1.63-fold (with a 90% CI of 1.58 – 1.69), suggesting mild inhibition, while digoxin, a P-gp substrate, exhibited negligible effects. *In vitro*, AGI-69460 is an inhibitor of BCRP and OATP1B3.

The potential DDI resulting from multiple doses of vorasidenib (50 mg) on UGT1A4 substrate was evaluated as part of a clinical investigation involving 22 healthy subjects, employing lamotrigine as a substrate. The study design was deemed suitable, and the findings indicated no significant impact on the AUC and Cmax of lamotrigine.

Pharmacokinetics using human biomaterials

In vitro DDI potential of vorasidenib and AGI-69460:

The ability of vorasidenib (AG-881) to be direct or time-dependent inhibitor (TDI) of CYP1A2, CYP2B6, CYP2C8, CYP2C9, 2C19, 2D6 and 3A4 was assessed as part of study AG881-N 005-R1. Results show that, at the highest tested concentrations of 10μM vorasidenib did not exert any or little direct or TDI inhibition towards the tested CYPs (IC50>10μM).

The ability of vorasidenib (AG-881) to inihibit UGT1A1 was assessed as part of the study AG881-N-006. The results show that vorasidenib directly inhibited UGT1A1 with an IC50 value of 8 μM.

Vorasidenib (AG-881) induction on CYP1A2, 2B6, 3A4, CYP2C8, CYP2C9, CYP2C19 and UGT1A4 effect was assessed in vitro. The results suggest that an induction effect of vorasideib on CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4/5, and UGT1A4 could not be ruled out.

Based on the in vitro study results a clinically autoinduction of vorasidenib metabolism is not expected, since is not an inducer of CYP1A2.

Based on the in vitro studies results, at concentrations up to 7.5 μM, vorasidenib exhibited less than 50% inhibition of BSEP, MRP2, MRP3, OATP1B1, OATP1B3, OAT1, OAT3, and OCT2. Similarly, at concentrations up to 25 μM, vorasidenib did not demonstrate more than 50% inhibition of MATE 1 and 2-K proteins. Therefore, at concentrations relevant to clinical use and covering the worst expected ones at the systemic and hepatic level, vorasidenib is not expected to have a DDI effect with substrates of these transporters.

Based on vitro study results, the metabolite, AGI-69460, is not an inhibitor of OATP1B1 (IC50 value of >10 μM), but is an inhibitor of OATP1B3, with an IC50 value of 2.97 μM.

Vorasidenib is a strong CYP3A4 inducer. Therefore, hormonal contraceptives that are substrates of CYP3A4 may have decreased plasma concentrations when co-administered with vorasidenib. Alternative contraceptive methods (e.g. barrier contraceptives) should be considered.

2.6.2.2. Pharmacodynamics

Mechanism of action

Vorasidenib (formerly known as AG-881) 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 the oncogenic metabolite 2-hydroxyglutarate (2-HG), resulting in impaired cellular differentiation and increased cellular proliferation contributing to oncogenesis. Inhibition of the IDH1- and IDH2-mutated proteins by vorasidenib inhibits the abnormal production of 2-HG which contributes to proliferation of malignant cells and a reduction in their proliferation.

Primary and secondary pharmacology

Primary pharmacology

Study AG881-C-002: Advanced Solid Tumours, Including Gliomas

In study AG881-C-002, the PK and PD following oral administration of vorasidenib 10 mg, 25 mg, 50 mg, 100 mg, 200 mg, 300 mg or 400 mg QD or vorasidenib 200 mg BID (F1) were evaluated in subjects with non-glioma tumours and in subjects with glioma, that harbour an IDH1 and/or IDH2 mutation.

Pharmacodynamics results

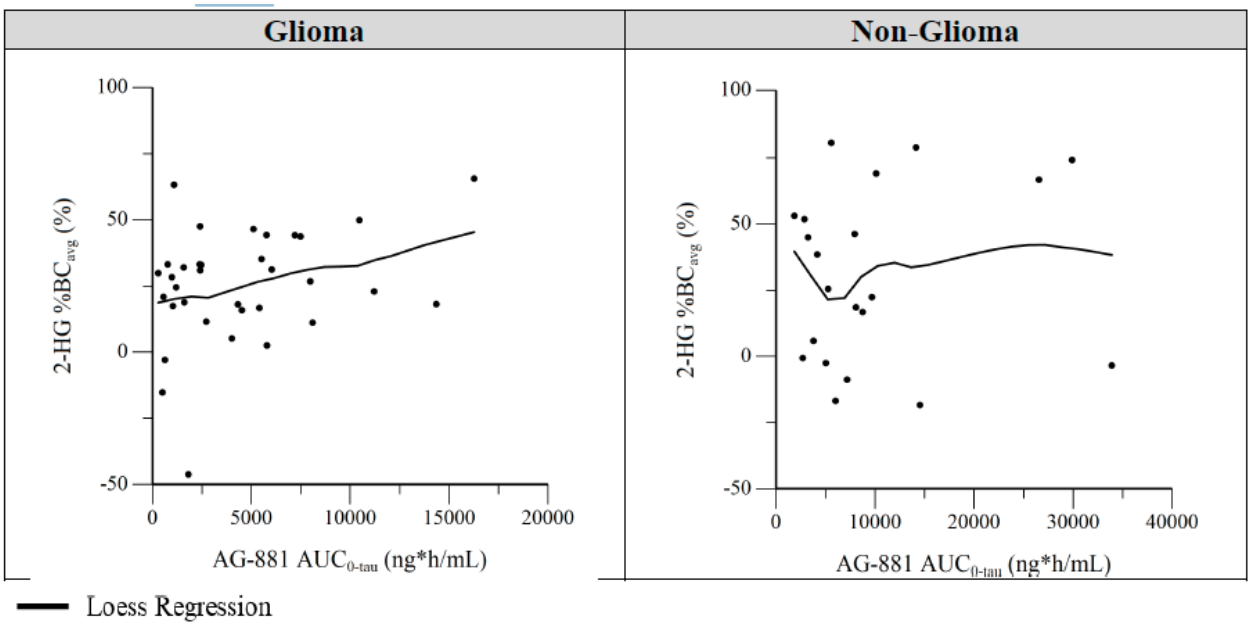
After multiple vorasidenib dose of 50 mg QD in subjects with glioma, median pre-dose 2-HG percent inhibition increased over time and a plateau was reached at approximately 25% inhibition following 2 weeks of QD dosing. No further increases in pre-dose 2-HG percent inhibition were observed after the C1D15 visit, and the inhibition was maintained from C1D15 onward. Median plasma 2-HG percent inhibition based on Cavg for the 50 mg QD dose level at C2D1 was 13.7 % and up to 33.2% in glioma patients. For non-glioma patients, median plasma 2-HG percent inhibition based on Cavg for the 50 mg QD dose level at C2D1 was 51.8 % to 53.1%. Median plasma 2-HG concentrations decreased to concentrations below those observed for healthy subjects (i.e. mean 2-HG concentration in healthy subjects is 72.6±21.8 ng/mL).

Pharmacokinetics/Pharmacodynamics

The PK/PD correlations at C1D15 and C2D1 for plasma vorasidenib (Cmax, Ctrough, and AUC0-tau [AUC0-12hr or AUC0-24hr]) versus 2-HG percent inhibition in plasma (%BCavg, [%BAUEC0-8hr]); 2-HG percent inhibition in urine; and pre-dose (trough) 4β-OHC concentrations, 4β-OHC:cholesterol ratios (change from baseline) were explored (AG881-C-002 PKPD).

At steady state (C2D1), inhibition of 2-HG in plasma was observed following vorasidenib dosing over the 10 to 300 mg QD dose range in glioma patients, with a trend of increasing inhibition as a result of increasing plasma vorasidenib AUC0-tau values. (See figure below)

Figure 4. Percent Inhibition of 2-HG in Plasma vs. Plasma AG-881 $AUC_{0\text{-}tau}$ - Cycle 2 Day 1



Based on the limited pre-dose data collected in urine at the dose of vorasidenib 50 mg QD, 2-HG percent inhibition in urine was observed with increases in plasma vorasidenib pre-dose concentrations over time

for subjects with glioma. Thus, urine 2-HG percent inhibition generally correlated with the plasma 2-HG percent inhibition.

At the 50 mg QD dose of vorasidenib, the mean 4β-OHC plasma concentrations at C2D1 increased 27.0% compared to baseline and the mean plasma 4β-OHC:Cholesterol ratio at C2D1 increased 27.0% compared to baseline.

Furthermore, for single dose in glioma patients on Day -3, the observed mean plasma 2-HG concentrations in glioma patients ranged from 59.9 to 76.1 ng/mL at baseline and generally fluctuated above and below baseline (±20% with a few rare exceptions) over the 72-hour post-dose period following a single dose of 10 to 300 mg AG-881 (vorasidenib). Considering the high inter-subject RSD% ranging from 82.8 to 564.4%, no clinically relevant decreases from baseline were observed in mean plasma 2-HG %BAUEC0-10 following a single dose of 10 to 300 mg AG-881 (vorasidenib).

Following multiple dose administration of AG-881 (vorasidenib) once daily, arithmetic mean plasma %BAUEC0-10 at C1D15 for plasma 2-HG increased from 8.6% at the 10 mg QD dose level to 35.9% at the 300 mg QD dose level. At C2D1, mean percent inhibition of plasma 2-HG based on BAUEC0-10 at C2D1 for plasma 2-HG increased from 19.2% at the 10 mg QD dose level to 45.6% at the 300 QD dose level, with the exception of the 50 mg QD dose level where %BAUEC0- 10 was only 10.2%.

Study AG120-881-C-001: Central Nervous System (CNS) Penetrance and Tumor 2-HG Suppression by Vorasidenib

Study AG120-881-C-001 evaluated the 2-HG suppression by vorasidenib in resected tumours following pre-surgical treatment with vorasidenib and the PK/PD relationship of vorasidenib (F1) in resected tumour tissue and plasma in study.

Pharmacodynamics results

Mean plasma 2-HG concentrations at baseline in subjects with glioma were close to or below the mean levels seen in healthy subjects (72.6 ng/mL). The relative plasma 2-HG average plasma concentration (Cavg) decrease from baseline (percent inhibition) during the pre-surgery period was 2.1% and 21.7% following treatment with vorasidenib 10 mg QD and 50 mg QD, respectively.

Summary of plasma 2-HG PD parameters following multiple oral administrations of vorasidenib are presented in the table below.

Table 11. Summary of Mean Plasma 2-HG Pharmacodynamic Parameters Following Multiple Oral Administrations of Vorasidenib – Day 22

PD Parameters	Statistic	10 mg vorasidenib QD (N=8)	50 mg vorasidenib QD (N=10)
Baseline (ng/mL)	Mean ±StD (RSD %) Median	56.1 ± 15.2 (27.1) 54.0	68.3 ± 20.6 (30.1) 63.9
$AUEC_{0-8}$ (hr•ng/mL)	Mean ±StD (RSD %) Median	429 ± 171 (39.8) 388	400 ± 78.2 (19.6) 408
$\%BAUEC_{0-8}$ (%)	Mean ±StD (RSD%) Median	2.13 ± 29.8 (1396.7) 10.2	21.7 ± 22.8 (105.2) 21.6
C_{avg} (ng/mL)	Mean ±StD (RSD %) Median	54.2 ± 22.0 (40.5) 49.0	50.2 ± 9.59 (19.1) 51.1
$\%BC_{avg}$ (%)	Mean ±StD (RSD%) Median	2.13 ± 29.8 (1396.7) 10.2	21.7 ± 22.8 (105.2) 21.6

Note: Negative values of percent inhibition represent an increase from baseline (stimulation), and positive values of percent change from baseline represent a decrease from baseline (inhibition).
AUEC0-8 is the area of the response curve from time point zero (pre-dose) up to 8 hr post-dose.
%BAUEC0-8 is the percent inhibition for AUEC0-8.
%Bcavg is the percent inhibition for Cavg over the 8-hr observed period.

The posterior median percentage reduction (95% credible interval) in tumour 2-HG was 92.6% (76.1%, 97.6%) in tumours from subjects treated with vorasidenib 50 mg QD, and 63.5% (-22.2%, 88.4%) in tumours from subjects treated with vorasidenib 10 mg QD, compared to tumours from subjects in untreated group.

Brain tumour tissue-to-plasma ratios of 2-HG concentrations following the pre-surgical 28-day treatment with vorasidenib 10 mg QD and 50 mg QD are presented in the table below. The brain tumour tissue-to-plasma concentration ratio for 2-HG was 12-fold lower in the 50 mg vorasidenib group compared to untreated control group. The mean 2-HG brain tumour tissue-to-plasma concentration ratios at the time of surgery was 6.5-fold lower for vorasidenib 50 mg QD compared to vorasidenib 10 mg QD, suggesting greater 2-HG suppression at the higher dose.

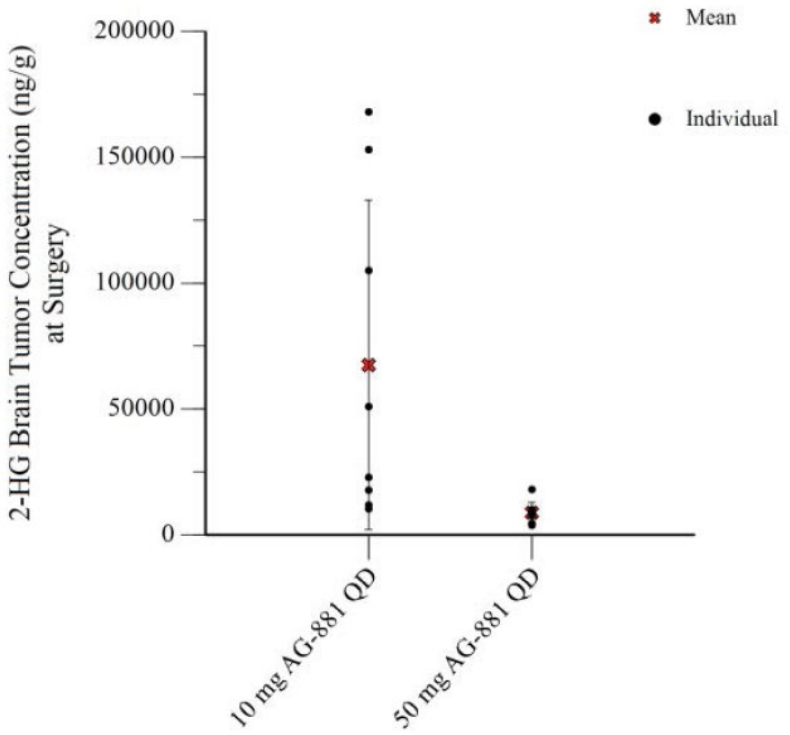
Table 12: Ratios of Brain Tumour Tissue-to-Plasma 2-HG Concentrations and Cavg at the Time of Surgery Following Multiple Oral Administrations of Vorasidenib

Treatment	Ratios[a]	
	2-HG Brain Tumor Tissue-to-Plasma Concentration Ratio	2-HG Brain Tumor Tissue-to-Plasma Cavg Ratio
10 mg vorasidenib QD	1645 (239-3051); 7	1621 (368-2875); 7
50 mg vorasidenib QD	251 (120-381); 7	179 (127-230); 9
Untreated	3067 (371-5763); 5	-

a. Mean (90%CI); n

A scatter plot with overlayed mean (±StD) tumour 2-HG concentrations in tumours resected following the pre-surgical 28-day treatment with vorasidenib 10 mg QD and 50 mg QD is presented in the figure below. The mean observed 2-HG brain tumour tissue concentration at the time of the surgery was 67,500 ng/g in the 10 mg QD vorasidenib dose group and 8,870 ng/g in the 50 mg QD vorasidenib dose group.

Figure 5. Mean (±StD) Tumor 2-HG Concentrations at the Day of Surgery Following Multiple Oral Administrations of Vorasidenib (Linear Scale)



The brain penetrance of vorasidenib 50 mg QD was observed with a brain-to-plasma ratio of 1.69.

Based on these data, a dose of 50 mg QD of F1 was initially selected as the dose for the pivotal study AG881-C-004.

Secondary pharmacology

Electrocardiogram QT prolongation was initially considered an important potential risk of vorasidenib based on non-clinical findings.

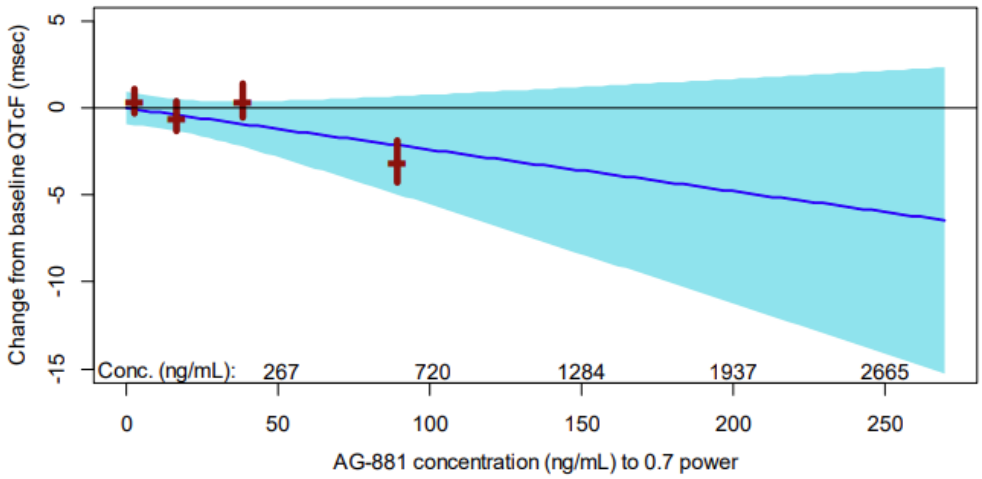
An analysis of QTc versus vorasidenib plasma concentration was conducted in 1905 time-matched triplicate electrocardiogram (ECG)-concentration pairs from 154 subjects across three studies: AG881-C-001, AG881-C-002, and AG120-881-C-001, and doses that ranged from 10 mg QD to 1100 mg QD F1.

A total of 1905 triplicate ECG measurements with time-matched concentration samples from 154 subjects were included in the analysis dataset; ΔQTcF was selected. The fit was optimized by raising concentration to the power 0.70, but neither the slope with transformed concentration nor the intercept itself was significant ($p<0.05$), with or without the selected model covariates. The selected covariates were a flag for baseline QTc greater than its population mean, a flag for magnesium greater than its population mean, and calcium value (all with a negative effect on ΔQTc). No study effects were significant. The 90% CI upper limit for ΔQTcF at the geometric mean C_{max} for Cycle 2 Day 1 therapeutic and supratherapeutic doses (50-200 mg QD) was <1 msec in base and final models, as well as in a sensitivity analysis without the power transformation of concentration.

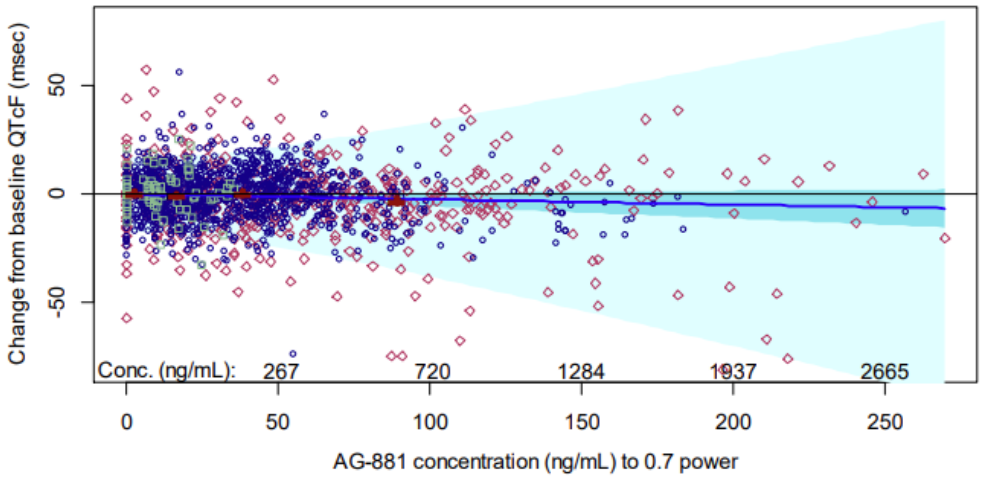
Mean ΔQTcF vs. vorasidenib plasma concentration predicted with the final model (with covariates set to their sample means) is shown with observed data in Figure 6.

Figure 6. Predicted Relationship Between ΔQTcF and Vorasidenib Plasma Concentration, Overlaid with Observations

a. Mean predictions with CI and quartile mean ± 90% CI bars



b. The same superimposed with data and prediction intervals



Points: data; center blue line: projected mean ΔQTcF (with covariates set to sample means); dark blue shaded area: its 90% CI; heavy vertical bars: mean ± 90% CI of ΔQTcF at the mean of each concentration quartile; light blue shaded area: 90% prediction interval including between-subject and residual variability. X-axis: Concentration0.70, e.g., 2670.70 = 50.0

The final model with mean covariate values, as well as base, and sensitivity-case models, were used to predict means and 90% CIs for ΔQTcF at geometric mean vorasidenib Cmax values (Table 13). These assumed steady state at Cycle 2 Day 1 for the 50 mg QD and 200 mg QD doses, combined across AG881-C-001 and AG881-C-002.

Table 137. Predictions of Mean (90% CI) ΔQTcF at 50 and 200 mg QD Dose

	ΔQTcF (msec) at 50 mg QD		ΔQTcF (msec) at 200 mg QD	
Model	**Mean**	**90% CI**	**Mean**	**90% CI**
Final	-1.1	(-2.6, 0.4)	-1.8	(-4.2, 0.6)
Base	-1.0	(-2.6, 0.5)	-1.7	(-4.2, 0.7)
Base linear	-0.8	(-2.2, 0.5)	-1.6	(-4.1, 0.9)

Note: C_{max} values are from non-compartmental analysis of Cycle 2 Day 1 in studies AG881-C-001 and AG881-C-002 at 50 mg QD (228 ng/mL, n=19) and 200 mg QD (474 ng/mL, n=17)

None of the three covariates would influence these results substantially. For the baseline QTcF > mean flag, the mean value (proportion of flagged subjects) is 0.464. Therefore, when the baseline is above average, ΔQTcF is adjusted by (1-0.464) times the coefficient of -4.21 msec, and otherwise ΔQTcF is adjusted by (0-0.464) (-4.21 msec) = 1.95 msec. For calcium, a subject at the 5th percentile of 2.10 rather than the mean of 2.30 mmol/L would have ΔQTcF adjusted by (2.10- 2.30) (-4.06) = 0.81 msec. The adjustment for below-average magnesium is even smaller.

Overall, analysis of the relationship of ΔQTcF to vorasidenib plasma concentration showed no statistically significant slope, with a 90% confidence interval (CI) upper bound of <1 msec for the prediction of ΔQTcF at the geometric mean Cmax for Cycle 2 Day 1 therapeutic (50 mg QD Formulation 1) and supratherapeutic (200 mg QD Formulation 1) doses.

2.6.3. Discussion on clinical pharmacology

Vorasidenib is a dual inhibitor of mutant IDH1 and IDH2 proteins and is thought to delay tumour progression by decreasing expression of the oncometabolite 2-hydroxyglutarate (2-HG). The contribution of AGI-69460 to the efficacy is considered minor.

Plasma 2-HG concentrations could not be used as a biomarker because at baseline in subjects with glioma they were close to or below the mean levels seen in healthy subjects and were not correlated with 2-HG concentrations in brain tumour tissue. It was shown that vorasidenib is distributed to brain tumour tissue. 2-HG concentrations in brain tumour tissue were higher than plasma concentrations with a very high intersubject variability. The mean 2-HG brain tumour tissue-to-plasma concentration ratios at the time of surgery was 6.5-fold lower for vorasidenib 50 mg QD compared to vorasidenib 10 mg QD, which may suggest greater 2-HG suppression at the higher dose. However, there was no correlation between vorasidenib and 2-HG concentrations in brain tumour tissue. Moreover, relation between 2-HG tumour levels with efficacy is not clear. Therefore, these data are considered inconclusive in proof of mechanism of action and as support of dose selection.

Analysis of the relationship between vorasidenib plasma concentrations and QTc interval using Fridericia's correction showed that vorasidenib had no effect on QTc prolongation (report AG881-C-META-CQT). The analysis is acceptable despite the fact that the drug belongs to a class at risk and because it shows a very modest effect in the range of concentrations observed.

Methods

The developed methods for the quantification of vorasidenib (and its metabolite AGI-69460) in several matrix are adequate and comply with the acceptance criteria of the bioanalytical method validation EMA guideline. Description and validation reports were provided with satisfactory results regarding specificity, sensitivity, precision, accuracy, dilution factor linearity, matrix effect. Short and long-term stability of the analytes in the biological matrix were tested and shown to be satisfactory.

Absolute bioavailability

Although vorasidenib is highly permeable in vitro, in study AG881-C-005, after a 50 mg oral dose of vorasidenib citrate containing approximately 100 µCi of [14C] AG-881 followed by a 0.1 mg [13C3 15N3] AG-881, an oral bioavailability of 34% was evaluated for vorasidenib. In this study a vorasidenib formulation was used which resulted in approximately 2-4-fold lower plasma exposures than exposures obtained with the F1 and F2 formulations (AG881 AUC_{inf} was 759 ng.h/mL in study AG881-C-005 vs AUC_{inf} of 2860 ng.h/mL with a dose of 40 mg F2 from study PKH-95032-009).

In addition, the bioanalytical assay for the IV administered vorasidenib had a 10-fold higher LLOQ, resulting in an underestimation of the IV administered vorasidenib AUC because terminal elimination phase could not be evaluated properly.

Food effect

Food has a significant impact on both the AUC and C_{max} of vorasidenib. Both a low-fat and high-fat meal caused an increase in C_{max} and AUC of vorasidenib. In all studies in patients, subjects were instructed to administer the drug at least 2 hours after a meal, or 1 hour before a meal. This is also reflected in section 4.2 of the SmPC.

Pharmacokinetic of the metabolite

AGI-69460 was discovered as part the ADME study AG881-C-005, radio-analysis report dated 23 March 2020. Consequently, it was characterized in a subset of studies in HV (PKH-95032-008/009) and in the pivotal study AG881-C-004. However, any reliable PK parameters characterising the PK of AGI-69460 (C_{max}, AUC, T_{max}, ½, CL/F, Vd/F) following a 40 mg dose in the target population is currently missing.

Despite its pharmacological activity and its concentration at steady-state (M/P of 1.173), no PPK analysis was performed and consequently the effects of renal impairment, age, weight, sex, gender and ethnicity on AGI-69460 are unknown. This will be evaluated as part of the joint PPK model to be submitted as a post approval measure (REC) by March 2026.

Pharmacokinetic in the target population

Overall, the methodology used to develop the PPK model for vorasidenib is supported, its output is less supported. As vorasidenib undergoes a double peak phenomenon, such behaviour was not accounted for and led to poor predictive performance particularly for the F1 formulation. Furthermore, the fact that no PPK analysis for the metabolite AGI-69460 was developed is not understood from a PK perspective. A joint PPK model for both compounds is requested to be provided as a post-authorisation measure (REC) by March 2026 (REC).

Extrapolation to adolescents

The only adolescent in the pivotal study was assigned to the placebo group. There was only one adolescent, aged 16 years and weighted > 40 kg, in study AG881-C-002, receiving vorasidenib. PK data for this subject were generally similar to those observed in the adult population.

Because metabolism mediated by CYP1A2 is mature in adolescents, it can be assumed that pharmacokinetics in adolescents with a similar body-weight as adults are comparable and therefore, for adolescents > 40 kg, which is also the within the body weight range in adults, the same dose as for adults is considered acceptable.

Since there were no subjects with body weight < 40 kg in the clinical studies and the popPK model was not suitable for such a high impact extrapolation, a dosing recommendation for patients weighing <40 kg cannot be provided. This is reflected in the sections 4.2, 5.1 and 5.2 of the SmPC.

Renal impairment

No dedicated study in subjects with renal impairment was conducted, which can be acceptable because vorasidenib is mainly eliminated by metabolism and unchanged vorasidenib was not excreted in the urine.

No starting dose adjustment is recommended for patients with renal impairment (estimated glomerular filtration rate [eGFR] > 40 mL/min/1.73 m2). The pharmacokinetics of vorasidenib and metabolite AGI 69460 have not been studied in patients with eGFR ≤ 40 mL/min/1.73 m2 or renal impairment requiring

dialysis. Vorasidenib should not be used in patients with eGFR ≤ 40 mL/min/1.73 m2 or who require dialysis (see sections 4.2, 4.4 and 5.2 of the SmPC).

Hepatic impairment

The dedicated study in subjects with moderate hepatic impairment (Child-Pugh B) showed that vorasidenib exposures were not increased to a clinically relevant extent. No starting dose adjustment is recommended for patients with mild or moderate (Child Pugh class A or B) hepatic impairment. The safety and efficacy of vorasidenib have not been established in patients with severe hepatic impairment (Child-Pugh classes C). Vorasidenib should be used with caution in patients with pre-existing severe hepatic impairment (Child-Pugh class C) and this patient population should be closely monitored (see sections 4.2, 4.4 and 5.2 of the SmPC).

Other special populations

No clinically significant effects on the pharmacokinetics of vorasidenib were observed based on age (16 to 75 years), race, ethnicity and body weight (43.5 to 168 kg). Female patients were observed to have a 1.6 fold higher vorasidenib exposure as compared to male patients.

PK Interactions

The in vitro findings that vorasidenib is a CYP1A2 substrate were confirmed in the clinical study when vorasidenib was coadministered with a potent CYP1A2 inhibitor (ciprofloxacin). Results showed a 1.29- and 2.53-fold increase in vorasidenib C_{max} and $AUC_{0\text{-}inf}$, respectively. Since ciprofloxacin is considered a moderate-to-strong rather than strong CYP1A2 inhibitor, the recommendation in the SmPC to avoid concomitant use of strong CYP1A2 inhibitors and consider alternative therapies that are not strong inhibitors of CYP1A2 during treatment with vorasidenib, is agreed.

Multiple PBPK models using SimCYP platform were developed to predict the effect of CYP1A2 inhibitors and inducers on the exposure of vorasidenib. Since only an *in vivo* interaction study was conducted with the moderate to strong CYP1A2 inhibitor ciprofloxacin, for which the Ki value needed to be optimized, there are uncertainties with the vorasidenib fraction metabolized (fm) by CYP1A2 and the PBPK model is considered to have too many uncertainties for quantitative predictions of the effects of CYP1A2 inhibitors and inducers on the exposure of vorasidenib. Nevertheless it has been estimated that, through the PBK model, co-administration of vorasidenib with moderate CYP1A2 inducers (phenytoin and rifampicin) may decrease vorasidenib plasma concentration. In such case alternative therapies that are not moderate CYP1A2 inducers during treatment with vorasidenib should be considered.

AGI-69460 is likely a downstream metabolite of the deschloro GSH conjugate of vorasidenib that undergoes hydrolysis to thiol, subsequent methylation and oxidation to deschloro-methyl sulfone likely via a combination of hepatic and extrahepatic pathways. Thus, the DDI with CYPs modulators and AGI-69460 are not expected.

To evaluate vorasidenib interaction potential, the applicant has studied all mandatory enzymes and transporters in vitro. There are no in vitro signals of vorasidenib being an inhibitor (direct or time-dependent) of any studied CYP-enzyme. However, it showed to be an inducer of CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4/5, and UGT1A4.

In vitro, vorasidenib is an inhibitor of breast cancer resistance protein (BCRP) with an IC50 of 1.22 µM, but not a P-gp transporter inhibitor. Caution should be exercised when administering vorasidenib with BCRP substrates (including, but not limited to, rosuvastatin).

The concentration range used (up to 5µM) does not cover the worst expected concentration at intestinal level, i.e. 38.58 µM. The applicant has justified not using a concentration higher than 5 µM due to the extremely low solubility of vorasidenib in aqueous media. Therefore, because of the low solubility and

the fact that no inhibition of Pgp was observed at 5 µM, a relevant inhibition at the intestinal level of Pgp is considered unlikely.

The applicant assessed the potential for direct and time-dependent inhibition (TDI) of the metabolite AGI-69460 on CYP450s enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) in human liver microsomes, using CYP-specific probe substrates. IC50 values for AGI-69460 were found to exceed 10 µM, which is significantly higher than steady state $C_{trough,u}$ concentrations of AGI-69460 (27.7 nM). Therefore, AGI-69460, as a CYP450 inhibitor, is unlikely to cause clinically relevant drug interactions.

Given that IC50 (2.94 µM) of AGI-69460 on OATP1B3 transporters is higher than the concentration expected at worst case 0.693 µM (calculated as 25 times the $C_{trough,u}$ of 0.0277 µM), the clinical DDI with OATP1B3 substrate could be ruled out.

The applicant has evaluated the inhibitory effects of AGI-69460 on various transporters beyond OATPs, specifically P-gp, BCRP, MATE1, MATE2-K, OAT1, OAT3, and OCT2. The findings indicate that AGI-69460 does not inhibit MDR1, MATE1, MATE2-K, OAT1, OAT3, or OCT2. Although AGI-69460 inhibits BCRP with an IC50 of 5.84 µM, the steady-state unbound plasma concentration ($C_{trough,u}$) of 27.7 nM suggests that it is unlikely to cause significant drug-drug interactions with BCRP substrates.

Co-administration of vorasidenib with CYP2C19 or CYP3A4 substrates with narrow therapeutic index may decrease the plasma concentrations of these medicinal products. Concomitant use of CYP2C19 and CYP3A4 substrates with narrow therapeutic index should be avoided in patients taking Voranigo. Co-administration of vorasidenib with sensitive substrates of CYP3A4 without narrow therapeutic index may decrease the plasma concentrations of these medicinal products. Alternative therapies should be considered that are not sensitive substrates of CYP3A4 during treatment with Voranigo.

The applicant had used the PBPK model to investigate the potential perpetrator effect of vorasidenib. However, although the PBPK model described single and multiple dose pharmacokinetics of vorasidenib adequately for the 40 mg F2 dose, there was not a sufficient number of inducers of CYPs and inhibitors of P-gp and BCRP especially with drugs with poor solubility to consider the PBPK model qualified to predict interactions with vorasidenib as inducer or inhibitor for transporters. Furthermore, it has been observed that, in the worst case (after sensitivity analysis using PBPK model), vorasidenib could potentially induce CYP2B6, CYP2C8 and CYP2C9, and have an inhibitory effect on BCRP substrates, the possibility of a DDI between vorasidenib and these CYPs and transporter substrates cannot be excluded. Therefore, interactions with vorasidenib as inducer of CYP3A4 (CYP2C8/9) and CYP2B6 and as inhibitor of BCRP and metabolite AGI-69460 as inhibitor of OATP1B3 are committed to be further investigated by the applicant as a post authorisation measure (REC). Until the in vivo data becomes a recommendation highlighting caution when co-administering vorasidenib with these CYPs (CYP2B6, CYP2C8, and CYP2C9) and transporter (BCRP) substrates, especially when they have a narrow therapeutic index has been included in section 4.5 of the SmPC.

The food effect study showed that administration of vorasidenib with a low-fat meal resulted in a 2.3-fold increase in Cmax and a 1.4-fold increase in AUC. When administered with a high-fat meal, mean Cmax increased by a factor of 3.1 and AUC by a factor of 1.4. Based on these results, patients are advised to avoid food for at least 2 hours before and 1 hour after taking vorasidenib as reflected in section 4.2 of the SmPC.

The multiple-dose administration of omeprazole (40 mg once daily) showed minimal impact on plasma vorasidenib AUC, with geometric mean ratios (GMRs) of 97.8% and 94.1% for AUC 0-t and AUC 0-inf, respectively. However, omeprazole did decrease vorasidenib Cmax by 28% (90% confidence interval: 36% to 18%) compared to vorasidenib administration without omeprazole. Despite this reduction, based on the exposure-response relationship, the observed decrease in Cmax (28%) is not anticipated to

compromise safety or efficacy. Consequently, it is deemed acceptable to co-administer vorasidenib with an acid-reducing agent.

In animals, embryo-foetal development toxicity has been shown to occur. The SmPC recommends to use a barrier method of contraception during the treatment and for at least 2 months after the last dose because the impact of vorasidenib on oral contraceptives is not known (see sections 4.4 and 4.6 of the SmPC). This recommendation is considered acceptable however vorasidenib is intended for long term treatment and encompasses women of childbearing potential. In addition, oral contraceptives have been reported to increase exposure of medicines that are mainly metabolised by CYP1A2 and thus may increase the exposure of vorasidenib. Since females have already a higher vorasidenib exposure compared to males, a potential further increase in vorasidenib exposure due to the use of oral contraceptives may warrant a dose reduction of vorasidenib in those females. As a consequence, the applicant committed to provide results from a DDI study with hormonal contraceptives as post authorisation measure (REC).

Pharmacodynamics

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 the 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 tumour size were not performed.

The pharmacodynamics of vorasidenib were evaluated using serial blood sampling and urine sampling in study AG881-C-002 and study AG120-881-C-001.

In study AG881-C-002, after multiple QD doses at the vorasidenib dose of 50 mg QD in subjects with glioma, median pre-dose 2-HG percent inhibition increased over time and a plateau was reached at approximately 25% inhibition following 2 weeks of QD dosing. No further increases in pre-dose 2-HG percent inhibition were observed after the C1D15 visit, and the inhibition was maintained from C1D15 onward.

In study AG120-881-C-001, vorasidenib demonstrated inhibition of the production of 2-hydroxyglutarate (2-HG) in subjects with recurrent Grade 2 or 3 IDH1 mutant glioma. The decrease in aberrant production of 2-HG in IDH1 mutant glioma is thought to increase DNA 5-hydroxymethylcytosine, reverse the 'proneural' and 'stemness' gene expression signatures, immune cell activation and decreased tumour cell proliferation.

A therapeutic daily dose of vorasidenib was observed to decrease 2-HG tumour concentrations in subjects with IDH1 or IDH2 mutated glioma.

2.6.4. Conclusions on clinical pharmacology

Overall, the PK of vorasidenib has been investigated, characterized and can be considered acceptable.

Remaining issues regarding the PK of its main active metabolite AGI-69460 as well as the insufficiently qualified PBPK modelling to predict drug interactions leaving some issues open in relation to drug interactions will be addressed with post-authorisation measures (RECs)to be provided by the applicant in the near future.

2.6.5. Clinical efficacy

2.6.5.1. Dose response studies

Results from the studies AG881-C-002, AG120-881-C-001, and AG881-C-004 in subjects with gliomas support the selection of vorasidenib 40 mg QD (intended commercial formulation) as the recommended dosage for the treatment of patients with predominantly non-enhancing gliomas with an IDH1 or IDH2 mutation following surgical intervention.

The vorasidenib dose selection was based on safety data from study AG881-C-002, a phase 1 dose escalation study in subjects with advanced solid tumours including glioma in which a favourable safety profile was observed for vorasidenib at dosages of < 100 mg QD (F1). In this study, the MTD was not reached by the Bayesian model. The elevation of liver transaminases was identified as a dose-limiting toxicity (DLT) at dose levels ranging from 100 to 300 mg QD in subjects with glioma.

Based on the exposure-safety relationship and the PK data generated from subjects with glioma during the AG881-C-002 study, in relation to the non-clinical exposure, the following doses were selected for further evaluation (pharmacodynamics, PK, clinical safety, and clinical efficacy) in subjects with glioma in study AG120-881-C-001:

- 50 mg was considered to have an acceptable safety and PK profile.
- 10 mg had sufficient separation in exposure-based PK variability and also provided >90% 2-HG suppression based on tumour xenograft mouse model.

In study AG120-881-001, treatment with vorasidenib resulted in a dose-dependent reduction in tumour 2- HG, with a posterior median percentage reduction of 92.6% (95% credible interval: 76.1%, 97.6%) in subjects treated with vorasidenib 50 mg QD and 63.5% (95% credible interval: 22.2%, 88.4%) in subjects treated with vorasidenib 10 mg QD compared to untreated control tumours. The results also demonstrated that the mean 2-HG brain tumour tissue-to-plasma ratios at the time of surgery were lower for vorasidenib 50 mg QD compared to vorasidenib 10 mg QD, suggesting greater 2-HG suppression at the higher dose. The brain penetrance of vorasidenib 50 mg QD was observed with a brain-to-plasma ratio of 1.69. Durable objective responses were also observed at this dose. Based on these data, a dose of 50 mg QD of F1 was initially selected as the dose for the pivotal AG881-C-004 study.

A new tablet formulation (F2) with film coating (intended commercial formulation) was developed for use in the pivotal study AG881-C-004. Results from a relative bioavailability study (AG881-C-007) showed that a 50 mg dose using F2 resulted in a higher exposure than a 50 mg dose using F1. A 40 mg QD dose of F2 was projected to achieve comparable exposures to those observed at the 50 mg QD dose of F1. Therefore, a 40 mg QD vorasidenib dose with the intended commercial formulation (F2) was introduced into the AG881-C-004 study shortly after its initiation in protocol amendment 1 (v2.0). Subjects who were randomized in the study and received 50 mg vorasidenib (N=5) or matched placebo (N=4) using F1 were switched to the 40 mg QD dose (or matched placebo) of F2 following its introduction into the study.

2.6.5.2. Main studies

Title of study: AG881-C-004 INDIGO Study: a phase 3, multicenter, randomized, double-blind, placebo-controlled study of AG881 in subjects with residual or recurrent grade 2 glioma with an IDH1 or IDH2 mutation.

Methods

- **Study Participants**

Key inclusion criteria

- Be at least 12 years of age and weigh at least 40 kg.
- Have Grade 2 oligodendroglioma or astrocytoma per WHO 2016 criteria.
- Have had at least 1 prior surgery for glioma (biopsy, sub-total resection, gross-total resection), with the most recent surgery having occurred at least 1 year (-1 month) and not more than 5 years (+3 months) before the date of randomization, and no other prior anticancer therapy, including chemotherapy and radiotherapy, and not be in need of immediate chemotherapy or radiotherapy in the opinion of the Investigator. (Note: Subjects undergoing biopsy solely to obtain tissue for central confirmation of IDH mutation status [e.g. tissue from previous surgery was exhausted or not available] will be considered an exception and will not need to wait an additional year from biopsy to be eligible.)
- Have confirmed IDH1 (IDH1 R132H/C/G/S/L mutation variants tested) or IDH2 (IDH2 R172K/M/W/S/G mutation variants tested) gene mutation status disease by central laboratory testing during the Prescreening period and available 1p19q status by local testing (e.g. fluorescence in situ hybridization, comparative genomic hybridization array, sequencing) using an accredited laboratory.
- Have MRI-evaluable, measurable, non-enhancing disease, as confirmed by the BIRC, assessed at Screening on 2D T2-weighted or 2D T2-weighted fluid-attenuated inversion recovery MRI with ≤4 mm slice thickness and no interslice gap. Measurable non-enhancing disease is defined as a least 1 target lesion measuring ≥1 cm × ≥1 cm (bidimensional). Enhancement that is centrally confirmed by the BIRC to be minimal, non-nodular, and non-measurable and that has not changed between the 2 most recent scans (including screening scan) will be permitted.
- Have a Karnofsky Performance Scale (KPS) score (for subjects ≥16 years of age) or Lansky Play Performance Scale (LPPS) score (for subjects <16 years of age) of ≥80%.

Key exclusion criteria

- 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, laser ablation, etc.
- Have features assessed as high-risk 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).

- **Treatments**

Eligible subjects were randomized 1:1 to receive vorasidenib or vorasidenib–matched placebo orally once daily (QD).

Vorasidenib was provided as 10-mg and 40-mg strength tablets to be administered orally, and the placebo was supplied as matched tablets to be administered orally.

A dose of 50 mg QD of vorasidenib (uncoated tablet, clinical formulation) was selected as the starting dose for subjects in the original protocol of this study. Following the first amendment (V2.0 dated from 09 MARCH 2020), the dose was changed from 50 mg QD of the uncoated tablet formulation to 40 mg QD of the film-coated tablet formulation.

The 50 mg dose was used in a small number of subjects until a relative bioavailability study showed that a dose of 40 mg QD (film-coated, commercial formulation) was projected to achieve plasma area under the concentration versus time curve (AUC) exposures comparable to the exposures observed from 50 mg QD of the clinical formulation. As of protocol amendment 1, the clinical formulation was replaced by the commercial formulation. Nine subjects were randomized under the original protocol and initially received the clinical formulation of the uncoated tablet, including 5 subjects who were randomized to and received vorasidenib and 4 subjects who were randomized to and received placebo. The 5 subjects randomized to vorasidenib who initially received the clinical formulation received between 1 month and 3 months of the clinical formulation before switching to the commercial formulation.

Subjects received study treatment in continuous 28-day cycles until centrally confirmed radiographic progressive disease (PD) by the blinded independent review committee (BIRC); development of unacceptable toxicity; need for initiation of chemotherapy, radio therapy (RT), or other anticancer therapy in the opinion of the Investigator; or until any other withdrawal criteria per the study protocol were met.

At the time of centrally confirmed radiographic progressive disease (PD), subjects randomized to placebo were given the option to crossover to receive vorasidenib if not in need of immediate chemotherapy or radiotherapy, or other treatment in the opinion of the Investigator. Subjects who crossed over to vorasidenib received vorasidenib until PD according to the Investigator, development of unacceptable toxicity, start of subsequent anticancer therapy, confirmed pregnancy, death, withdrawal of consent from treatment, lost to follow-up, or Sponsor ending the study, whichever occurred first.

- **Objectives/Outcomes/endpoints**

The primary objective of the study was to demonstrate the superior efficacy of AG-881 based on *radiographic PFS* per BIRC compared with placebo in subjects with residual or recurrent Grade 2 as their only treatment.

Assuming a proportional hazards model for PFS, the following null hypothesis was tested:

H_{01} (null hypotheses): $\Theta_1 \geq 0$ vs H_{a1} (alternative hypotheses): $\Theta_1 < 0$, where Θ_1 is the log HR of PFS in the AG-881 arm versus the placebo arm.

The applicant did not make use of the estimand framework. Nevertheless, the following estimand attributes are implied by the statistical analysis details that are provided as part of the SAP.

Table 14. Estimand for primary objective

Population	**Patients with residual or recurrent grade 2 glioma with an IDH1 or IDH2 mutation.**
Treatment conditions	Assignment to vorasidenib in the hypothetical scenario of no subsequent anticancer therapy, compared to assignment to placebo in the hypothetical scenario of no subsequent anticancer therapy or crossover.
Endpoint (variable)	Progression Free Survival (PFS) defined as the time from date of randomization to the date of first occurrence of centrally confirmed radiographic PD by modified RANO-LGG assessed by the BIRC or death from any cause, whichever occurred earlier.
Population-level summary	Hazard Ratio (HR) from a Cox proportional hazards model stratified by randomisation stratification factors.
Intercurrent events and strategy to handle them	
Subsequent anticancer therapy (including crossover)	Hypothetical: censored in primary analysis at the last tumour assessment before subsequent anticancer therapy, thereby ignoring data after subsequent anticancer therapies and assuming censored at random
Death	Composite: event, to reflect treatment failure

The key secondary objective is to demonstrate the superiority efficacy of vorasidenib based on *Time To Next Intervention (TTNI)* compared with placebo.

Table 15. Estimand for key secondary objective

Population	**Patients with residual or recurrent grade 2 glioma with an IDH1 or IDH2 mutation.**
Treatment conditions	Assignment to vorasidenib compared to assignment to placebo.
Endpoint (variable)	Time To Next Intervention (TTNI) defined as the time from date of randomization to the initiation of first subsequent anticancer therapy (including vorasidenib for subjects randomized to placebo who subsequently crossover to vorasidenib) or death due to any cause.
Population-level summary	Hazard Ratio (HR) from a Cox proportional hazards model stratified by randomisation stratification factors.
Intercurrent events and strategy to handle them	
Death	Composite: a death due to any cause is considered as an event in the statistical analysis.

- **Sample size**

Approximately 340 subjects were to be randomized to the treatment arms using a 1:1 randomization, stratified by chromosome 1p19q co-deletion status (co-deleted or not co-deleted) and baseline tumour size per local assessment (longest diameter of ≥2 cm or <2 cm).

For the primary endpoint, a total of 164 PFS events were required to have at least 90% power to detect a hazard ratio (HR) of 0.6 using a 1-sided log-rank test stratified by the randomization stratification factors at a significance level of 0.025, and a 3-look group sequential design with a Gamma family (-24) α-spending function to determine the efficacy boundaries and a Gamma family (-5) β-spending function to determine the nonbinding futility boundary.

For TTNI, a total of 152 TTNI events were required to have approximately 80% power to detect an HR of 0.636 using a 1-sided log-rank test stratified by the randomization stratification factors at a significance level of 0.025, and a 2-look group sequential design with a Gamma family (-22) α-spending function to determine the efficacy boundaries.

The sample size for the study was determined based on the following assumptions.

- Based on a retrospective natural history study in patients with Grade 2 and Grade 3 predominantly non-enhancing IDH mutation-positive glioma, the median time from surgery to next intervention was approximately 24 months (Huang R et al. 2017). Given the requirement of at least 1 year from the most recent surgery for eligibility, the median PFS for subjects in the placebo arm was assumed to be 18 months and the median PFS for subjects in the vorasidenib arm was assumed to be 30 months; this corresponds to an HR of 0.6 under the exponential model assumption.
- Assuming TTNI to be equal to PFS plus an additional 3 months to accommodate any required washout periods for subsequent anticancer therapy and to prepare for subsequent anticancer therapy, the median TTNI for subjects in the placebo arm was estimated to be 21 (18+3) months, and the median TTNI for subjects in the vorasidenib arm was estimated to be 33 (30+3) months; this corresponds to an HR of 0.636 under the exponential model assumption.
- PFS and TTNI dropout rates of approximately 10% at 12 months
- Non-uniform recruitment period of approximately 42 months.

- **Randomisation and Blinding (masking)**

The randomization schedule was generated by an independent statistical group using an interactive web response system (IWRS).

Subjects who met all study eligibility criteria were randomized 1:1 to receive either oral 40 mg QD vorasidenib or matched placebo. Randomization was stratified by local 1p19q status (co-deleted or not co-deleted) and baseline tumour size per local assessment (longest diameter of ≥2 cm or <2 cm).

Study subjects, investigators, and clinical site staff were blinded to study treatment assignment for the duration of the study until centrally confirmed radiographic PD by the BIRC. The Sponsor remained blinded to the treatment assignment and data until the FA for the primary endpoint, except for select individuals who had access to crossover data for heuristic review of subject data, and/or treatment assignment as needed for safety reporting. Vorasidenib and placebo were packaged and labelled identically so that the study pharmacist remained blinded to treatment assignment.

The IWRS assigned each subject specific Medication ID-labelled study drug containers. Each subject's treatment assignment was unblinded via the IWRS after centrally confirmed radiographic PD by the BIRC. The Investigator could request unblinding of a subject's treatment assignment to determine if the subject was eligible for crossover only after centrally confirmed radiographic PD by the BIRC.

In the event of a medical emergency or confirmed pregnancy in a female subject or in the sexual partner of a male subject, in which knowledge of the investigational product was critical to the subject's management, the Investigator could access the IWRS to reveal the identity of the treatment for that subject. Investigators were encouraged to discuss in advance a plan to break the blinding code with the Medical Monitor or the Sponsor's Responsible Medical Officer. Once the decision to unblind was made, the Investigator had to record the nature of the emergency that required the unblinding, along with the date and time of the unblinding, on the proper source documentation and notify the Sponsor's Medical Monitor (or Responsible Medical Officer) of the unblinding.

Select identified Sponsor and CRO individuals had access to crossover data as necessary. Details regarding access to crossover data were detailed in a separate blinding plan.

- **Statistical methods**

Analysis populations

Analysis Set	Description	Endpoints
Full Analysis Set (FAS)	Included all subjects randomized. Subjects were classified according to the randomized treatment arm according to the ITT principle.	Demographic and other baseline characteristics, disposition, major protocol deviations, subsequent therapies, and efficacy.
Per Protocol Set (PPS)	A subset of FAS. Subjects who met any of the following criteria were excluded from the PPS: • Did not receive at least 1 dose of the randomized treatment • Did not have any measurable lesions at baseline as assessed by the BIRC per modified RANO-LGG • Did not have histopathologically diagnosed Grade 2 oligodendroglioma or astrocytoma per WHO 2016 criteria (ie, do not meet Inclusion Criterion #3). • Had had any prior anticancer therapy other than surgery (biopsy, subtotal resection, gross-total resection) for treatment of glioma including systemic chemotherapy, radiotherapy, vaccines, small-molecules, IDH inhibitors, investigational agents, etc. (ie, met Exclusion Criterion #1).	PFS and TTNI
Safety Analysis Set (SAS)	Include all subjects who received at least 1 dose of the study treatment. Subjects were classified according to the treatment received; subjects randomized to placebo who received at least one dose of vorasidenib prior to crossover, were classified to the vorasidenib arm.	Exposure and concomitant therapies, and safety

Primary endpoint

The censoring and event dates to be considered for the PFS analysis are presented below.

Scenario	Date of Event or Censoring	Outcome
No adequate baseline assessment	Date of randomization[a]	Censored[a]
PD or death • after at most 1 missing or inadequate postbaseline tumor assessment, or • ≤24 weeks after randomization	Date of PD or death	Event
PD or death • after 2 or more missing or inadequate tumor assessments	Date of last adequate tumor assessment[b] documenting no PD prior to subsequent anticancer therapy or missed tumor assessments	Censored
No PD		
Subsequent anticancer therapy given prior to PD or death		

Source: SAP (Appendix 16.1.9)
Abbreviations: PD = progressive disease; PFS = progression-free survival; SAP = statistical analysis plan.
a. If the subject died ≤24 weeks after randomization and did not initiate subsequent anticancer therapy, the death was an event with date on death date.
b. If there were no adequate postbaseline tumor assessments prior to the PD or death, then the time without adequate assessment was measured from randomization; if the criteria were met the censoring was on the date of randomization.

The primary efficacy analysis compared the PFS between the 2 treatment arms using a 1-sided stratified log-rank test. The test was stratified by 1p19q status and baseline tumour size. With regards to the data for the stratification factors, the primary analysis used data as entered into IWRS and the sensitivity analyses used data as entered into the eCRF.

A Cox proportional hazards (PH) model stratified by randomization stratification factors was used to estimate the HR of PFS, along with its 95% CI. Kaplan-Meier estimates (product-limit estimates) were presented by treatment arm together with a summary of associated statistics, including the median PFS per the BIRC with 2-sided 95% CI.

In particular, the PFS rate per the BIRC at 3, 6, 12, 18, 24, 30, 36, 42, and 48 months were estimated with corresponding 2-sided 95% CIs. The CIs for the median were calculated according to Brookmeyer and Crowley (Brookmeyer R and Crowley JJ 1982), and the CIs for the survival function estimates at the time points defined above were derived using the log-log transformation according to Kalbfleisch and Prentice (John D. Kalbfleisch RLP 2002) with back transformation to a CI on the untransformed scale. The estimate of the standard error was computed using the Greenwood formula.

Sensitivity analyses

The following sensitivity analyses were performed to explore the robustness of the primary analysis results. The sensitivity analyses repeated the primary analysis (p-value, hazard ratio and 95% CI) with the modifications below:

- PFS based on BIRC assessment and counting all PD and deaths as events regardless of missing assessments or timing of the event
- PFS based on BIRC assessment on the PPS
- PFS based on BIRC assessment using an unstratified analysis
- PFS based on BIRC assessment using strata derived according to eCRF data instead of those entered in IWRS

- PFS based on BIRC assessment modifying the censoring rules to consider all deaths as events
- PFS based on BIRC assessment modifying the censoring rules with initiation of subsequent anticancer therapy not used as a censoring reason
- PFS based on BIRC assessment on the FAS excluding subjects who received vorasidenib uncoated tablet formulation 50 mg QD or matched placebo.

Key secondary endpoint

TTNI was defined as the time from randomization to initiation of first subsequent anticancer therapy (including vorasidenib, for subjects randomized to placebo who subsequently crossed over) or death due to any cause. If a subject did not initiate a subsequent anticancer therapy or did not die by the data cut-off date, TTNI was censored at the last known alive date.

TTNI was compared between the 2 treatment arms using a 1-sided stratified log-rank test following the testing strategy described in the SAP. The test was stratified by 1p19q status and baseline tumour size. A Cox PH model stratified by randomization stratification factors was used to estimate the HR of TTNI, along with its 95% CI.

Similar Kaplan-Meier analyses for the primary endpoint were also performed for TTNI.

Other secondary endpoints

Additional efficacy endpoints included tumour growth rate (TGR), best overall response (BOR), objective response, complete response (CR)+ partial responses (PR), time to response (TTR), time to CR+PR, duration of response (DoR), duration of CR+PR, OS, HRQoL as measured by the FACT-Br scores, and PFS assessed by the Investigator. Unless otherwise specified, analyses for efficacy response endpoints were performed separately based on the BIRC assessment and based on the Investigator assessment per modified RANO-LLG.

Tumour Growth Rate (TGR)

Tumour growth rate was defined as the on-treatment percentage change in tumour volume every 6 months. The difference in TGR between the vorasidenib and placebo arms was assessed by slope of tumour growth over time using a linear mixed model on log-transformed tumour volume measured by the BIRC at baseline and at each post randomization tumour assessment. The model included baseline tumour volume (log), 1p19q status, time from randomization to tumour assessment (in months), treatment arm, and time by treatment arm interaction as fixed effects, and intercept and slope of time as random effects. An unstructured covariance structure was used to model the covariance matrix for the vector of random intercept and slope of time for each subject. If the estimation algorithm did not converge, a compound symmetry matrix was considered. The log-likelihood ratio test was used to test for the homogeneity between the residuals across treatment groups. If the homogeneity of the test was rejected at the 2-sided 0.05 significance level, a heterogeneous model with different residual variances across treatment groups was to be used.

Subgroup analyses

Subgroup analyses to be performed for PFS by BIRC assessment, TTNI, and OR by BIRC are presented below.

Table 16. Subgroup analyses

Subgroup	Categories
Chromosome 1p19q codeletion status (IWRS)	Co-deleted, Not co-deleted
Tumor size at baseline (IWRS)	Longest diameter of ≥2 cm, <2 cm
Gender	Male, Female
Race	Asian, Black or African American, White, Other
Ethnicity	Hispanic or Latino, Not Hispanic or Latino
Geographic Region	North America, Western Europe, rest of the world
Age	<18, 18-<40, 40-<65, ≥65 years
Pre-treatment tumor growth	<4, 4-<8, ≥8 mm/year
Number of prior surgeries	≤1, ≥2
Type of most recent surgery	Gross total, Subtotal or biopsy
Time from last surgery to randomization	<2, 2-<4, ≥4 years
Location of tumor at initial diagnosis	Frontal, Non-Frontal
MGMT hypermethylation	Yes, No, Unknown
TERT promoter mutation	Yes, No, Unknown
ATRX mutation	Yes, No, Unknown

Adjustment for multiplicity and interim analyses

To preserve the overall type I error in the study, the fixed sequence testing procedure was followed across primary endpoint PFS and key secondary endpoint TTNI. TTNI was to be tested only if PFS reached statistical significance (at the time of IA2 for PFS or FA for PFS).

The interim and the final analyses for PFS were to be performed based on the FAS after the target number of events had occurred as described below. A maximum of 3 distinct data cut-offs were planned in the study:

- Interim Analysis 1 (IA1, futility only): at the time when approximately 55 PFS events (33.5% of the expected 164 events) have occurred; this data cut was only to be used for a futility assessment of PFS although an α of 3x10-9 will be spent, per the α-spending function, to protect the integrity of the study
- Interim Analysis 2 (IA2, superiority and futility): at the time when approximately 123 PFS events (75% of the expected 164 events) have occurred and all subjects have been randomized in the study
- Final Analysis (FA): at the time when 164 PFS events have occurred and all subjects have been randomized in the study

The table below displays the maximum number of analyses expected, and the associated efficacy and futility boundaries for the primary endpoint, if the analyses were performed at the planned number of events as shown in the table.

- The futility boundaries were non-binding, but the study could be stopped for futility if at the time of IA1 or IA2, PFS crossed the futility boundary.
- If the efficacy boundary for PFS was crossed at IA2 or FA, then the primary objective of the study was demonstrated.

Table 17. Efficacy and futility boundaries for PFS

Analysis	IA1	IA2	FA
Number of events (Information fraction)	55 (33.5%)	123 (75%)	164(100%)
1-sided p-value (z-value) for efficacy	NA[a]	≤0.00006 (≤-3.838)	<0.025 (<-1.96)
1-sided p-value (z-value) for futility[b]	≥0.806 (≥0.864)	≥0.185 (≥-0.898)	NA

Abbreviations: IA1=interim analysis 1, IA2=interim analysis 2, FA=final analysis, NA=not applicable
[a] The study will not stop for efficacy at IA1. However, to preserve the integrity of the study, 1-sided $\alpha=3x10^{-9}$ will be spent at the time of IA1.
[b] Non-binding.
The observed number of events at the interim analyses may not match the planned number of events. The efficacy and futility boundaries will be updated based on the actual number of observed events using the pre-specified α-and β-spending functions.

There were 2 planned analyses for TTNI to test for superiority, at the time of the PFS IA2 and FA, respectively.

The significance levels for the analyses of TTNI were determined by the hierarchical testing strategy and the α-spending function for TTNI (Gamma (-22)). The table below displays the analysis triggers for TTNI and the associated efficacy boundaries, if the analyses were performed at the planned number of events as shown in the table.

Table 18: Efficacy boundaries for TTNI

Analysis	IA	FA
Analysis cutoff trigger	123 PFS events	164 PFS events
Number of TTNI events (Information fraction)[a]	110 (72.4%)	152 (100%)
1-sided p-value (z-value) for efficacy	<0.00006 (<-3.858)	<0.025 (<-1.96)

Abbreviations: FA = final analysis; IA = interim analysis.
[a] Number of events expected under H_{12} assuming a hazard ratio for TTNI of 0.636
The observed number of events at the interim analysis may not match the planned number of events. The efficacy boundary will be updated based on the actual number of observed events using the pre-specified α-spending function.

Because the observed number of events at IA1 for PFS, IA2 for PFS, or IA for TTNI may not be exactly equal to the planned number of events, the efficacy and, for the primary endpoint, futility boundaries were to be updated based on the actual number of observed events using the pre-specified α-and β-spending functions. Therefore, the observed Z-test statistics at the interim analyses was compared with the updated efficacy and, for the primary endpoint, futility boundaries. If the study continued to final analysis, the p-value to declare statistical significance at the final analysis would be based on the actual number of events documented at the cutoff date for the final analysis, the α already spent at the interim analyses, and the hierarchical testing strategy.

Changes from planned analyses

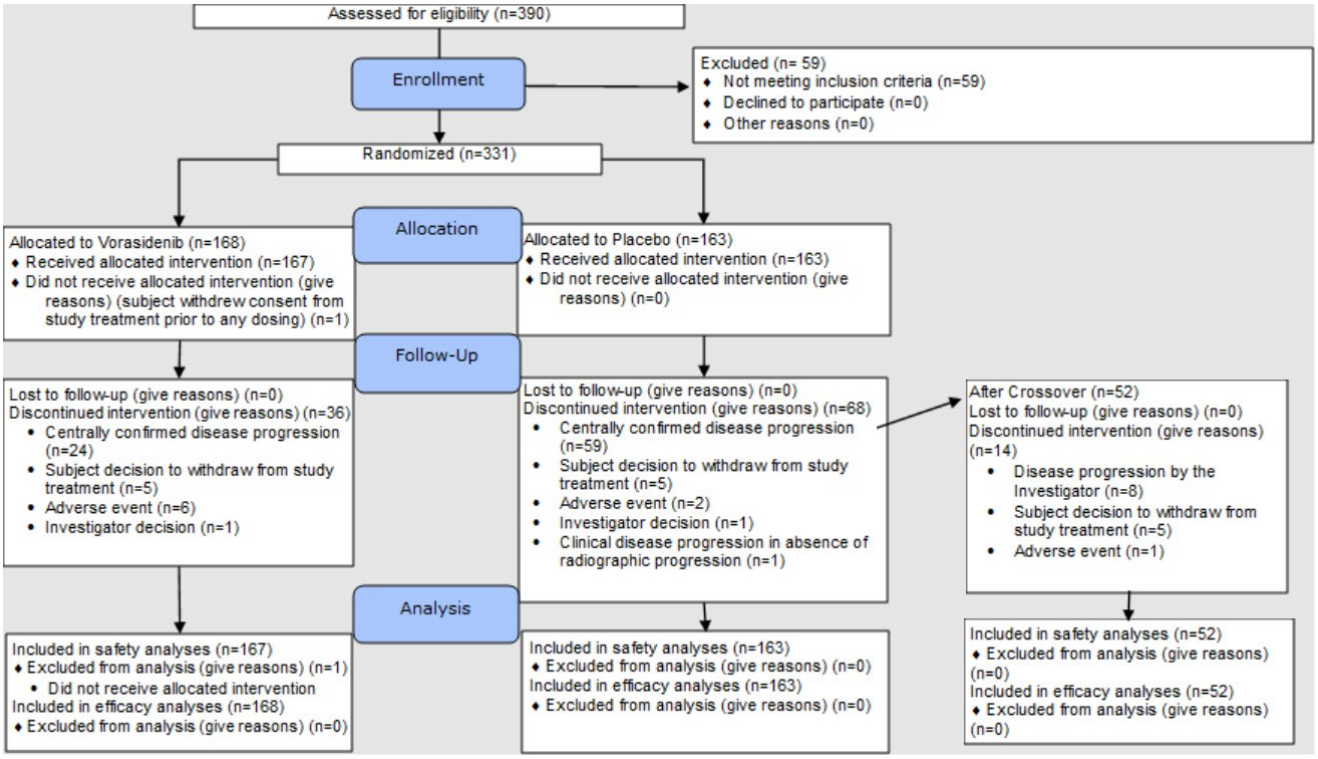
The main changes in planned analyses were introduced with protocol amendment 2, version 3.0 (17 December 2020):

- Revised the statistical design (including testing hierarchy, sample size and interim decision rules) as well as study power and HR assumption.
- Removed TGR from the testing order and identified TTNI as the only key secondary endpoint.
- Modified the definition of TTNI to include death as an event.
- Added CR+ PR, time to CR+PR, and duration of CR+PR as secondary efficacy endpoints.
- Added exploratory objective to evaluate TGR before and after treatment with vorasidenib and placebo.
- Added PGI, PGI-S, and PGI-F as additional measures of HRQoL.
- Added PPS to the analysis sets.

Results

- **Participant flow**

A total of 466 subjects entered pre-screening for central confirmation of IDH mutation status; of these, 76 subjects were considered pre-screen failures, the majority due to IDH mutation status not being centrally confirmed.



At the time of data cut-off (06 September 2022) for this primary clinical study report (CSR), a higher proportion of subjects (78.0%, n=131) were continuing their assigned treatment in the vorasidenib arm than in the placebo arm (58.3%, n=95). In the vorasidenib arm, 36 subjects (21.4%) had discontinued their assigned treatment compared to 68 subjects (41.7%) in the placebo arm.

The most commonly reported reasons for treatment discontinuation were:

• Centrally confirmed disease progression, which was more common in the placebo arm (36.2%, n=59) than in the vorasidenib arm (14.3%, n=24).

• AE, which was more common in the vorasidenib arm (3.6%, n=6) than in the placebo arm (1.2%, n=2).

The proportion of subjects discontinuing treatment for other reasons was consistent between the placebo and vorasidenib arms and included: subject decision to withdraw from study treatment, investigator decision, and clinical disease progression in the absence of radiographic progression.

As of the data cut-off date (06 September 2022) the proportion of subjects continuing in the study was consistent between both treatment arms. Four subjects in each treatment arm prematurely discontinued overall study participation (voluntary withdrawal by the subject).

Table 19. Subject Disposition (Full Analysis Set)

Status[a, b]	Placebo N=163 n (%)	Vorasidenib N=168 n (%)
Randomized subjects		
Treated, n (%)	163 (100)	167 (99.4)
Not treated, n (%)	0	1 (0.6)
Treatment status		
Ongoing	95 (58.3)	131 (78.0)
Discontinuation from treatment	68 (41.7)	36 (21.4)
Reason for discontinuation		
Centrally confirmed disease progression	59 (36.2)	24 (14.3)
Subject decision to withdraw from study treatment	5 (3.1)	5 (3.0)
AE	2 (1.2)	6 (3.6)
Investigator decision	1 (0.6)	1 (0.6)
Clinical disease progression in absence of radiographic progression	1 (0.6)	0
Study status		
On study	159 (97.5)	164 (97.6)
Discontinued from study	4 (2.5)	4 (2.4)
Reason for discontinuation		
Voluntary withdrawal from overall study participation by subject	4 (2.5)	4 (2.4)
PFS follow-up status		
Ongoing	4 (2.5)	7 (4.2)
Discontinued from PFS follow-up	2 (1.2)	0
Reason for discontinuation from PFS follow-up		
Centrally confirmed disease progression	1 (0.6)	0
Withdrawal of consent from overall study participation	1 (0.6)	0
OS follow-up status		
Ongoing	4 (2.5)	25 (14.9)
Discontinued from OS follow-up	0	0

Abbreviations: AE = adverse event; FAS = Full Analysis Set; N = number of subjects in the FAS within each treatment arm; n = number of subjects in the FAS within each treatment arm in each category; OS = overall survival; PFS = progression-free survival.
a. No subjects discontinued the treatment, the study, PFS follow-up or OS follow-up due to COVID-19.
b. There were no deaths during the study.

Note: The denominator used to calculate percentages is N.

- **Recruitment**

Ten countries participated in this study and enrolled subjects: Canada (2 sites), France (3 sites), Germany (4 sites), Israel (4 sites), Italy (4 sites), Netherlands (3 sites), Spain (3 sites), Switzerland (2 sites), United Kingdom (4 sites) and United States (38 sites).

- **Conduct of the study**

Table 20. Substantial Protocol Amendments

Protocol Amendment Number	Substantial Change
Amendment 1, version 2.0 09 March 2020	The protocol was primarily amended to switch from one formulation of AG-881, which had been used for all clinical studies of AG-881 to date including the initiation of this study, to a second formulation of AG-881, which is the intended commercial formulation and is being introduced in this study now based on results of a recently completed relative bioavailability study. The first amendment occurred shortly after the initiation of the study. Subjects who were randomized in the study and received 50 mg vorasidenib (N=5) or matched placebo (N=4) using F1 were switched to the 40 mg QD dose (or matched placebo) of F2 following its introduction into the study. The substantial changes included in the current amendment are itemized as follows: • Changed formulation of AG-881 from AG-881 uncoated tablets to AG-881 film-coated tablets. • Changed the starting dose of AG-881 from 50 mg QD of the uncoated tablet formulation to 40 mg QD of the film-coated tablet formulation. • Changed the dose reduction levels to reflect the film-coated tablet formulation and the new starting dose. • Added the Lansky Play Performance Scale as a performance assessment measure for subjects <16 years of age. • Added the Bedside Schwartz method as a way of measuring creatinine clearance for subjects <18 years of age. • Removed the lamotrigine exclusion criterion.

Amendment 2, version 3.0 17 December 2020	• Revised the statistical design, including study power and HR assumption. • Removed TGR from the testing order and identified TTNI as the only key secondary endpoint. • Modified the definition of TTNI to include death as an event. • Added the evaluation of vorasidenib's circulating metabolite AGI 69460 in plasma to the PK secondary objective. • Added CR+ PR, time to CR+PR, and duration of CR+PR as secondary efficacy endpoints. • Added exploratory objective to evaluate TGR before and after treatment with vorasidenib and placebo. • Added PGI, PGI-S, and PGI-F as additional measures of HRQoL. • Added more details in the statistical methods section. • Added PPS to the analysis sets. • Added guidance on allowable temporary modifications to study conduct during COVID-19 public health emergencies during which adherence to protocol-specified procedures may be impeded. • Revised definition of women of childbearing potential and clarified definition of abstinence. • Updated prohibited concomitant medications to include medications that are CYP2C8 or CYP2C19 substrates with a narrow therapeutic index. • Added 40-mg strength tablets. • Removed language around vorasidenib possibly being a phototoxicant. • Added Tanner staging of sexual maturity at the C1D1 visit for all subjects 12-17 years of age at time of enrollment as well as on- treatment assessment at regular intervals in subjects who are less than Stage 5 at the C1D1 assessment. • Increased the frequency of height collection for subjects 12-17 years of age who are being assessed for Tanner stage to occur at the same visits as the Tanner stage assessments.
Amendment 3, version 4.0 20 July 2021	Sponsor was changed from Agios Pharmaceuticals, Inc. (Agios) to Institut de Recherches Internationales Servier (I.R.I.S.).

Abbreviations: C1D1 = cycle 1 day 1; COVID-19 = coronavirus disease 2019; CR = complete response; CYP = cytochrome P450; HR = hazard ratio; HRQoL = health-related quality of life; PGI = patient global impression; PGI-F = patient global impression of frequency; PGI-S = patient global impression of severity; PK = pharmacokinetics; PPS = per protocol set; PR = partial response; TGR = tumor growth rate; TTNI = time to next intervention.

- **Baseline data**

Demographic Characteristics

Table 21. Summary of Demographic Characteristics and Physical Measurements at Baseline (Full Analysis Set)

	Placebo N=163	Vorasidenib N=168
Age (years)		
n	163	168
Mean (StD)	39.8 (9.53)	40.9 (10.51)
Median (Q1, Q3)	39.0 (34.0, 45.0)	40.5 (34.0, 46.5)
Min, max	16, 65	21, 71
Age category (years), n (%)		
<16[a]	0	0
16 - <18	1 (0.6)	0
18 - <40	87 (53.4)	76 (45.2)
40 - <65	74 (45.4)	90 (53.6)
≥65	1 (0.6)	2 (1.2)
Sex, n (%)		
Male	86 (52.8)	101 (60.1)
Female	77 (47.2)	67 (39.9)
Race, n (%)		
American Indian or Alaska Native	0	1 (0.6)
Asian	8 (4.9)	5 (3.0)
Black or African American	1 (0.6)	2 (1.2)
Native Hawaiian or other Pacific Islander	0	0
White	132 (81.0)	125 (74.4)
Other	1 (0.6)	2 (1.2)
Not reported	21 (12.9)	33 (19.6)
Ethnicity, n (%)		
Hispanic or Latino	9 (5.5)	9 (5.4)
Not Hispanic or Latino	135 (82.8)	122 (72.6)
Not Reported	19 (11.7)	37 (22.0)
BMI (kg/m^2)		
n	162	166
Mean (StD)	26.52 (5.887)	26.81 (5.748)
Median (Q1, Q3)	25.48 (22.32, 29.10)	25.91 (23.29, 29.20)
Min, max	17.7, 48.9	17.6, 60.3

Data Cutoff Date: 06Sep2022
Abbreviations: BMI = body mass index; N = number of subjects in the FAS within each treatment arm; n = number of subjects in the FAS within each treatment arm in each category; Q1 = first interquartile range; Q3 = third interquartile range; StD = standard deviation.
Notes: The denominator used to calculate percentages is N.
Baseline is defined as the last assessment on or before the date of randomization (for subjects randomized and not dosed), and as the last assessment on or before the start of study treatment (for subjects randomized and dosed).

Age (years): (year of informed consent – year of birth). BMI = weight (kg) / height (cm)2. a.The minimum age for enrollment was 12 years.

Baseline Disease Characteristics

The main disease characteristics at enrollment for subjects in the FAS, are summarized by treatment arm in the table below.

Table 22. Summary of Baseline Disease Characteristics and Prior Surgeries for Glioma (Full Analysis Set)

	Placebo N=163 n (%)	Vorasidenib N=168 n (%)
Histological subtype, n (%)		
Oligodendroglioma	84 (51.5)	88 (52.4)
Astrocytoma	79 (48.5)	80 (47.6)
Chromosome 1p19q co-deletion status (source: eCRF)		
Co-deleted	84 (51.5)	88 (52.4)
Not co-deleted	79 (48.5)	80 (47.6)
Not available	0	0
CDKN2A homozygous deletion	93 (57.1)	109 (64.9)
Present	2 (1.2)	0
Absent	91 (55.8)	109 (64.9)
Karnofsky Performance Scale Score, n (%)[a]		
100	87 (53.4)	90 (53.6)
90-80	76 (46.6)	77 (45.8)
70-60	0	1 (0.6)
Time from initial diagnosis to randomization (months)		
n	163	168
Mean (StD)	37.52 (29.407)	39.60 (28.873)
Median (Q1, Q3)	29.60 (19.15, 50.23)	35.37 (22.26, 46.05)
Min, Max	11.0, 230.1	11.9, 233.9
Tumor size at baseline (cm) (Source: eCRF)		
Longest diameter of ≥2 cm	137 (84.0)	139 (82.7) 136 (81.0)
Longest diameter of <2 cm	26 (16.0)	29 (17.3)
Pre-treatment tumor growth (mm/year)		
n[b]	68	56
Mean (StD)	2.79 (4.479)	2.17 (2.980)
Median (Q1, Q3)	2.00 (0.55, 4.60)	1.95 (0.30, 4.10)
Min, Max	-7.9, 22.1	-4.8, 9.6
<4	46 (28.2)	41 (24.4)
4-<8	16 (9.8)	14 (8.3)
≥8	6 (3.7)	1 (0.6)
Subjects with prior surgeries for Glioma, n (%)		
0	0	0
1	134 (82.2)	126 (75.0)
⩾2	29 (17.8)	42 (25.0)

	Placebo N=163 n (%)	Vorasidenib N=168 n (%)
Time from last surgery for Glioma to randomization (year)		
n	163	168
Mean (StD)	2.60 (1.285)	2.66 (1.139)
Median (Q1, Q3)	2.21 (1.50, 3.68)	2.52 (1.61, 3.52)
Min, Max	0.9, 5.0	0.2, 5.2
>1-2	71 (43.6)	56 (33.3)
>2-4	57 (35.0)	88 (52.4)
>4	34 (20.9)	22 (13.1)
Laterality at initial diagnosis, n (%)		
Left	77 (47.2)	89 (53.0)
Right	84 (51.5)	79 (47.0)
Bilateral	2 (1.2)	0
IDH1 positive	152 (93.3)	163 (97.0)
R132C	7 (4.3)	8 (4.8)
R132G	1 (0.6)	5 (3.0)
R132H	138 (84.7)	146 (86.9)
R132L	4 (2.5)	2 (1.2)
R132S	2 (1.2)	2 (1.2)
IDH2 positive	11 (6.7)	5 (3.0)
R172G	0	2 (1.2)
R172K	10 (6.1)	3 (1.8)
R172M	0	0
R172S	0	0
R172W	1 (0.6)	0
MGMT promoter status, n (%)		
Methylated	52 (31.9)	39 (23.2)
Unmethylated	18 (11.0)	14 (8.3)
Unknown	3 (1.8)	3 (1.8)
Not reported	90 (55.2)	112 (66.7)
TERT promoter status, n (%)		
Yes	24 (14.7)	34 (20.2)
No	18 (11.0)	18 (10.7)
Unknown	0	1 (0.6)
Not reported	121 (74.2)	115 (68.5)

	Placebo N=163 n (%)	Vorasidenib N=168 n (%)
ATRX mutation status, n (%)		
Yes	64 (39.3)	60 (35.7)
No	51 (31.3)	61 (36.3)
Unknown	2 (1.2)	3 (1.8)
Not reported	46 (28.2)	44 (26.2)
P53 mutation status, n (%)		
Yes	65 (39.9)	58 (34.5)
No	46 (28.2)	47 (28.0)
Unknown	2 (1.2)	7 (4.2)
Not reported	50 (30.7)	56 (33.3)

Data Cutoff Date: 06Sep2022
Abbreviations: ATRX= α-thalassemia/mental-retardation-syndrome-X-linked gene; eCRF = electronic case report form; FAS = Full Analysis Set; IDH = isocitrate dehydrogenase; IWRS = interactive web response system; Max = maximum; MGMT= O6 methylguanine-DNA-methyltransferase; Min = minimum; N = number of subjects in the FAS within each treatment arm; n = number of subjects in the FAS within each treatment arm in each category; Q1 = first interquartile range; Q3 = third interquartile range; StD = standard deviation; TERT = telomerase reverse transcriptase.
a. There were no Karnofsky Performance Scale scores for 50-40, or 30-10. No data were reported for the Lansky Play-Performance Scale score.
b. For pre-treatment growth rate, n is the number of subjects with pre-treatment volume data available.

Table 23. Summary of Prior Surgery for Glioma (Full Analysis Set)

	Placebo N=163 n (%)	Vorasidenib N=168 n (%)	Overall N=331 n (%)
Subjects with prior surgeries for Glioma, n (%)			
0	0	0	0
1	134 (82.2)	126 (75.0)	260 (78.5)
≥2	29 (17.8)	42 (25.0)	71 (21.5)
Type of surgery, n (%)			
Gross Total	94 (57.7)	85 (50.6)	179 (54.1)
Sub-Total	67 (41.1)	81 (48.2)	148 (44.7)
Biopsy	20 (12.3)	24 (14.3)	44 (13.3)

Medical History and Concurrent Illnesses

The table below summarizes prior and ongoing medical history reported in ≥10% of subjects. Most prior and ongoing medical history preferred terms were classified as nervous system disorders. Prior and ongoing nervous system disorders were reported overall in 294 (88.8%) and 276 subjects (83.4%), respectively.

Table 24. Summary of Prior and Ongoing Medical History Preferred Terms in ⩾10% of Subjects in Any Treatment Arm (Full Analysis Set)

System Organ Class Preferred Term	Placebo N=163		Vorasidenib N=168	
	Prior n (%)	Ongoing n (%)	Prior n (%)	Ongoing n (%)
Subjects with any medical history	160 (98.2)	156 (95.7)	165 (98.2)	160 (95.2)
Nervous system disorders	140 (85.9)	134 (82.2)	154 (91.7)	142 (84.5)
Seizure	106 (65.0)	91 (55.8)	112 (66.7)	88 (52.4)

Headache	57 (35.0)	56 (34.4)	48 (28.6)	44 (26.2)
Migraine	18 (11.0)	18 (11.0)	13(7.7)	13(7.7)
Psychiatric disorders	74 (45.4)	72 (44.2)	74 (44.0)	71 (42.3)
Anxiety	47 (28.8)	47 (28.8)	41 (24.4)	40 (23.8)
Depression	30 (18.4)	29 (17.8)	27 (16.1)	26 (15.5)
Insomnia	25 (15.3)	24 (14.7)	15 (8.9)	15 (8.9)
Immune system disorders	37 (22.7)	35 (21.5)	37 (22.0)	37 (22.0)
Seasonal allergy	21 (12.9)	20 (12.3)	20 (11.9)	20 (11.9)
General disorders and administration site conditions	36 (22.1)	34 (20.9)	27 (16.1)	24 (14.3)
Fatigue	31 (19.0)	30 (18.4)	22 (13.1)	20 (11.9)
Vascular disorders	28 (17.2)	23 (14.1)	33 (19.6)	25 (14.9)
Hypertension	25 (15.3)	21 (12.9)	23 (13.7)	20 (11.9)

Data Cutoff Date: 06Sep2022
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in the FAS within each treatment arm; n = number of subjects in the FAS within each treatment arm in each category; PT = preferred term; SOC = system organ class.
Notes: The denominator used to calculate percentages is N.
Medical and surgical history are coded using MedDRA version 25.1.
A subject is counted only once for a SOC and a PT within the corresponding SOC.

Prior Medications

Prior medication used by ≥15% of subjects in any treatment arm classified by Anatomical Therapeutic Chemical 3 (ATC3) categories is shown in the table below.

Most subjects were receiving medications before the start of the study: 153 (93.9%) and 143 (85.6%) in the placebo and vorasidenib arms, respectively.

The majority of subjects in both arms had received at least 1 antiepileptic medication prior to first dose of study treatment. The most commonly (≥10%) reported medications in this class included:

- Levetiracetam: 77 (47.2%) and 76 (45.5%)
- Lacosamide: 19 (11.7%) and 19 (11.4%)
- Lamotrigine: 17 (10.4%) and 14 (8.4%).

Table 25. Summary of Prior Medications (ATC Classes) in ≥15% of Subjects in Either Treatment Arm (Safety Analysis Set)

Anatomical Therapeutic Chemical (ATC3)	Placebo N=163 n (%)	Vorasidenib N=167 n (%)
Subjects with at least one prior medication	153 (93.9)	143 (85.6)
Antiepileptics	114 (69.9)	106 (63.5)
Other analgesics and antipyretics	41 (25.2)	34 (20.4)
Viral vaccines	25 (15.3)	34 (20.4)
Antidepressants	26 (16.0)	19 (11.4)
Anxiolytics	23 (14.1)	26 (15.6)

Data Cutoff Date: 06Sep2022
Abbreviations: ATC = anatomical therapeutic chemical; N = number of subjects in the SAS within each treatment arm; n = number of subjects in the SAS within each treatment arm in each category; SAS = Safety Analysis Set.
Notes: The denominator used to calculate percentages is N.

Prior medications are medications that were initiated before the first dose of the study treatment, regardless of when they were ended.
A subject was counted only once for an ATC category and a preferred name within the corresponding ATC category.
One preferred name may be represented under several different ATC categories based on its possible therapeutic properties.
Medications were coded using the World Health Organization Drug Dictionary 2022, and ATC classification level 3 was used.

- **Numbers analysed**

Table 26. Summary of Analysis Sets (Full Analysis Set)

	Placebo N=163 n (%)	Vorasidenib N=168 n (%)	Overall N=331 n (%)
Full Analysis Set	163 (100)	168 (100)	331 (100)
Safety Analysis Set	163 (100)	167 (99.4)	330 (99.7)
Per Protocol Set	163 (100)	166 (98.8)	329 (99.4)

Data Cutoff Date: 06Sep2022
Abbreviations: FAS = Full Analysis Set; N = number of subjects in the FAS within each treatment arm; n = number of subjects in the FAS within each treatment arm in each category; PPS = per protocol analysis set; SAS = Safety Analysis Set.
Notes: The denominator used to calculate percentages is N.

- **Outcomes and estimation**

Primary Endpoint: Progression-Free Survival

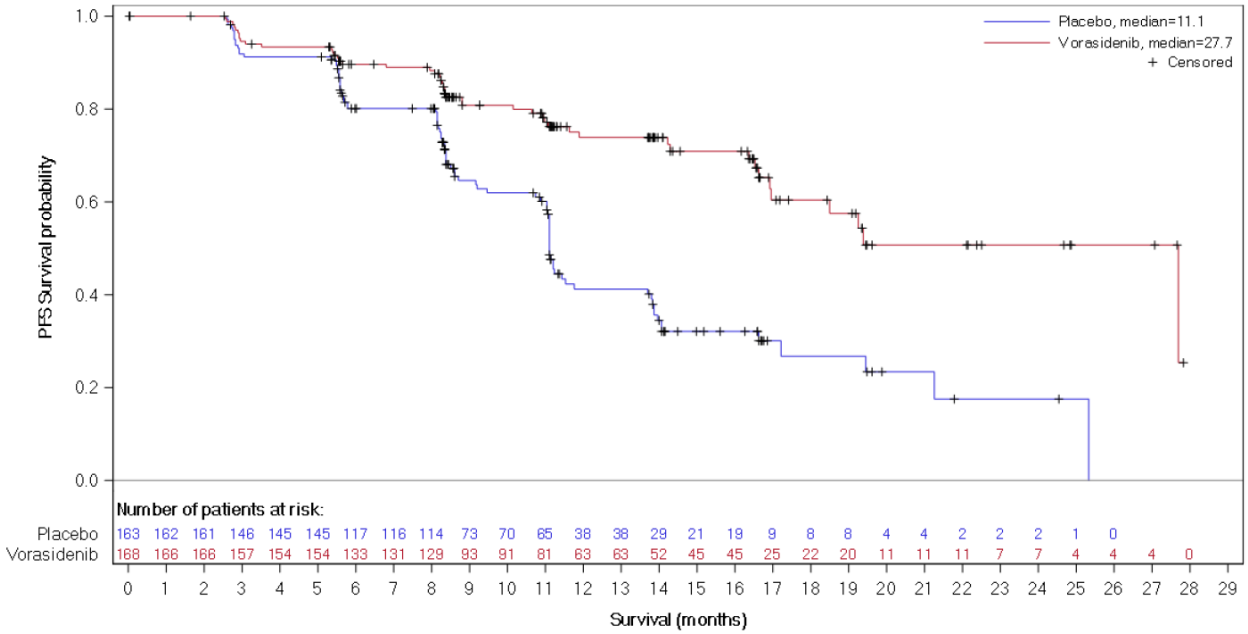
The median follow-up duration was 13.7 (95% CI, 11.2, 14.1) months and 14.1 (95% CI, 11.1, 15.2) months in the vorasidenib and placebo arms, respectively.

Table 27. Progression-Free Survival per the BIRC (FAS)

	Placebo (N = 163)	Vorasidenib (N = 168)
PFS (months)[a]		
Number of events, n (%)	88 (54.0)	47 (28.0)
Progressive disease	88 (54.0)	47 (28.0)
Death	0	0
Number censored, n (%)[b]	75 (46.0)	121 (72.0)
Start of subsequent anticancer therapy	1 (0.6)	1 (0.6)
No adequate baseline assessment	0	1 (0.6)
Withdrawal of consent	4 (2.5)	4 (2.4)
Ongoing without an event[c]	70 (42.9)	115 (68.5)
25th percentile (95% CI)[d]	8.2 (5.7, 8.5)	11.9 (8.8, 16.6)
Median (95% CI)	11.1 (11.0, 13.7)	27.7 (17.0, NE)
75th percentile (95% CI)	19.4 (14.1, 25.3)	NE (27.7, NE)
Hazard ratio (95% CI)[e]		0.39 (0.27, 0.56)
(95% repeated CI)[f]		(0.21, 0.73)
p-value[g]		0.000000067
Kaplan-Meier survival rate (%) (95% CI)[h,i]		
3 months	91.8 (86.4, 95.2)	94.6 (89.8, 97.1)
6 months	80.1 (72.9, 85.6)	89.6 (83.8, 93.4)
12 months	41.2 (32.1, 50.1)	73.8 (65.3, 80.6)
18 months	26.7 (17.1, 37.4)	60.4 (48.3, 70.5)
24 months	17.6 (7.1, 31.9)	50.7 (36.2, 63.5)

Data cutoff date 06 September 2022.
Note: PFS per BIRC refers to death or documented radiographic PD as assessed by the BIRC per modified RANO-LGG.
a. PFS = (date of event or censoring – randomization date + 1) / 30.4375.
b. Subjects with no adequate Baseline tumour assessment or with no adequate post-baseline tumour assessments within 24 weeks after randomization were censored on the date of randomization, unless the subject died within 24 weeks after randomization, in which case, death was an event on date of death. If a subsequent anticancer therapy was started prior to an event, the subject was censored on the date of the last adequate tumour assessment that documented no PD prior to the start of the subsequent anticancer therapy. Subjects without an event or with an event after 2 or more inadequate or missing post-Baseline tumour assessments were censored on the date of the last adequate tumour assessment that documented no PD; regardless, deaths within 24 weeks after randomization for subjects who did not initiate subsequent anticancer therapy were considered an event. Ongoing without an event were censored at the last adequate post-Baseline assessment date.
c. Five subjects crossed over to receive vorasidenib following centrally confirmed radiographic PD by the BIRC; however, these subjects are censored as Ongoing without an event for the primary analysis for PFS per the BIRC.
d. Quartile estimates from product-limit (Kaplan-Meier) method. CIs were calculated from Brookmeyer and Crowley method (Brookmeyer R and Crowley JJ 1982) with log-log transformation.
e. HR was calculated from the Cox regression model stratified by the randomization strata with placebo as the denominator, with two-sided 95% CIs.
f. The 2-sided repeated CI for the HR was calculated for HR based on the method from Jennison and Turnbull (2000).
g. P-value was calculated from the one-sided log-rank test stratified by the randomization factors (Local chromosome 1p19q codeletion status and Tumour size at Baseline per local assessment per IWRS). For IA2, PFS was tested at a one-sided efficacy α-level of 0.000359, based on an updated efficacy boundary corresponding to the 82% information fraction observed at IA2.
h. Based on Survival Distribution Function estimates from product-limit method.
i. Kaplan-Meier survival rate was not evaluable from 30 to 48 months, inclusive.

Figure 7. Kaplan-Meier Plot for PFS per BIRC (FAS)



Data Cutoff Date: 06Sep2022
Abbreviations: BIRC = Blinded Independent Review Committee; PD = progressive disease; PFS = progression-free survival; RANO-LGG = Response Assessment in Neuro-oncology for Low-grade Gliomas.
PFS = (Date of event or censoring – Randomization Date + 1) / 30.4375.
PFS based on the BIRC refers to death or documented radiographic PD as assessed by the BIRC per modified RANO-LGG.
Subjects with no adequate Baseline tumour assessment or with no adequate post-Baseline tumour assessments within 24 weeks after randomization will be censored on the date of randomization, unless the subject dies within 24 weeks after randomization, in which case, death will be an event on date of death; If a subsequent anticancer therapy is started prior to an event, the subject will be censored on the date of the last adequate tumour assessment that documented no PD prior to the start of the subsequent anticancer therapy; Subjects without an event or with an event after 2 or more inadequate or missing post-Baseline tumour assessments will be censored on the date of the last adequate tumour assessment that documented no PD; regardless, deaths within 24 weeks after randomization for subjects who did not initiate subsequent anticancer therapy will be considered an event; Ongoing without an event are censored at the last adequate post-Baseline assessment date.
NE: not estimable.

As of the second interim analysis (IA2) data cut-off date (06 September 2022), the observed information fraction was 82% (135/164 PFS events) for the primary. With longer follow up, vorasidenib continued to demonstrate a clinically meaningful benefit compared to placebo. The applicant has performed follow-up analyses of PFS of the blinded data collected after 06 September 2022 (the data cut-off for IA2 and the basis for the marketing authorization application) until 07 March 2023 study unblinding date. As of 07 March 2023, an additional 23 PFS events by BIRC have occurred, representing an observed information fraction of 96.3% (158 out of 164 events). An additional 7 PFS events in the vorasidenib arm (from 47 to 54) and an additional 16 events in the placebo arm (from 88 to 104) were observed in this period. All events were progressive disease (PD), and there were no deaths in either arm. Consistent with previously presented results, PFS by BIRC was improved in the vorasidenib arm compared with that in the placebo arm, with an HR of 0.35 (95% CI, 0.25, 0.49). The median PFS was not estimable (NE) (95% CI: 22.1, NE) in the vorasidenib arm and was 11.4 (95% CI: 11.1, 13.9) months in the placebo arm. At 24 months, the PFS rate was 58.8% (95% CI: 48.4, 67.8) in the vorasidenib arm and 26.2% (17.9, 35.3) in the placebo arm.

Key Secondary Endpoint: Time to Next Intervention

Table 27. Time to Next Intervention (Full Analysis Set)

	Placebo (N = 163)	Vorasidenib (N = 168)
Time to next intervention (months)[a]		
Number of events, n (%)	58 (35.6)	19 (11.3)
First subsequent anticancer therapy (except crossover)	6 (3.7)	19 (11.3)
Crossover to Vorasidenib	52 (31.9)	0
Death	0	0
Number censored, n (%)[b]	105 (64.4)	149 (88.7)
Ongoing without an event	101 (62.0)	145 (86.3)
Withdrawal of consent	4 (2.5)	4 (2.4)
25th percentile (95% CI)[c]	12.0 (9.6, 12.7)	NE (18.0, NE)
Median (95% CI)	17.8 (15.0, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (23.9, NE)	NE (NE, NE)
Hazard ratio (95% CI)[d]		0.26 (0.15, 0.43)
(95% repeated CI)[e]		(0.07, 0.94)
p-value[f]		0.000000019
Kaplan-Meier survival rate (%) (95% CI)[g,h]		
3 months	100 (NE, NE)	100 (NE, NE)
6 months	97.5 (93.5, 99.1)	97.6 (93.7, 99.1)
12 months	75.4 (67.1, 81.8)	90.1 (83.7, 94.0)
18 months	47.4 (35.8, 58.2)	85.6 (77.8, 90.8)
24 months	27.0 (7.9, 50.8)	83.4 (74.0, 89.6)

Data Cutoff Date: 06Sep2022

Abbreviations: BIRC = Blinded Independent Review Committee; CI = confidence interval; EOS = end of study; HR = hazard ratio; IA2 = Interim Analysis 2; N = number of subjects in each treatment arm; n = number of observed values; NE = not estimable; PD = progressive disease; PFS = progression-free survival; RANO-LGG = Response Assessment in Neuro-oncology for Low-grade Gliomas; TTNI = time to next intervention.

Note: PFS per the BIRC refers to death or documented radiographic PD as assessed by the BIRC per modified RANO-LGG.

a.TTNI = (date of event or censoring – randomization date + 1) / 30.4375.

b.Censoring criteria are described in Section 9.7.4.

c.Quartile estimates from product-limit (Kaplan-Meier) method. CIs were calculated from Brookmeyer and Crowley method (Brookmeyer R and Crowley JJ 1982) with log-log transformation.

d.HR was calculated from the Cox regression model stratified by the randomization strata with placebo as the denominator, with two-sided 95% CIs.

e.The 2-sided repeated CI for the HR was calculated for HR based on the method from (Jennison C andTurnbull B 2000).

f.P-value was calculated from the one-sided log-rank test stratified by the randomization factors(Chromosome 1p19q co-deletion status and Tumor size at Baseline per local assessment). For IA2, TTNIwas tested at a 1-sided α-level of 0.00000048, based on an updated efficacy boundary corresponding to the51% information fraction observed at the IA2, provided that primary endpoint was statistically significant atIA2.

g.Based on Survival Distribution Function estimates from product-limit method.

Other Secondary Efficacy Endpoints

Tumour Growth Rate

Patients were included in post-treatment TGR analysis if they had at least 1 MRI record during the corresponding period.

The post-treatment tumour volume decreased in subjects randomized to vorasidenib by a mean of 2.5% (TGR mean of -2.5% [95% CI, -4.7%, -0.2%]) every 6 months, while tumour volume increased by a mean of 13.9% (TGR mean of 13.9% [95% CI, 11.1%, 16.8%]) every 6 months for the placebo arm. The mean percentage change on tumour volumes over time suggests that vorasidenib induced tumour shrinkage, while aggregate data from subjects on placebo showed continuous tumour growth.

Progression-Free Survival per Investigator

PFS was assessed by the Investigator per modified RANO-LGG. Results of the Investigator assessment of PFS were consistent with the primary efficacy analysis assessed by the BIRC. Investigator-assessed PFS was improved in the vorasidenib arm compared with placebo arm with an HR of 0.35 (95% CI, 0.23, 0.54; P=0.000000243). The median PFS was not evaluable for the vorasidenib arm (the lower bound of the 95% CI was 27.1 months). The median PFS in the placebo arm was 14.1 (95% CI, 11.2, 18.5) months. All events were PD, and there were no death events in either arm.

Progression-Free Survival – Concordance Between the BIRC and Investigator

The total PFS event discrepancy rate was 22.7% for placebo and 16.1% for vorasidenib. Overall, the Investigator and the BIRC agreement was 84.0% in the vorasidenib arm and 77.3% in the placebo arm. The table below summarizes the assessment of PFS concordance between the BIRC and the Investigator. The Investigator and the BIRC agreed that:

- A PFS event occurred in 26 subjects (15.5%) in the vorasidenib arm, and 61 (37.4%) subjects in the placebo arm.
- No PFS event occurred for 115 subjects (68.5%) in the vorasidenib arm and65 (39.9%) subjects in the placebo arm.

Overall, the BIRC reported PFS events more frequently than the Investigators, and the frequency of discordant events was consistent between both arms. In 21 subjects (12.5%) in the vorasidenib arm, and 27 subjects (16.6%) in the placebo arm, the BIRC reported a PFS event where Investigator did not. In 6 subjects (3.6%) in the vorasidenib arm, and 10 subjects (6.1%) in the placebo arm, the Investigator reported a PFS event where the BIRC did not.

Table 28. Summary of Concordance of Progression-Free Survival (PFS) Events Between the BIRC and Investigator (Full Analysis Set)

		Vorasidenib - BIRC[a] N=168	
		Events, n (%)	Censored, n (%)
Vorasidenib - Investigator N=168	Events, n (%)	26 (15.5)	6 (3.6)
	Censored, n (%)	21 (12.5)	115 (68.5)
		Placebo – BIRC[a] N=163	
		Events, n (%)	Censored, n (%)
Placebo - Investigator N=163	Events, n (%)	61 (37.4)	10 (6.1)
	Censored, n (%)	27 (16.6)	65 (39.9)

Data Cutoff Date: 06Sep2022
Abbreviations: BIRC = Blinded Independent Review Committee; N = number of subjects in the FAS within each treatment arm; n = number of observed values; PD = progressive disease; PFS = progression-free survival; RANO-LGG = Response Assessment in Neuro-oncology for Low-grade Gliomas.
Notes: Percentages are based on the number of subjects in the FAS in each column (denominator).
PFS per the BIRC refers to death or documented radiographic PD as assessed by the BIRC per modified RANO-LGG.
a.PFS based on the BIRC refers to death or documented radiographic PD as assessed by the BIRC per modified RANO-LGG.

Overall Survival

No subject in either treatment arm had a death event by the time of data cut-off. Median OS follow-up was consistent between the placebo and vorasidenib arms: 14.3 (95% CI, 12.7, 15.4) months and 14.0 (95% CI, 12.9, 15.4) months, respectively.

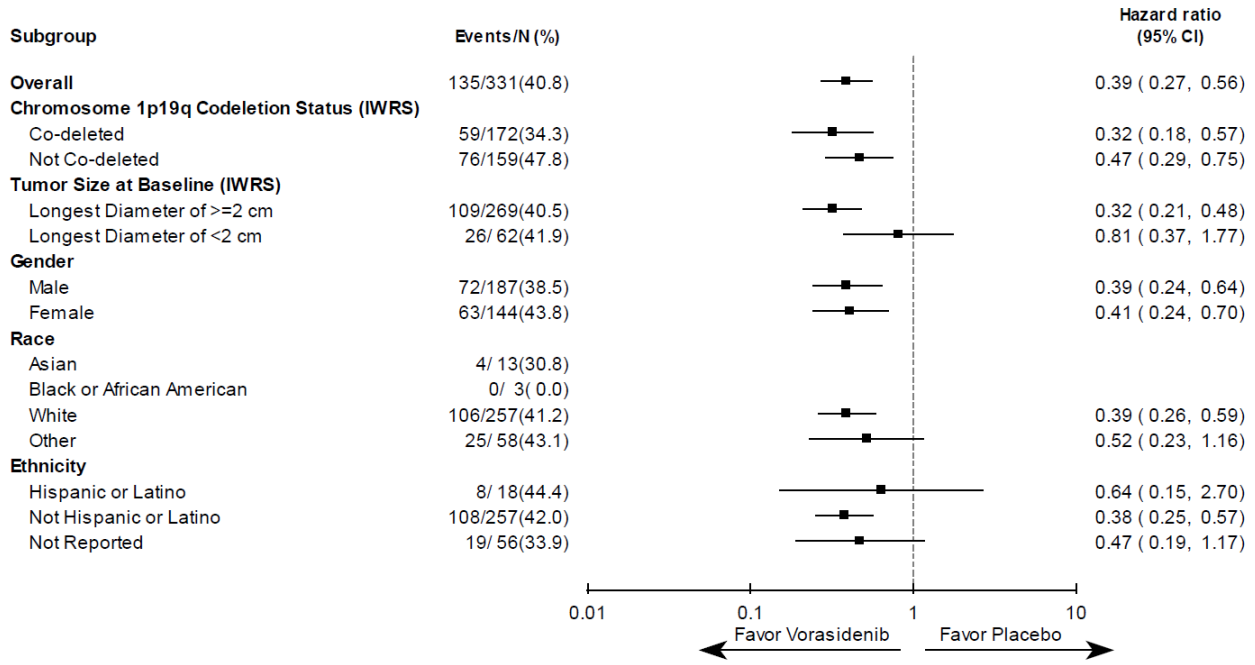
- **Ancillary analyses**

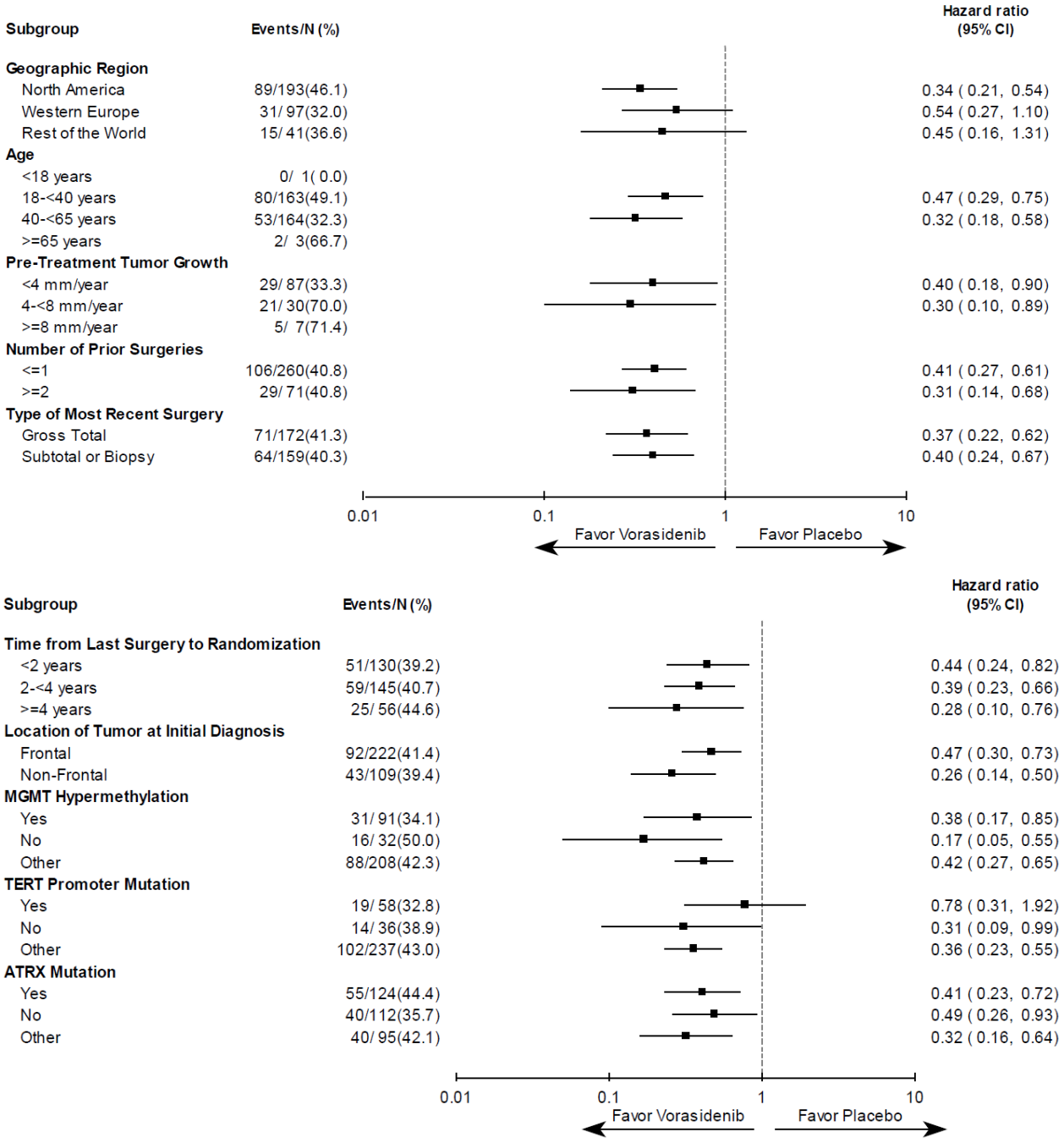
Progression-Free Survival Sensitivity Analyses

PFS results per the BIRC in the per-protocol-set (PPS) were consistent with the results in the FAS. PFS was improved in the vorasidenib arm compared with placebo arm with an HR of 0.39 (95% CI, 0.27, 0.56; P=0.000000067).

There were 19 subjects for whom the stratification factor of baseline tumour size was discrepant between IWRS used for primary efficacy analysis and the eCRF data. Per the BIRC, the results of the sensitivity analysis of the primary efficacy endpoint with the strata for baseline tumour size derived according to the data reported in the eCRF were consistent with the results obtained using the baseline tumour size as reported in the IWRS. PFS was improved in the vorasidenib arm compared with placebo arm with an HR of 0.40 (95% CI, 0.28, 0.57; P=0.000000161).

Figure 8. Forest Plot of Hazard Ratios for Progression-Free Survival per BIRC by Subgroup (FAS)





Data Cutoff Date: 06Sep2022

Abbreviations: ATRX = α-thalassemia/mental-retardation-syndrome-X-linked gene; BIRC = Blinded Independent Review Committee; CI = confidence interval; IWRS = interactive web response system; MGMT = O6 methylguanine-DNA-methyltransferase gene; PD = progressive disease; PFS = progression-free survival; RANO-LGG = Response Assessment in Neuro-oncology for Low-grade Gliomas; TERT = telomerase reverse transcriptase.

Notes: PFS = (date of event or censoring – randomization date + 1) / 30.4375.

PFS based on the BIRC refers to death or documented radiographic PD as assessed by the BIRC per modified RANO-LGG.

Hazard ratios for each subgroup were calculated from the unstratified Cox regression model. Two-sided 95% CIs are displayed. Time from last surgery to randomization (years) = (date of randomization – date of last surgery + 1)/365.25.

- **Summary of main efficacy results**

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

Table 29. Summary of Efficacy for trial AG881-C-004

Title: 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 identifier	AG881-C-004 EudraCT number 2019-002481-13 www.clinicaltrials.gov NCT04164901		
Design	Phase 3, global, multicenter, randomized, double-blind, placebo-controlled study. At the time of centrally confirmed radiographic PD, subjects randomized to placebo were given the option to crossover to receive vorasidenib.		
	Duration of main phase:		Vorasidenib arm; administered orally, daily, until centrally confirmed radiographic progression by BIRC, unacceptable toxicity, need for initiation of chemotherapy, RT, or other anticancer therapy in the opinion of the Investigator. Placebo arm; administered orally, daily, until centrally confirmed radiographic progression by BIRC, unacceptable toxicity, need for initiation of chemotherapy, RT, or other anticancer therapy in the opinion of the Investigator. Patients with confirmed radiographic progression and randomised to placebo had the option to crossover to receive open-label vorasidenib if they were still candidate for a watch-and-wait approach.
	Duration of Run-in phase:		NA
	Duration of Extension phase:		Vorasidenib arm: Treatment continued indefinitely as appropriate, as outlined above. Placebo arm: Treatment continued indefinitely as appropriate, as outlined above.
Hypothesis	Superiority		
Treatments groups	Vorasidenib (V) arm		168 patients randomized
	Placebo (P) arm		163 patients randomized
Endpoints and definitions	Primary endpoint: Progression Free Survival	PFS	Defined as the time from date of randomization to the date of first occurrence of centrally confirmed radiographic PD by modified RANO-LGG assessed by the BIRC or death from any cause, whichever occurred earlier.
	Key Secondary endpoint: Time To Next Intervention	TTNI	Defined as the time from date of randomization to the initiation of first subsequent anticancer therapy (including vorasidenib for subjects randomized to placebo who subsequently crossover to vorasidenib) or death due to any cause.
Database lock	06 September 2022		
Results and Analysis			

Title: 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 identifier	AG881-C-004 EudraCT number 2019-002481-13 www.clinicaltrials.gov NCT04164901			
Analysis description	**Primary Analysis**			
Analysis population and time point description	FAS			
Descriptive statistics and estimate variability	Treatment group	Vorasidenib	Placebo	*Effect estimate per comparison*
	Number of subject	168	163	
	Median PFS (95% CI)	27.7 months (17.0, NE)	11.1 months (11.0, 13.7)	HR of 0.39 (0.27, 0.56; one-sided P=0.000000067, one-sided alpha-level = 0.000359)
Notes	NA			
Analysis description	**Secondary analysis**			
Analysis population and time point description	FAS			
Descriptive statistics and estimate variability	Treatment group	Vorasidenib	Placebo	*Effect estimate per comparison*
	Number of subject	168	163	
	Median TTNI (95% CI)	not reached	17.8 months (15.0 to NE)	HR of 0.26 (0.15, 0.43; one-sided P=0.000000019, one-sided alpha-level = 0.00000048)
Notes	TTNI results are confounded by the crossover design, refer to the Efficacy discussion for further details			

2.6.5.3. In vitro biomarker test for patient selection for efficacy

An in vitro companion diagnostic device (Oncomine DxTarget Test [ODxTT]) to select patients with IDH-mutated glioma for the safe and effective use of vorasidenib is under development in partnership with Thermo Fisher Scientific Inc.

Of note, ODxTT is currently approved under IVDD (98/79/EC) and is under review by a notified body to obtain an IVDR - CE Mark status (Regulation (EU) 2017/746) with a different intended use. The intended use for the selection of glioma patients with IDH1/IDH2 mutation will be added to aid in selecting patients for treatment with vorasidenib as targeted therapy in a sequential submission step.

Up to 340 clinical FFPE IDH1/IDH2 positive samples from Grade 2 glioma containing the variants listed in the table below have been included in the bridging study, in addition to approximately 130 commercially procured negative samples which were screened with the enrolling CTA assay (ODxTT) and TOS500 Assay for confirmation. Due to the varying prevalence rate among all variants listed in the table below, it was not guaranteed that all variants would be included in the clinical trial.

Table 30. List of Potential Variants to be Evaluated

Gene	Variant	Cosmic ID	Nucleotide Change
IDH1	R132H	COSM28746	c.395G>A
	R132C	COSM28747	c.394C>T
	R132G	COSM28749	c.394C>G
	R132S	COSM28748	c.394C>A
	R132L	COSM28750	c.395G>T
IDH2	R172K	COSM333733	c.515G>A
	R172M	COSM33732	c.515G>T
	R172W	COSM34039	c.514A>T
	R172S	COSM34090	c.516G>T
		COSM133672	c.516G>C
	R172G	COSM33731	c.514A>G

The overall objectives and acceptance criteria are outlined in the table below.

Table 31. Summary of the Design Validation Study, Objectives, and Acceptance Criteria

Design Validation Study	Objectives	Acceptance Criteria
Clinical Validation-Analytical Accuracy	The objective of this study is to demonstrate the ability of ODxT Test to accurately detect IDH1 and IDH2 mutations from FFPE Solid tumors in reference to a validated orthogonal method.	• The ODxT Test must have an observed PPA of ≥90% for the IDH1/2 variant when compared to a validated orthogonal method in a clinical validation study. • The ODxT Test must have an observed NPA of ≥90% for the IDH1/2 variant when compared to a validated orthogonal method in a clinical validation study.

Description of the analytical method:

The principle of the test is the following: IDH1 and IDH2 mutation detection (IMD) via the Oncomine Dx Target Test is intended to detect somatic variants in glioma FFPE tumour specimens and this test is based on a high-throughput, parallel-sequencing technology.

The specimen used are slides from glioma formalin-fixed paraffin embedded tissue (FFPE) blocks. Prior to performing runs, the H&E-stained tissue section on a slide will be examined by a pathologist for confirmation of correct sample type (percent tumour content per tissue section (TC) for example). If tumour content is greater than or equal to 20%, the tissue sections will be extracted. If tumour content is less than 20%, and region of interest is greater than or equal to 10%, the sections will be macro dissected and enriched for tumour cells. After extraction of nucleic acid from the specimen (FFPE) blocks, 10 ng of sample is used.

Material, reagents and consumables have been described:

The workflow is the following:

The test utilizes the laboratory workflow consisting of the following steps:

1) Sample information entry and Planned Runs generation using the Torrent Suite Dx Software

2) DNA and RNA extraction from an FFPE sample and nucleic acid quantitation

3) cDNA synthesis

4) Sample library preparation

5) Templating

6) Sequencing

7) Data analysis and test report generation.

The libraries are templated onto Ion Sphere Particles (ISP, which are proprietary beads). The sequencing is realized with the beads and reagents to allow the sequencing reactions to take place. The sequencing includes the nucleotide incorporation on a chip which leads to a signal generation. The signal is translated into base calls and then reads. The reads are mapped to references. The end result of this workflow is a set of variant calls that correspond to the original sample. The end result will be noted on the Lab Report for each sample.

The test was analytically validated at the Life Technologies Clinical Services Laboratory following New York State Department of Health next-generation sequencing (NGS) guidelines for somatic genetic variant detection (January 2018 revision). The analytical performances are the following:

Analytical Accuracy:

Three well-characterized reference samples were sequenced with three technical replicates. The samples used were NA12878, NA24149, and NA24385.

100% Overall Percent Agreement.

Analytical Sensitivity (Limit-of-Detection):

FFPE clinical samples with two different variants (One variant at IDH1 R132 and one variant at IDH2 R172) were tested at five different levels of allelic fraction (AF) (10%, 8%, 6% 4% & 2.5%) and ran with up to 20 replicates per AF level.

IDH1: 95% sensitivity at 4% allelic fraction.

IDH2: 100% sensitivity at 6% allelic fraction.

Orthogonal Confirmation (Method Comparison):

FFPE clinical specimens and cell lines were tested via IMD (IDH1/IDH2 Mutation Detection) to compare presence/absence of IDH1 or IDH2 mutations obtained via orthogonal testing (Sanger Sequencing Methodology).

77 positives samples: 3 failed – 70 Glioma and 4 FFPE cell line.

On the 77 positives samples, 43 samples are positive with Sanger method and IMD (IDH1/IDH2 Mutation Detection) - (33 IDH1 mutation positive and 10 IDH2 mutation positive).

100% Positive Percent Agreement on 43 samples.

717 samples are negative with Sanger method and IMD (IDH1/IDH2 Mutation Detection).

54 samples lead to No Call for IMD (IDH1/IDH2 Mutation Detection).

Precision (Repeatability and Reproducibility):

Four positive FFPE clinical samples were run in triplicate on the same run (repeatability).

In addition, 5 positive FFPE clinical samples were tested across multiple runs, operators, instruments, barcodes and days (reproducibilitv).

100% concordance across all replicates.

2.6.5.4. Supportive studies

Study AG881-C-002

Study AG881-C-002 is a phase 1, multicenter, open-label, dose-escalation study designed to evaluate the safety, PK/PD, and preliminary efficacy of vorasidenib in subjects with advanced IDH-mutant solid tumours including gliomas. All enrolled subjects had a histologically or cytologically confirmed solid tumour, including glioma, with documented IDH1/2 mutation, that had recurred after or had not responded to initial standard therapy including any number of prior treatments including surgery, chemotherapy, RT, or experimental therapy (including ivosidenib or enasidenib) or for whom the investigator believed there was no suitable therapy.

The primary objectives of the study were to determine the maximum tolerated doses (MTDs) and/or recommended phase 2 dose (RP2D) of vorasidenib and to assess the safety and tolerability of treatment with vorasidenib. Secondary objectives included characterization of the PK of vorasidenib; evaluation of the PK/pharmacodynamics relationship of vorasidenib and 2-HG inhibition; and evaluation of preliminary clinical activity of vorasidenib including ORR (RANO-LGG criteria) by Investigator assessment.

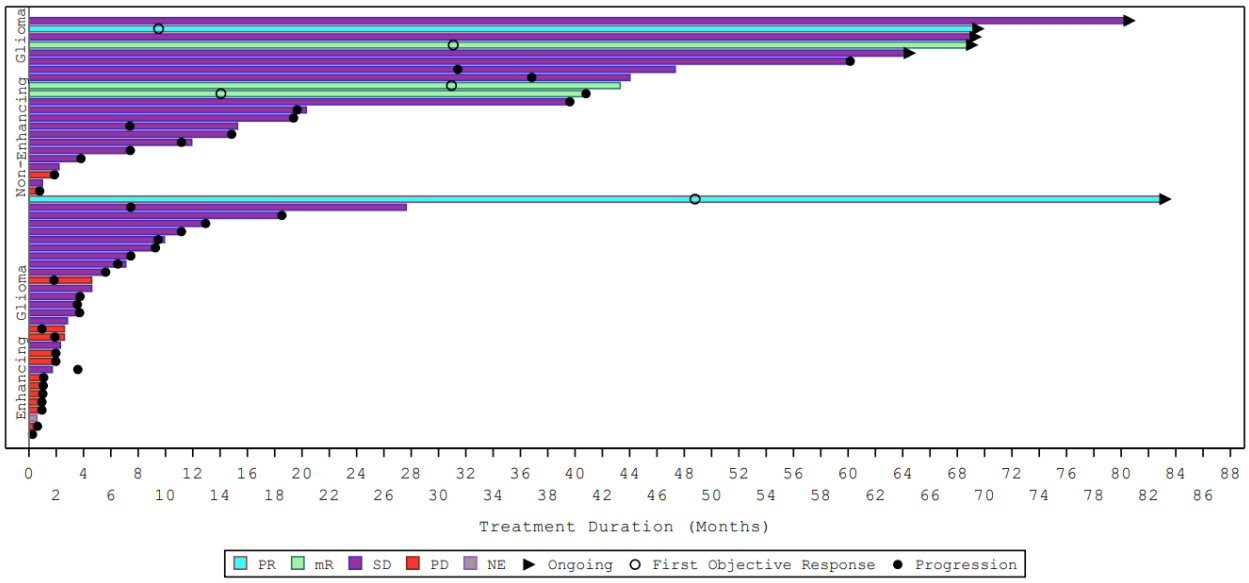
A total of 52 subjects with gliomas (22 with non-enhancing glioma and 30 with enhancing glioma) were enrolled and treated with vorasidenib. Of the 22 subjects with non-enhancing gliomas, 5 remained on treatment as of the cut-off date; the most common reason for treatment discontinuation was PD (13 subjects [59.1%]). The median (range) treatment duration for the subjects with non-enhancing gliomas was 29.96 (1.0, 80.5) months.

The median (range) age of the 22 subjects with non-enhancing glioma was 47 (16, 73) years. One 16-year old patient received vorasidenib at a dose of 100 mg QD in this study. Based on the allowance of prior treatment, 14 (63.6%) subjects had received prior systemic therapies and 21 (95.5%) subjects had prior surgery.

In AG881-C-002 in patients with non-enhancing IDH-mutant gliomas:

- The median (range) treatment duration was 29.96 (1.0, 80.5) months. At 12, 24, and 36 months, 15 (68.2%), 11 (50.0%), and 11 (50.0%) subjects remained on treatment, respectively. The longest treatment duration was 80.526 months.
- The ORR was 18.2% (5.19%, 40.28%), including 1 (4.5%) PR and 3 (13.6%) mRs. Sixteen subjects (72.7%) achieved a BOR of SD.
- The median PFS was 36.8 months (95% CI: 14.9, 60.2).

Figure 9. Swim Lane Plot of Treatment Duration and Best Overall Response in Subjects with Gliomas (Full Analysis Set)



Data cutoff date 17 October 2022. Abbreviations: FAS=Full Analysis Set; mR=minor response; NE=not evaluable; PD=progressive disease; PR=partial response; RANO=Response Assessment in Neuro-oncology; RANO LGG=RANO for low-grade glioma; SD=stable disease. FAS: all subjects who were enrolled and received at least 1 dose of study treatment. For subjects with non-enhancing glioma, responses to treatment are based on RANO LGG criteria. For subjects with enhancing glioma, responses to treatment are based on modified RANO criteria.

Study AG120-881-C-001

Study AG120-881-C-001 is an ongoing phase 1, multicenter, randomized, controlled, open-label, perioperative study of orally administered vorasidenib in subjects with recurrent, primarily non-enhancing, Grade 2/3 low grade glioma (LGG) with an IDH1 R132H mutation for whom surgical resection was indicated. This study was designed to confirm the brain penetrance of vorasidenib and measure the % reduction of 2-hydroxyglutarate (2-HG) in resected samples relative to untreated control samples.

Subjects must have had histologically or cytologically confirmed recurrent Grade 2 or Grade 3 oligodendroglioma or astrocytoma (according to WHO 2016 classification), documented IDH1-R132H gene mutation by local testing and known 1p19q or ATRX mutation status by local testing and were candidates for clinical resection but for whom surgery is not urgently indicated. The study allowed subjects who have received any number of prior treatments including surgery, chemotherapy, RT, or experimental therapy (including ivosidenib or enasidenib).

The primary analysis of study AG120-881-C-001 compared the 2-HG concentration in tumours following treatment with vorasidenib 50 mg QD relative to the untreated control group. The clinical activity of vorasidenib was evaluated by Investigator assessment of response to treatment according to modified RANO-LGG.

A total of 24 subjects with non-enhancing gliomas were treated with vorasidenib; 12 (50%) subjects remained on treatment as of the cut-off date. The most common reason for treatment discontinuation was PD (9 [37.5%] subjects). The median (range) overall treatment duration in all subjects receiving vorasidenib (N=24) was 38.23 (2.0, 47.1) months.

The overall median (range) age of subjects treated with vorasidenib was 49 (range 31 to 75) years.

Preliminary clinical activity per RANO-LGG criteria was observed following post-operative treatment with vorasidenib with an ORR (CR+PR+mR) of 50.0% for subjects treated with vorasidenib 50 mg QD, and an ORR of 37.5% for subjects treated with vorasidenib 10 mg QD. Across all 22 subjects in the Efficacy Analysis Set who received post-operative vorasidenib treatment, 4 subjects (18.2%) achieved a PR, and 6 subjects (27.3%) achieved a mR, based on Investigator assessment.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal study supporting the current application is the INDIGO study, an ongoing Phase 3, global, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of vorasidenib compared to placebo in subjects with residual or recurrent predominantly non-enhancing Grade 2 oligodendroglioma or astrocytoma with an IDH1 or IDH2 mutation.

Study population

The selection of patients with predominantly non-enhancing Grade 2 oligodendroglioma or astrocytoma to be randomized in the study and the overall inclusion/exclusion criteria are adequate to identify a population that would benefit from the targeted therapy. Only patients with good performance status (score ≥80%) were included in the study considering Karnofsky Performance Scale score (for subjects ≥ 16 years of age) or Lansky Play Performance Scale score (for subjects <16 years of age). Patients with features assessed as high-risk 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, or uncontrolled seizures were excluded from the study, and this is agreed in a context of a study with placebo as comparator arm.

Adolescent patients (12 years and older) were included in the pivotal trial. Although only 1 adolescent subject was enrolled in the INDIGO study and this subject was determined to be in the placebo arm upon unblinding the study, nevertheless, the disease similarity across populations in terms of similar biology, disease behaviour and clinical prognosis in adolescents with 'adult-type' IDH1/2 mutant low grade gliomas is endorsed.

Dose

To be eligible for the INDIGO study, patients needed to be at least 12 years of age and to weigh at least 40 kg. Based on the preliminary population PK analysis for vorasidenib in adult subjects and extrapolation to adolescent subjects, adolescents 12 to <18 years of age were planned in the INDIGO study to receive the same fixed dose administered in adults (40 mg QD of the film-coated tablet formulation). However, no adolescent received vorasidenib in the INDIGO study; thus, there are no PK data available in adolescents. Consequently, the applicant predicted the PK of vorasidenib in the adolescent (12 to < 18 years) subject population using a pop PK model built on adult data, as agreed in the PIP. Based on this analysis using a scaled pop PK model and an exposure matching approach between the adolescent and adult population, the applicant has proposed in the SmPC two doses as follows: 40 mg or 20 mg once daily for patients weighing ≥40 kg or <40 kg respectively. However, the popPK model is not considered suitable and since no adults with body-weight < 40 kg were included in the clinical studies, there are too many uncertainties in the modelling approach to conclude on comparable vorasidenib exposures between adults and adolescents < 40 kg with the proposed dose 20 mg QD. Therefore, no dose recommendation can be made in patients weighing less than 40 kg because of the lack of clinical data in this population. This is reflected in the SmPC accordingly.

Design, endpoints and estimands assessment

As there are currently no approved therapies for Grade 2 IDH-mutant diffuse gliomas, the current treatment regimen for IDH-mutant diffuse glioma at the time of initial diagnosis includes maximal safe resection of the tumour followed by either radiation therapy (RT) and/or chemotherapy or an alternative active monitoring approach with serial MRI. Particularly, active observation is the standard of care in patients with grade 2 IDH mutant gliomas who are not in immediate need of chemoradiotherapy. The choice of a placebo-controlled study is thus supported.

Non-enhancing IDH-mutant gliomas have in general a favourable natural history, but all non-enhancing gliomas eventually progress, develop contrast enhancement, and transform to a more aggressive form with an associated poor prognosis. The outcome of these tumours is ultimately fatal in most patients and therefore the unmet medical need for additional therapeutic options targeting low grade IDH-mutant gliomas early in their development, delaying the tumour progression, and postponing the use of standard chemo-radio-therapy and their toxicities, in a group of young patients otherwise in good general condition, is recognized.

Patients with confirmed radiographic progression and randomised to placebo had the option to crossover to receive open-label vorasidenib. The option to crossover was not supported by CHMP in the scientific advice (EMA/CHMP/SAWP/398727/2019) due to its potential confounding effect on primary and secondary endpoints. The cross-over eligibility criteria is specified in the SmPC.

The primary endpoint is radiographic PFS by BIRC. This selection of the primary endpoint was also discussed by the CHMP during the scientific advice. PFS was discouraged by CHMP as the primary endpoint for the reason that "because of the slow progression, radiographic progression does not necessarily singularly translate into need for treatment which is a clinical multifactorial decision." Instead, the CHMP recommended to use time to intervention as the primary endpoint, and rPFS as key secondary endpoint. It is noted that the applicant has not followed the CHMP's advice by keeping rPFS as primary endpoint. It is acknowledged that TTNI was defined as the key secondary endpoint, and defined as the time from randomization to the initiation of the first subsequent anticancer therapy (including surgery, radiotherapy, chemotherapy, and crossover to vorasidenib for subjects who were randomized to placebo) or death due to any cause. This may be seen as partly addressing the CHMP's request for a similar endpoint, although the endpoint was made secondary (not primary). However, the definition does not align with the one discussed with the CHMP as it incorporates the elements of crossover and death due to any cause. Indeed, there are critical concerns with the interpretation of TTNI in the context of the crossover design, as further discussed below.

The 1:1 randomisation procedure and its stratification factors (local 1p19q status and baseline tumour size) are generally deemed acceptable. These factors were discussed during the scientific advice and were supported (EMA/CHMP/SAWP/398727/2019). The protocol was amended shortly after the initiation of the INDIGO study to switch from one formulation of AG-881 (F1, uncoated tablets) to a second formulation of AG-881 (F2, film-coated tablets; intended commercial formulation). The Formulation 2 was introduced based on results of a completed relative bioavailability study (AG881-C-007) which showed that 40 mg QD dose of F2 was projected to achieve comparable exposures to those observed at the 50 mg QD dose of F1. The starting dose of AG-881 was thus changed from 50 mg QD of the uncoated tablet formulation (F1) to 40 mg QD of the film-coated tablet formulation (F2) shortly after the initiation of the INDIGO study. Nine subjects were randomized under the original protocol and initially received the clinical formulation of the uncoated tablet (F1), before it was replaced by the commercial formulation (F2). The randomisation procedure was not impacted by the change in formulation.

Subjects and investigators/sites were blinded until centrally confirmed radiographic PD by the BIRC. Data collected after radiographic PD may therefore be susceptible to some level of reporting bias, depending on the subjectivity of the relevant measures (e.g. PRO data). It is stated that the applicant remained blinded until the final analysis, except for select individuals who had access to crossover data.

The method used for the assessment of the primary efficacy endpoint is appropriate with submission of all MRI to a central imaging vendor, at screening for confirmation of the presence of measurable predominantly non-enhancing disease and thereafter for disease response assessment by the BIRC. Disease response assessment schedule is consistent with what it is recommended in the guidelines and what is done in clinical practice.

The censoring rules defined for PFS are not in line with the PFS censoring rules described in appendix 1 to the guideline on anticancer medicinal products (EMA/CHMP/27994/2008/Rev.1). A treatment policy strategy would have been preferred for the primary analysis, with no censoring applied prior to subsequent anticancer therapy/crossover nor in case of missing tumour assessments. An additional analysis has been provided where the initiation of subsequent anticancer therapy, including crossover to vorasidenib for placebo patients, is not used as a censoring reason. It is noted that four additional events are included in the placebo arm in this analysis. The results from this additional analysis, more in line with the EMA guidance, are consistent with the primary analysis results. The frequency of censored patients due to consent withdrawal, which might indicate informative censoring, appears to be limited and balanced across treatment groups.

More importantly, the confounding impact of crossover on efficacy analyses is of concern. In principle, the PFS analysis should not have been substantially impacted by crossover as confirmed radiographic progression was a requirement for crossover to be considered. Although five patients crossed over from placebo to vorasidenib before their PFS event, the above-mentioned PFS sensitivity analysis with all PFS events included regardless of subsequent anticancer therapy or crossover provided reassurance with results consistent with the primary analysis results.

On the other hand, the key secondary endpoint TTNI is clearly confounded by the crossover design. The definition of subsequent anticancer therapy includes crossover, which can only be an option for patients in the placebo arm. Whether as many patients would have initiated a subsequent anticancer therapy in the absence of crossover, and whether these subsequent therapies would have been initiated at the same time point, is entirely speculative. The vast majority of TTNI events in the placebo arm are due to crossover (n=52) to vorasidenib whereas only a few events (n=6) are due to other subsequent anticancer therapy. This does not allow for any meaningful comparison between treatment arms. It is considered highly likely that the key secondary endpoint is biased, and consequently that the type I error is inflated. The postponed use of radiation therapy and chemotherapy as next intervention has not been demonstrated within this application.

Several arguments were provided by the applicant to support the assumption that patients who were candidates for crossover were expected to start another therapy: the median time from documented progression to the initiation of a subsequent therapy is comparable between crossover and other subsequent anticancer therapies, continued observation beyond progression is not a common practice, the median time from most recent surgery to crossover in placebo patients is similar to other subsequent anticancer therapy. However, none of these arguments provide convincing evidence that placebo patients who crossed over to vorasidenib would have all initiated another subsequent therapy in the absence of crossover, and within the same timeframe. In addition, one of the cross-over eligibility criteria was to be not in need of an immediate chemotherapy, radiotherapy, or other treatment in the opinion of the Investigator. The proportion of patients who do not have a TTNI event out of patients with a confirmed radiographic progression, appears to be larger in the vorasidenib arm than in the placebo arm. This could be interpreted as an indication of the suspected bias in favour of the vorasidenib arm. Unfortunately, this critical uncertainty regarding TTNI cannot be resolved retrospectively. The key secondary endpoint TTNI is deemed uninterpretable due to its clear confounding by the crossover design.

Due to the slow progression of the disease, the CHMP had previously commented that "radiographic progression does not necessarily translate into need for treatment which is a clinical multifactorial

decision" (EMA/CHMP/SAWP/398727/2019). A demonstration of efficacy primarily based on radiographic PFS was therefore seen as problematic, because a change in rPFS would have to be "weighed against the burden of early initiation of treatment, in a setting where the current standard is no treatment". However, the standard of care is so far an active observation because there is no other suitable therapeutic option for this population of young patients, and the only option consists of aggressive therapies associated with neurocognitive effects and functional decline which are postponed for as long as possible. It is considered that delaying progression could lead to a prolongation of the time to malignant transformation and delay the initiation of further treatments. Since 2019, the use of PFS per BIRC or PFS based on RANO-LGG criteria as primary endpoints is considered problematic, therefore the use of rPFS is considered acceptable as primary endpoint. The CHMP agrees that radiographic progression could be an objective and major driver of initiation of next therapy.

Tumour growth rate was assessed by slope of tumour growth over time using a linear mixed model on log-transformed tumour volume measured by the BIRC at baseline and at each post randomization tumour assessment.

Other secondary endpoint analyses appear to be generally standard and acceptable.

The sample size calculations can be followed, and the multiplicity adjustment procedure would have been agreeable, in principle. A group-sequential design with three interim analyses (IA1: futility, IA2: futility and superiority, and final analysis) was specified for the trial, together with an alpha-spending function. The p-values should therefore be interpreted according to the corresponding significance thresholds (one-sided alpha of 0.000359 for rPFS, and 0.00000048 for TTNI). It is noted that both the primary and the key secondary endpoint reached statistical significance. However, please refer to above critical concerns regarding confounding of TTNI. The consequences on bias and the type I error makes TTNI unsuitable as a key secondary endpoint in this crossover design. Only the primary endpoint PFS is considered to be adequately controlled for type I error.

Several important changes to the study design and planned analyses were introduced with protocol amendment 2, version 3.0 (17 December 2020), including revised (key) secondary endpoints and updated testing hierarchy. Any major changes to the planned analyses (such as changing the key secondary endpoint and the testing hierarchy) should generally be avoided to exclude any (even partially) informed decision with an impact on study primary or secondary objectives. Nevertheless, the only key secondary endpoint in the latest protocol version is TTNI which is not deemed interpretable due to its confounding by crossover.

Efficacy data and additional analyses

The study enrolled a total of 331 subjects across 10 countries from February 2020 through February 2022, in a 1:1 randomization, with 168 subjects randomized to vorasidenib and 163 subjects randomized to placebo.

In the vorasidenib arm, 36 subjects (21.4%) had discontinued their assigned treatment compared to 68 subjects (41.7%) in the placebo arm. The most commonly reported reasons for treatment discontinuation were centrally confirmed disease progression, which was more common in the placebo arm (36.2%, n=59) than in the vorasidenib arm (14.3%, n=24); and adverse events (AE), which was more common in the vorasidenib arm (3.6%, n=6) than in the placebo arm (1.2%, n=2).

As of the DCO (06 September 2022), of the 163 subjects treated in the placebo arm, 52 (31.9%) crossed over to receive vorasidenib following centrally confirmed disease progression.

The patient population enrolled in the INDIGO study is representative of subjects with predominantly non-enhancing grade 2 IDH-mutant glioma. Overall, the 2 arms were well balanced regarding demographics and disease characteristics. The study enrolled only 1 adolescent subject (16 years of age at enrolment) who was randomized to placebo arm.

As of the DCO (06 September 2022) for the interim analysis 2 (IA2), the median follow-up duration was 13.7 months (95% CI, 11.2, 14.1) and 14.1 months (95% CI, 11.1, 15.2) in the vorasidenib and placebo arms, respectively. Vorasidenib statistically significantly improved rPFS per the BIRC compared with the placebo arm with an HR of 0.39 (95% CI, 0.27, 0.56; one-sided P=0.000000067, one-sided alpha-level = 0.000359). The median rPFS was 27.7 months (95% CI, 17.0, not estimable) for the vorasidenib arm and 11.1 months (95% CI, 11.0, 13.7) for the placebo arm (Δ PFS gain 16.6 months). All events were PD (88/163 [54.0%] in the placebo arm and 47/168 [28.0] in the vorasidenib arm); no death events occurred in either arm.

As of the second interim analysis (IA2) data cut-off date (06 September 2022), the observed information fraction was 82% (135/164 PFS events) for the primary endpoint. With longer follow up, vorasidenib continued to demonstrate a clinically meaningful benefit compared to placebo. The applicant has performed follow-up analyses of PFS of the blinded data collected after 06 September 2022 (the data cut-off for IA2 and the basis for the marketing authorization application) until the 07 March 2023 study unblinding date. As of 07 March 2023, an additional 23 PFS events by BIRC have occurred, representing an observed information fraction of 96.3% (158 out of 164 events). An additional 7 PFS events in the vorasidenib arm (from 47 to 54) and an additional 16 events in the placebo arm (from 88 to 104) were observed in this period. All events were progressive disease (PD), and there were no deaths in either arm. Consistent with previously presented results, PFS by BIRC was improved in the vorasidenib arm compared with that in the placebo arm, with an HR of 0.35 (95% CI, 0.25, 0.49). The median PFS was not estimable (NE) (95% CI: 22.1, NE) in the vorasidenib arm and was 11.4 (95% CI: 11.1, 13.9) months in the placebo arm. At 24 months, the PFS rate was 58.8% (95% CI: 48.4, 67.8) in the vorasidenib arm and 26.2% (17.9, 35.3) in the placebo arm.

Sensitivity analysis of rPFS per the BIRC in the per-protocol-set (PPS) were consistent with the results in the FAS. Radiographic PFS was improved in the vorasidenib arm compared with placebo arm with an HR of 0.39 (95% CI, 0.27, 0.56; one-sided P=0.000000067). Moreover, per the BIRC, the results of the sensitivity analysis of the rPFS with the strata for baseline tumour size derived according to the data reported in the eCRF were consistent with the results obtained using the baseline tumour size as reported in the IWRS. Radiographic PFS was improved in the vorasidenib arm compared with placebo arm with an HR of 0.40 (95% CI, 0.28, 0.57; one-sided P=0.000000161).

Presented subgroup results of PFS showed an overall consistent treatment effect across all the subgroups tested, including co-deletion status.

The robustness of rPFS by BIRC results is not questioned and the size of the effect observed is considered important. Although these results cannot be supported by the key secondary endpoints of OS and TTNI due to the cross-over design of the study, the Tumor Growth Rate (TGR) endpoint is considered supportive although exploratory and confirms a pharmacological activity of vorasidenib on the tumor. An MMRM analysis of tumour growth that does not assume linearity of measurements over time. does not contradict the linearity assumption of the main CSR analysis model and shows some separation between treatment arms.

The change in FACT-BR total and subscale scores were also analysed with the questionable assumptions of linearity of observations over time (using a linear mixed model), as well as of missing data at random. An additional analysis that does not assume linearity over time (MMRM) has been provided by the applicant with no impact on the interpretation of FACT-BR results.

TTNI was also statistically significantly improved in the vorasidenib arm compared with the placebo arm however, the key secondary endpoint TTNI is clearly confounded by the crossover design, and this does not allow for any meaningful comparison between treatment arms.

Furthermore, due to the lack of information on patients weighting less than 40 Kg for which the PopPK model was not able to provide reassurance of a more suitable dose, the indication has been restricted to patient weighting 40kg and above (see Pharmacology section above for further details).

2.6.7. Conclusions on the clinical efficacy

Vorasidenib showed a statistically significant and clinically relevant improvement in rPFS per the BIRC compared with the placebo arm in patients with predominantly non-enhancing Grade 2 astrocytoma or oligodendroglioma with a susceptible IDH1 or IDH2 mutation following surgical intervention. Updated rPFS by BIRC analysis continued to show benefit of vorasidenib compared to placebo. Additionally, the exploratory analyses of tumour growth rate (TGR) support the claimed efficacy of vorasidenib.

2.6.8. Clinical safety

The primary integrated population providing evidence of safety for this initial marketing application of vorasidenib is the pooled glioma population treated with vorasidenib 40 mg QD across studies AG881-C-004, AG881-C-002, and AG120-881-C-001. Discussion of data for this pooled population focuses on the vorasidenib arm without crossover (N=167), placebo arm (N=163), and overall subjects treated with vorasidenib 40 mg QD (N=244).

In addition, supportive data are provided by a pooled population of all subjects with glioma treated with any vorasidenib dose (include < and >40 mg QD). This population included data from subjects treated with vorasidenib in studies AG881-C-004, AG881-C-002 (N=93 treated with vorasidenib) a dose escalation and expansion study in patients with advanced solid tumour including glioma, and AG120-881-C-001 (N=24 treated with vorasidenib), a phase 1 randomized controlled study in patients with grade 2 or 3 oligodendroglioma or astrocytoma. An additional pool was the population of subjects with all solid tumours including glioma who were treated at any dose of vorasidenib which has been provided as a larger pool for potential signal detection. This population included data from subjects treated with vorasidenib in studies AG881-C-004, AG881-C-002, and AG120-881-C-001.

Finally, data from subjects with advanced hematologic malignancies (N=46) (study AG881-C-001) was also provided.

All in all, the safety data package of this submission includes data from 493 patients who received either vorasidenib (N=382) or placebo (N=163) across 4 clinical studies.

2.6.8.1. Patient exposure

Glioma Population Treated With Vorasidenib 40 mg QD

Table 328. Study Drug Exposure – Glioma with Vorasidenib 40 mg QD (Safety Analysis Set)

	Vorasidenib 40 mg QD [a]					Placebo
	AG881-C-004 without crossover [b] N=167	AG881-C-004 post-crossover [c] N=52	AG881-C-002 N=11	AG120-881-C-001 N=14	Overall [d] N=244	AG881-C-004 pre-crossover [e] N=163
Treatment duration (months)						
Mean (StD)	13.27 (6.083)	5.53 (4.129)	14.78 (25.243)	31.04 (18.038)	12.71 (10.162)	11.75 (4.977)
Median	12.65	4.93	2.60	40.59	10.69	11.17

Table 328. Study Drug Exposure – Glioma with Vorasidenib 40 mg QD (Safety Analysis Set)

	Vorasidenib 40 mg QD [a]					Placebo
	AG881-C-004 without crossover [b] N=167	AG881-C-004 post-crossover [c] N=52	AG881-C-002 N=11	AG120-881-C-001 N=14	Overall [d] N=244	AG881-C-004 pre-crossover [e] N=163
Q1, Q3	8.67, 17.48	1.63, 8.03	1.08, 15.28	15.64, 44.58	6.70, 16.71	8.44, 14.95
Min, Max	1.0, 29.9	0.0, 16.6	1.0, 80.5	1.9, 48.4	0.0, 80.5	0.6, 26.2
Treatment duration category (months), n (%)						
>0 – 6	14 (8.4)	30 (57.7)	7 (63.6)	3 (21.4)	54 (22.1)	14 (8.6)
>6 – 12	64 (38.3)	18 (34.6)	1 (9.1)	0	83 (34.0)	85 (52.1)
>12 – 18	53 (31.7)	4 (7.7)	1 (9.1)	1 (7.1)	59 (24.2)	46 (28.2)
>18 – 24	25 (15.0)	0	0	0	25 (10.2)	16 (9.8)
>24 – 30	11 (6.6)	0	0	2 (14.3)	13 (5.3)	2 (1.2)
>30 – 36	0	0	0	0	0	0
>36 – 40	0	0	0	1 (7.1)	1 (0.4)	0
>40	0	0	2 (18.2)	7 (50.0)	9 (3.7)	0
Cumulative dose (mg)						
Mean (StD)	15186.3 (7520.25)	6491.7 (4872.22)	48109.1 (118532.61)	46682.1 (27349.89)	16624.7 (27966.74)	14017.0 (6066.68)
Median	14360.0	5680.0	3850.0	61500.0	12140.0	13440.0
Q1, Q3	9680.0, 20440.0	1980.0, 9600.0	1550.0, 22700.0	23750.0, 67400.0	7100.0, 19425.0	9840.0, 18040.0
Min, Max	1160, 37200	40, 19400	1100, 400650	3000, 72450	40, 400650	720, 31280
Planned dose intensity (mg/month)						
Mean (StD)	1228.8 (70.62)	1415.1 (1350.06)	1847.2 (1056.85)	1521.9 (0.00)	1313.2 (674.13)	1232.2 (129.27)
Median	1217.5	1217.5	1483.3	1521.9	1217.5	1217.5
Q1, Q3	1217.5, 1219.8	1217.5, 1221.2	1429.6, 1519.6	1521.9, 1521.9	1217.5, 1222.4	1217.5, 1221.9
Min, Max	1218, 2065	1218, 10958	1417, 4978	1522, 1522	1218, 10958	1120, 2841
Actual dose intensity (mg/month)						
Mean (StD)	1147.7 (178.58)	1188.2 (99.88)	1819.0 (1070.12)	1513.7 (55.91)	1207.6 (309.90)	1191.4 (74.38)
Median	1213.2	1217.5	1483.3	1518.6	1217.5	1214.2
Q1, Q3	1185.6, 1217.5	1210.2, 1217.5	1429.6, 1519.6	1511.8, 1521.9	1196.8, 1217.5	1197.3, 1217.5
Min, Max	317, 1324	596, 1218	1155, 4975	1338, 1574	317, 4975	584, 1306
Relative dose intensity (%)						

Table 328. Study Drug Exposure – Glioma with Vorasidenib 40 mg QD (Safety Analysis Set)

	Vorasidenib 40 mg QD [a]					Placebo
	AG881-C-004 without crossover [b] N=167	AG881-C-004 post-crossover [c] N=52	AG881-C-002 N=11	AG120-881-C-001 N=14	Overall [d] N=244	AG881-C-004 pre-crossover [e] N=163
Mean (StD)	93.6 (15.00)	95.2 (14.69)	98.1 (5.53)	99.5 (3.67)	94.5 (14.27)	97.2 (7.62)
Median	99.4	99.7	100.0	99.8	99.5	99.4
Q1, Q3	97.0, 100.0	97.8, 100.0	99.2, 100.0	99.3, 100.0	97.6, 100.0	97.4, 100.0
Min, Max	26, 100	11, 100	81, 100	88, 103	11, 103	43, 100

Data Cutoff Dates: AG120-881-C-001 (30 May 2022); AG881-C-002 (17 October 2022); AG881-C-004 (06 September 2022).
Notes: The Safety Analysis Set for this table includes all subjects from AG881-C-004 who have received at least 1 dose of vorasidenib or placebo, and subjects from AG881-C-002 and AG120-881-C-001 who have received at least 1 dose of vorasidenib.
Duration of exposure (month) = (last non-zero dose date-first non-zero dose date+1)/30.4375.
Cumulative dose (mg) = sum of the actual doses.
Planned Dose Intensity (DI) (mg/month) = Planned cumulative dose (mg)/duration of exposure (month).
Actual Dose Intensity (DI) (mg/month) = Cumulative dose (mg)/duration of exposure (month).
Relative Dose Intensity (RDI) (%) = 100xActual Dose Intensity (mg/month)/Planned Dose Intensity (mg/month).
StD: Standard deviation, Q1: Quartile 1, Q3: Quartile 3

a. 40 mg QD population includes subjects treated with vorasidenib 50 mg QD uncoated.
b. Includes data from subjects in Study AG881-C-004 who were randomized to and treated with vorasidenib 40 mg QD, those randomized to placebo but received at least one dose of vorasidenib without crossover, and pre-crossover data from subjects who received at least one dose of vorasidenib prior to cross over.
c. Includes data from subjects who were randomized to placebo who subsequently crossed over to receive vorasidenib 40 mg QD in Study AG881-C-004. Only data after crossover is included in this column.
d. Includes data from subjects treated with vorasidenib 40 mg QD in Study AG881-C-004, post crossover data from subjects 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 with glioma treated with vorasidenib 50 mg QD in Study AG881-C-002.
e. 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.

Median treatment duration in patients with all solid tumours treated with vorasidenib 40 mg was 10.58 months and 109 patients were treated for > 12 months. Relative dose intensity was > 99% in all groups even in patients who received > 40 mg (although median duration was 3.52 months).

Baseline Characteristics and Prior Therapy

Glioma Population Treated With Vorasidenib 40 mg QD

Table 339. Baseline Characteristics and Prior Therapy – Glioma with Vorasidenib 40 mg QD (Safety Analysis Set)

	Vorasidenib 40 mg QD [a]					Placebo
	AG881-C-004 without crossover [b] N=167	AG881-C-004 post-crossover [c] N=52	AG881-C-002 N=11	AG120-881-C-001 N=14	Overall [d] N=244	AG881-C-004 pre-crossover [e] N=163
ECOG Performance Status, n (%)						
0	0	0	6 (54.5)	0	6 (2.5)	0
1	0	0	4 (36.4)	0	4 (1.6)	0
2	0	0	1 (9.1)	0	1 (0.4)	0
Unknown	167 (100)	52 (100)	0	14 (100)	233 (95.5)	163 (100)
Karnofsky Performance Scale, n (%)						
100	90 (53.9)	25 (48.1)	0	5 (35.7)	120 (49.2)	87 (53.4)

Table 339. Baseline Characteristics and Prior Therapy – Glioma with Vorasidenib 40 mg QD (Safety Analysis Set)

	Vorasidenib 40 mg QD [a]					Placebo
	AG881-C-004 without crossover [b] N=167	AG881-C-004 post-crossover [c] N=52	AG881-C-002 N=11	AG120-881-C-001 N=14	Overall [d] N=244	AG881-C-004 pre-crossover [e] N=163
90-80	76 (45.5)	27 (51.9)	0	9 (64.3)	112 (45.9)	76 (46.6)
70-60	1 (0.6)	0	0	0	1 (0.4)	0
Unknown	0	0	11 (100)	0	11 (4.5)	0
Histological subtype, n (%)						
Astrocytoma	80 (47.9)	32 (61.5)	4 (36.4)	6 (42.9)	122 (50.0)	79 (48.5)
Oligodendroglioma	87 (52.1)	20 (38.5)	5 (45.5)	8 (57.1)	120 (49.2)	84 (51.5)
Other	0	0	2 (18.2)	0	2 (0.8)	0
Time from initial diagnosis to randomization or first dose (months)						
n	167	52	11	14	244	163
Mean (StD)	39.569 (28.9573)	51.764 (35.9958)	130.673 (69.1191)	68.834 (36.6586)	47.954 (38.7238)	37.524 (29.4067)
Median	35.023	42.694	109.930	64.657	39.179	29.602
Q1, Q3	22.111, 46.062	32.444, 58.546	71.589, 183.326	43.992, 89.133	26.267, 54.144	19.154, 50.234
Min, Max	11.93, 233.92	20.63, 245.36	45.24, 248.28	3.68, 149.22	3.68, 248.28	11.04, 230.11
Number of prior surgeries, n (%)						
<2	125 (74.9)	39 (75.0)	4 (36.4)	12 (85.7)	180 (73.8)	134 (82.2)
≥2	42 (25.1)	13 (25.0)	7 (63.6)	2 (14.3)	64 (26.2)	29 (17.8)
Type of most recent surgery, n (%)						
Gross total	81 (48.5)	30 (57.7)	3 (27.3)	5 (35.7)	119 (48.8)	90 (55.2)
Subtotal	75 (44.9)	19 (36.5)	6 (54.5)	6 (42.9)	106 (43.4)	64 (39.3)
Biopsy	11 (6.6)	3 (5.8)	0	3 (21.4)	17 (7.0)	9 (5.5)
None	0	0	1 (9.1)	0	1 (0.4)	0
Other	0	0	1 (9.1)	0	1 (0.4)	0
Baseline renal function by creatinine clearance (mL/min), n (%)						
Normal (≥90)	156 (93.4)	49 (94.2)	9 (81.8)	11 (78.6)	225 (92.2)	154 (94.5)
Mild (60-<90)	10 (6.0)	3 (5.8)	2 (18.2)	3 (21.4)	18 (7.4)	9 (5.5)
Moderate (30-<60)	1 (0.6)	0	0	0	1 (0.4)	0
Severe (15-<30)	0	0	0	0	0	0
Baseline renal function by eGFR (mL/min/1.73m^2), n (%)						
Normal (≥90)	123 (73.7)	39 (75.0)	5 (45.5)	5 (35.7)	172 (70.5)	129 (79.1)
Mild (60-<90)	42 (25.1)	12 (23.1)	6 (54.5)	7 (50.0)	67 (27.5)	33 (20.2)

Table 339. Baseline Characteristics and Prior Therapy – Glioma with Vorasidenib 40 mg QD (Safety Analysis Set)

	Vorasidenib 40 mg QD [a]					Placebo
	AG881-C-004 without crossover [b] N=167	AG881-C-004 post-crossover [c] N=52	AG881-C-002 N=11	AG120-881-C-001 N=14	Overall [d] N=244	AG881-C-004 pre-crossover [e] N=163
Moderate (30-<60)	2 (1.2)	1 (1.9)	0	2 (14.3)	5 (2.0)	1 (0.6)
Severe (15-<30)	0	0	0	0	0	0
Baseline liver function by NCI ODWG criteria, n (%)						
Normal	148 (88.6)	48 (92.3)	9 (81.8)	12 (85.7)	217 (88.9)	157 (96.3)
Mild	19 (11.4)	4 (7.7)	2 (18.2)	2 (14.3)	27 (11.1)	5 (3.1)
Moderate	0	0	0	0	0	1 (0.6)
Severe	0	0	0	0	0	0

Data Cutoff Dates: AG120-881-C-001 (30 May 2022); AG881-C-002 (17 October 2022); AG881-C-004 (06 September 2022).
Notes: The Safety Analysis Set for this table includes all subjects from AG881-C-004 who have received at least 1 dose of vorasidenib or placebo, and subjects from AG881-C-002 and AG120-881-C-001 who have received at least 1 dose of vorasidenib.
Baseline is defined as the last assessment collected on or prior to the date of start of study treatment.
Percentages are calculated based on N in each column.
StD: Standard deviation, Q1: Quartile 1, Q3: Quartile 3.
The Unknown category includes both Unknown and Not Reported.
Only Study AG881-C-002 collected ECOG Performance Status, and only Studies AG120-881-C-001 and AG881-C-004 collected Karnofsky Performance Scale.
a. 40 mg QD population includes subjects treated with vorasidenib 50 mg QD uncoated.
b. Includes data from subjects in Study AG881-C-004 who were randomized to and treated with vorasidenib 40 mg QD, those randomized to placebo but received at least one dose of vorasidenib without crossover, and pre-crossover data from subjects who received at least one dose of vorasidenib prior to cross over.
c. Includes data from subjects who were randomized to placebo who subsequently crossed over to receive vorasidenib 40 mg QD in Study AG881-C-004. Only data after crossover is included in this column.
d. Includes data from subjects treated with vorasidenib 40 mg QD in Study AG881-C-004, post crossover data from subjects 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 with glioma treated with vorasidenib 50 mg QD in Study AG881-C-002.
e. 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.

All Solid Tumours Including Glioma Population by Vorasidenib Dose

Table 3410. Baseline Characteristics and Prior Therapy – All Solid Tumours Including Glioma (Safety Analysis Set)

	Glioma and Non-glioma Solid Tumours [a]			
	<40 mg N=26	40 mg [b] N=251	>40 mg [c] N=59	Overall N=336
ECOG Performance Status, n (%)				
0	5 (19.2)	7 (2.8)	21 (35.6)	33 (9.8)
1	10 (38.5)	9 (3.6)	37 (62.7)	56 (16.7)
2	1 (3.8)	2 (0.8)	1 (1.7)	4 (1.2)
Unknown	10 (38.5)	233 (92.8)	0	243 (72.3)
Karnofsky Performance Scale, n (%)				
100	4 (15.4)	120 (47.8)	0	124 (36.9)
90-80	6 (23.1)	112 (44.6)	0	118 (35.1)

Table 3410. Baseline Characteristics and Prior Therapy – All Solid Tumours Including Glioma (Safety Analysis Set)

	Glioma and Non-glioma Solid Tumours [a]			
	<40 mg N=26	**40 mg [b] N=251**	**>40 mg [c] N=59**	**Overall N=336**
70-60	0	1 (0.4)	0	1 (0.3)
Unknown	16 (61.5)	18 (7.2)	59 (100)	93 (27.7)
Histological subtype, n (%)				
Astrocytoma	10 (38.5)	122 (48.6)	16 (27.1)	148 (44.0)
Oligodendroglioma	11 (42.3)	120 (47.8)	10 (16.9)	141 (42.0)
Bile ductular	1 (3.8)	1 (0.4)	4 (6.8)	6 (1.8)
Conventional	0	0	2 (3.4)	2 (0.6)
Intraductal	1 (3.8)	0	0	1 (0.3)
Other	1 (3.8)	4 (1.6)	10 (16.9)	15 (4.5)
Unknown	2 (7.7)	4 (1.6)	17 (28.8)	23 (6.8)
Time from initial diagnosis to randomization or first dose (months)				
n	26	251	59	336
Mean (StD)	98.144 (75.2231)	47.282 (38.6431)	56.070 (56.9082)	52.761 (47.7667)
Median	87.573	39.031	33.610	39.179
Q1, Q3	22.702, 144.986	25.593, 54.505	16.986, 78.784	23.556, 60.698
Min, Max	12.45, 274.43	2.43, 248.28	2.96, 287.01	2.43, 287.01
Number of prior surgeries, n (%)				
<2	10 (38.5)	186 (74.1)	23 (39.0)	219 (65.2)
≥2	16 (61.5)	65 (25.9)	36 (61.0)	117 (34.8)
Type of most recent surgery, n (%)				
Gross total	8 (30.8)	119 (47.4)	12 (20.3)	139 (41.4)
Subtotal	14 (53.8)	107 (42.6)	14 (23.7)	135 (40.2)
Biopsy	1 (3.8)	21 (8.4)	19 (32.2)	41 (12.2)
None	1 (3.8)	2 (0.8)	4 (6.8)	7 (2.1)
Other	2 (7.7)	2 (0.8)	10 (16.9)	14 (4.2)
Baseline renal function by creatinine clearance (mL/min), n (%)				
Normal (≥90)	16 (61.5)	228 (90.8)	39 (66.1)	283 (84.2)
Mild (60-<90)	8 (30.8)	21 (8.4)	18 (30.5)	47 (14.0)
Moderate (30-<60)	2 (7.7)	2 (0.8)	2 (3.4)	6 (1.8)
Severe (15-<30)	0	0	0	0
Baseline renal function by eGFR (mL/min/1.73m^2), n (%)				
Normal (≥90)	8 (30.8)	175 (69.7)	23 (39.0)	206 (61.3)
Mild (60-<90)	14 (53.8)	69 (27.5)	32 (54.2)	115 (34.2)
Moderate (30-<60)	4 (15.4)	7 (2.8)	4 (6.8)	15 (4.5)
Severe (15-<30)	0	0	0	0
Baseline liver function by NCI ODWG criteria, n (%)				

Table 3410. Baseline Characteristics and Prior Therapy – All Solid Tumours Including Glioma (Safety Analysis Set)

	Glioma and Non-glioma Solid Tumours [a]			
	<40 mg N=26	40 mg [b] N=251	>40 mg [c] N=59	Overall N=336
Normal	24 (92.3)	220 (87.6)	49 (83.1)	293 (87.2)
Mild	2 (7.7)	31 (12.4)	9 (15.3)	42 (12.5)
Moderate	0	0	1 (1.7)	1 (0.3)
Severe	0	0	0	0

Data Cutoff Dates: AG120-881-C-001 (30 May 2022); AG881-C-002 (17 October 2022); AG881-C-004 (06 September 2022)
Notes: The Safety Analysis Set for this table includes all subjects from AG881-C-004 who have received at least 1 dose of vorasidenib or placebo, and subjects from AG881-C-002 and AG120-881-C-001 who have received at least 1 dose of vorasidenib.
Baseline is defined as the last assessment collected on or prior to the date of start of study treatment.
Percentages are calculated based on N in each column.
StD: Standard deviation, Q1: Quartile 1, Q3: Quartile 3.
The Unknown category includes both Unknown and Not Reported.
Only Study AG881-C-002 collected ECOG Performance Status, and only Studies AG120-881-C-001 and AG881-C-004 collected Karnofsky Performance Scale.
a. Glioma and non-glioma solid tumours population includes data from subjects treated with vorasidenib in Study AG881-C-004, post crossover data from subjects treated with vorasidenib after crossover in Study AG881-C-004, data from subjects treated with vorasidenib in Study AG120-881-C-001, and data from subjects with glioma and non-glioma solid tumours treated with vorasidenib in Study AG881-C-002.
b. 40 mg QD population includes subjects treated with 50 mg QD uncoated.
c. >40 mg QD population does not include subjects treated with 50 mg QD uncoated.

Hematologic Malignancies Population

In subjects with hematologic malignancies treated with any vorasidenib dose (N=46), most had an ECOG Performance Status score of 1 (29 [63.0%] subjects) or 0 (11 [23.9%] subjects). Baseline characteristic and prior therapy in subjects with hematologic malignancies by vorasidenib dose level is presented in study AG881-C-001 CSR.

2.6.8.2. Adverse events

Table 3511: Overall Summary of Treatment-Emergent Adverse Events – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

	Vorasidenib 40 mg QD [a]					Placebo
Number (%) of subjects with	AG881-C-004 without crossover [b] N=167 n (%)	AG881-C-004 post-crossover [c] N=52 n (%)	AG881-C-002 N=11 n (%)	AG120-881-C-001 N=14 n (%)	Overall [d] N=244 n (%)	AG881-C-004 pre-crossover [e] N=163 n (%)
Any TEAEs	158 (94.6)	40 (76.9)	11 (100)	14 (100)	223 (91.4)	152 (93.3)
Grade ≥3 TEAEs	38 (22.8)	6 (11.5)	3 (27.3)	9 (64.3)	56 (23.0)	22 (13.5)
Treatment-related TEAEs	109 (65.3)	23 (44.2)	8 (72.7)	11 (78.6)	151 (61.9)	95 (58.3)
Grade ≥3 treatment-related TEAEs	22 (13.2)	4 (7.7)	0	1 (7.1)	27 (11.1)	6 (3.7)
Serious TEAEs	11 (6.6)	4 (7.7)	1 (9.1)	7 (50.0)	23 (9.4)	8 (4.9)
Serious treatment-related TEAEs	3 (1.8)	2 (3.8)	0	1 (7.1)	6 (2.5)	0

Table 3511: Overall Summary of Treatment-Emergent Adverse Events – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

	Vorasidenib 40 mg QD [a]					Placebo
Number (%) of subjects with	AG881-C-004 without crossover [b] N=167 n (%)	AG881-C-004 post-crossover [c] N=52 n (%)	AG881-C-002 N=11 n (%)	AG120-881-C-001 N=14 n (%)	Overall [d] N=244 n (%)	AG881-C-004 pre-crossover [e] N=163 n (%)
TEAEs leading to study treatment discontinuation	6 (3.6)	1 (1.9)	0	1 (7.1)	8 (3.3)	2 (1.2)
TEAEs leading to study treatment interruption	50 (29.9)	11 (21.2)	2 (18.2)	4 (28.6)	67 (27.5)	37 (22.7)
TEAEs leading to study treatment dose reduction	18 (10.8)	2 (3.8)	1 (9.1)	1 (7.1)	22 (9.0)	5 (3.1)
TEAEs leading to death	0	0	0	0	0	0
Treatment-related TEAEs leading to death	0	0	0	0	0	0
Any AESIs [f]	73 (43.7)	15 (28.8)	5 (45.5)	8 (57.1)	101 (41.4)	34 (20.9)
Serious AESIs	1 (0.6)	1 (1.9)	0	1 (7.1)	3 (1.2)	0
AESIs leading to death	0	0	0	0	0	0

Data Cutoff Dates: AG120-881-C-001 (30 May 2022); AG881-C-002 (17 October 2022); AG881-C-004 (06 September 2022).

Notes: The Safety Analysis Set for this table includes all subjects from AG881-C-004 who have received at least 1 dose of vorasidenib or placebo, and subjects from AG881-C-002 and AG120-881-C-001 who have received at least 1 dose of vorasidenib.

Treatment-emergent adverse events (TEAEs) presented in the summary tables include the AEs that begin or worsen from baseline during the on-treatment period.

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.

A subject with multiple occurrences of an AE is counted only once in the AE category. If a same AE appears more than once with different intensity or grade, then the event with the highest grade is considered.

Percentages are calculated based on N in each column.

TEAEs with relationship missing (unknown), probable, or possible are also considered as treatment-related.

a. 40 mg QD population includes subjects treated with vorasidenib 50 mg QD uncoated.

b. Includes data from subjects in Study AG881-C-004 who were randomized to and treated with vorasidenib 40 mg QD, those randomized to placebo but received at least one dose of vorasidenib without crossover, and pre-crossover data from subjects who received at least one dose of vorasidenib prior to cross over.

c. Includes data from subjects who were randomized to placebo who subsequently crossed over to receive vorasidenib 40 mg QD in Study AG881-C-004. Only data after crossover is included in this column.

d. Includes data from subjects treated with vorasidenib 40 mg QD in Study AG881-C-004, post crossover data from subjects 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 with glioma treated with vorasidenib 50 mg QD in Study AG881-C-002.

e. 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.

f. In Studies AG881-C-004, AG881-C-002, and AG120-881-C-001, Grade 2 or higher elevated liver transaminases (ie alanine aminotransferase increased or aspartate aminotransferase increased) were reported as AESIs. For the purpose of this Summary of Clinical Safety, adverse events of special interest (AESIs) are defined by a broad standard MedDRA query (SMQ) of liver-related investigations, signs, and symptoms that included medically equivalent terminology that could represent potential hepatic enzyme elevations.

Common Adverse Events

Table 3612. Summary of Most Common (≥10%) Treatment-Emergent Adverse Events Overall (N=244) by System Organ Class and Preferred Term – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

System Organ Class (SOC) Preferred Term (PT)	Vorasidenib 40 mg QD [a]					Placebo
	AG881-C-004 without crossover [b] N=167 n (%)	AG881-C-004 post-crossover [c] N=52 n (%)	AG881-C-002 N=11 n (%)	AG120-881-C-001 N=14 n (%)	Overall [d] N=244 n (%)	AG881-C-004 pre-crossover [e] N=163 n (%)
Subjects with any events	158 (94.6)	40 (76.9)	11 (100)	14 (100)	223 (91.4)	152 (93.3)
Nervous system disorders	93 (55.7)	15 (28.8)	10 (90.9)	10 (71.4)	128 (52.5)	84 (51.5)
Headache	45 (26.9)	5 (9.6)	8 (72.7)	6 (42.9)	64 (26.2)	44 (27.0)
Seizure	23 (13.8)	3 (5.8)	4 (36.4)	4 (28.6)	34 (13.9)	19 (11.7)
Dizziness	25 (15.0)	2 (3.8)	4 (36.4)	2 (14.3)	33 (13.5)	26 (16.0)
Investigations	85 (50.9)	18 (34.6)	6 (54.5)	9 (64.3)	118 (48.4)	49 (30.1)
Alanine aminotransferase increased	65 (38.9)	14 (26.9)	5 (45.5)	7 (50.0)	91 (37.3)	24 (14.7)
Aspartate aminotransferase increased	48 (28.7)	9 (17.3)	4 (36.4)	4 (28.6)	65 (26.6)	13 (8.0)
Gamma-glutamyltransferase increased	26 (15.6)	4 (7.7)	1 (9.1)	2 (14.3)	33 (13.5)	8 (4.9)
Gastrointestinal disorders	85 (50.9)	11 (21.2)	9 (81.8)	11 (78.6)	116 (47.5)	79 (48.5)
Diarrhoea	41 (24.6)	2 (3.8)	2 (18.2)	6 (42.9)	51 (20.9)	27 (16.6)
Nausea	36 (21.6)	3 (5.8)	4 (36.4)	6 (42.9)	49 (20.1)	37 (22.7)
Constipation	21 (12.6)	1 (1.9)	1 (9.1)	4 (28.6)	27 (11.1)	20 (12.3)
Infections and infestations	79 (47.3)	10 (19.2)	2 (18.2)	10 (71.4)	101 (41.4)	76 (46.6)
COVID-19	55 (32.9)	9 (17.3)	1 (9.1)	3 (21.4)	68 (27.9)	47 (28.8)
General disorders and administration site conditions	71 (42.5)	10 (19.2)	5 (45.5)	9 (64.3)	95 (38.9)	69 (42.3)
Fatigue	54 (32.3)	9 (17.3)	4 (36.4)	7 (50.0)	74 (30.3)	52 (31.9)

Data Cutoff Dates: AG120-881-C-001 (30 May 2022); AG881-C-002 (17 October 2022); AG881-C-004 (06 September 2022).
Notes: The Safety Analysis Set for this table includes all subjects from AG881-C-004 who have received at least 1 dose of vorasidenib or placebo, and subjects from AG881-C-002 and AG120-881-C-001 who have received at least 1 dose of vorasidenib.
Treatment-emergent adverse events (TEAEs) presented in the summary tables include the AEs that begin or worsen from baseline during the on-treatment period.
A subject with multiple occurrences of an AE under one treatment is counted only once in the PT for that treatment.
A subject with multiple AEs within the same SOC is counted only once in the SOC.
System organ classes and preferred terms are coded from MedDRA v25.1.
Percentages are calculated based on N in each column.
a. 40 mg QD population includes subjects treated with vorasidenib 50 mg QD uncoated.
b. Includes data from subjects in Study AG881-C-004 who were randomized to and treated with vorasidenib 40 mg QD, those randomized to placebo but received at least one dose of vorasidenib without crossover, and pre-crossover data from subjects who received at least one dose of vorasidenib prior to cross over.
c. Includes data from subjects who were randomized to placebo who subsequently crossed over to receive vorasidenib 40 mg QD in Study AG881-C-004. Only data after crossover is included in this column.
d. Includes data from subjects treated with vorasidenib 40 mg QD in Study AG881-C-004, post crossover data from subjects 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 with glioma treated with vorasidenib 50 mg QD in Study AG881-C-002.

e. 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.

The summary of TEAEs by SOC and PT in the glioma population who received any dose of vorasidenib was overall consistent with the findings in the pivotal study. Moreover, data suggest an increase in incidence of AST and ALT increase with the dose (i.e. 22.7% in doses< 40 mg, 27.3% for vorasidenib 40mg and 55.2% in vorasidenib > 40mg for ALT (and similar findings for AST)). Of note incidence of oropharyngeal pain was notable higher in the >40 mg group (13.8%).

Data in patients with all solid tumours who received Vorasidenib any dose were consistent with the incidences in the pivotal study, although vomiting and decreased appetite were of very common frequency (> 10%). A higher incidence of AST increase, ALT increase and decreased appetite with the dose was also observed.

Most common treatment-related Adverse Events are presented in the table below.

Table 3713. Summary of Most Common (≥10%) Related Treatment-Emergent Adverse Events by Preferred Term – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

	Vorasidenib 40 mg QD [a]					Placebo
Preferred Term (PT)	AG881-C-004 without crossover [b] N=167 n (%)	AG881-C-004 post-crossover [c] N=52 n (%)	AG881-C-002 N=11 n (%)	AG120-881-C-001 N=14 n (%)	Overall [d] N=244 n (%)	AG881-C-004 pre-crossover [e] N=163 n (%)
Subjects with any events	109 (65.3)	23 (44.2)	8 (72.7)	11 (78.6)	151 (61.9)	95 (58.3)
Alanine aminotransferase increased	61 (36.5)	10 (19.2)	5 (45.5)	5 (35.7)	81 (33.2)	18 (11.0)
Aspartate aminotransferase increased	41 (24.6)	7 (13.5)	4 (36.4)	3 (21.4)	55 (22.5)	9 (5.5)
Fatigue	35 (21.0)	6 (11.5)	4 (36.4)	4 (28.6)	49 (20.1)	29 (17.8)
Nausea	25 (15.0)	1 (1.9)	3 (27.3)	2 (14.3)	31 (12.7)	26 (16.0)
Gamma-glutamyltransferase increased	22 (13.2)	3 (5.8)	1 (9.1)	1 (7.1)	27 (11.1)	5 (3.1)

Data Cutoff Dates: AG120-881-C-001 (30 May 2022); AG881-C-002 (17 October 2022); AG881-C-004 (06 September 2022).
Notes: The Safety Analysis Set for this table includes all subjects from AG881-C-004 who have received at least 1 dose of vorasidenib or placebo, and subjects from AG881-C-002 and AG120-881-C-001 who have received at least 1 dose of vorasidenib.
Treatment-emergent adverse events (TEAEs) presented in the summary tables include the AEs that begin or worsen from baseline during the on-treatment period.
Most common related TEAEs are defined as the related TEAEs reported by ≥10% subjects overall under a PT.
A subject with multiple occurrences of an AE under one treatment is counted only once in the PT for that treatment.
Preferred terms are coded from MedDRA v25.1.
Percentages are calculated based on N in each column.
a. 40 mg QD population includes subjects treated with vorasidenib 50 mg QD uncoated.
b. Includes data from subjects in Study AG881-C-004 who were randomized to and treated with vorasidenib 40 mg QD, those randomized to placebo but received at least one dose of vorasidenib without crossover, and pre-crossover data from subjects who received at least one dose of vorasidenib prior to cross over.
c. Includes data from subjects who were randomized to placebo who subsequently crossed over to receive vorasidenib 40 mg QD in Study AG881-C-004. Only data after crossover is included in this column.
d. Includes data from subjects treated with vorasidenib 40 mg QD in Study AG881-C-004, post crossover data from subjects 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 with glioma treated with vorasidenib 50 mg QD in Study AG881-C-002.
e. 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.

Related TEAE in the glioma patients and in all solid tumours who received vorasidenib any dose were overall consistent with above results

Common grade ≥ 3 adverse events

Table 3814. Summary of Most Common (≥2%) Grade ≥3 Treatment-Emergent Adverse Events Overall (N=244) by System Organ Class and Preferred Term – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

System Organ Class (SOC) Preferred Term (PT)	Vorasidenib 40 mg QD [a]					Placebo
	AG881-C-004 without crossover [b] N=167 n (%)	AG881-C-004 post-crossover [c] N=52 n (%)	AG881-C-002 N=11 n (%)	AG120-881-C-001 N=14 n (%)	Overall [d] N=244 n (%)	AG881-C-004 pre-crossover [e] N=163 n (%)
Subjects with any events	38 (22.8)	6 (11.5)	3 (27.3)	9 (64.3)	56 (23.0)	22 (13.5)
Investigations	21 (12.6)	3 (5.8)	0	2 (14.3)	26 (10.7)	3 (1.8)
Alanine aminotransferase increased	16 (9.6)	3 (5.8)	0	2 (14.3)	21 (8.6)	0
Aspartate aminotransferase increased	7 (4.2)	2 (3.8)	0	1 (7.1)	10 (4.1)	0
Gamma-glutamyltransferase increased	5 (3.0)	0	0	0	5 (2.0)	2 (1.2)
Nervous system disorders	11 (6.6)	2 (3.8)	2 (18.2)	3 (21.4)	18 (7.4)	11 (6.7)
Seizure	7 (4.2)	1 (1.9)	2 (18.2)	1 (7.1)	11 (4.5)	4 (2.5)

Data Cutoff Dates: AG120-881-C-001 (30 May 2022); AG881-C-002 (17 October 2022); AG881-C-004 (06 September 2022).
Notes: The Safety Analysis Set for this table includes all subjects from AG881-C-004 who have received at least 1 dose of vorasidenib or placebo, and subjects from AG881-C-002 and AG120-881-C-001 who have received at least 1 dose of vorasidenib.
Treatment-emergent adverse events (TEAEs) presented in the summary tables include the AEs that begin or worsen from baseline during the on-treatment period.
A subject with multiple occurrences of an AE under one treatment is counted only once in the PT for that treatment.
A subject with multiple AEs within the same SOC is counted only once in the SOC.
System organ classes and preferred terms are coded from MedDRA v25.1.
Percentages are calculated based on N in each column.
a. 40 mg QD population includes subjects treated with vorasidenib 50 mg QD uncoated.
b. Includes data from subjects in Study AG881-C-004 who were randomized to and treated with vorasidenib 40 mg QD, those randomized to placebo but received at least one dose of vorasidenib without crossover, and pre-crossover data from subjects who received at least one dose of vorasidenib prior to cross over.
c. Includes data from subjects who were randomized to placebo who subsequently crossed over to receive vorasidenib 40 mg QD in Study AG881-C-004. Only data after crossover is included in this column.
d. Includes data from subjects treated with vorasidenib 40 mg QD in Study AG881-C-004, post crossover data from subjects 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 with glioma treated with vorasidenib 50 mg QD in Study AG881-C-002.
e. 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.

Grade ≥3 TEAEs in patients with glioma who received vorasidenib any dose was consistent with the above data. In patients with all solid tumours who received vorasidenib 40 mg and any dose, AST, ALT and seizure were the most frequent grade ≥3 TEAEs consistently with the pivotal study.

The summary of treatment-related grade ≥3 Adverse Events are presented in the table below.

Table 3915. Summary of Grade ≥3, Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

System Organ Class (SOC) Preferred Term (PT)	Vorasidenib 40 mg QD [a]					Placebo
	AG881-C-004 without crossover [b] N=167 n (%)	AG881-C-004 post-crossover [c] N=52 n (%)	AG881-C-002 N=11 n (%)	AG120-881-C-001 N=14 n (%)	Overall [d] N=244 n (%)	AG881-C-004 pre-crossover [e] N=163 n (%)
Subjects with any events	22 (13.2)	4 (7.7)	0	1 (7.1)	27 (11.1)	6 (3.7)
Investigations	19 (11.4)	3 (5.8)	0	1 (7.1)	23 (9.4)	1 (0.6)
Alanine aminotransferase increased	16 (9.6)	3 (5.8)	0	1 (7.1)	20 (8.2)	0
Aspartate aminotransferase increased	7 (4.2)	2 (3.8)	0	0	9 (3.7)	0
Gamma-glutamyltransferase increased	4 (2.4)	0	0	0	4 (1.6)	1 (0.6)
Bilirubin conjugated increased	1 (0.6)	0	0	0	1 (0.4)	0
Blood bilirubin increased	1 (0.6)	0	0	0	1 (0.4)	0
Neutrophil count decreased	1 (0.6)	0	0	0	1 (0.4)	0
Hepatobiliary disorders	2 (1.2)	0	0	0	2 (0.8)	0
Autoimmune hepatitis	1 (0.6)	0	0	0	1 (0.4)	0
Hepatic failure	1 (0.6)	0	0	0	1 (0.4)	0
Hepatic necrosis	1 (0.6)	0	0	0	1 (0.4)	0
Gastrointestinal disorders	1 (0.6)	0	0	0	1 (0.4)	1 (0.6)
Diarrhoea	1 (0.6)	0	0	0	1 (0.4)	1 (0.6)
General disorders and administration site conditions	1 (0.6)	0	0	0	1 (0.4)	1 (0.6)
Fatigue	1 (0.6)	0	0	0	1 (0.4)	1 (0.6)
Nervous system disorders	0	1 (1.9)	0	0	1 (0.4)	1 (0.6)
Seizure	0	1 (1.9)	0	0	1 (0.4)	0
Headache	0	0	0	0	0	1 (0.6)
Respiratory, thoracic and mediastinal disorders	1 (0.6)	0	0	0	1 (0.4)	0
Dyspnoea	1 (0.6)	0	0	0	1 (0.4)	0
Blood and lymphatic system disorders	0	0	0	0	0	1 (0.6)
Neutropenia	0	0	0	0	0	1 (0.6)
Musculoskeletal and connective tissue disorders	0	0	0	0	0	1 (0.6)
Arthralgia	0	0	0	0	0	1 (0.6)
Skin and subcutaneous tissue disorders	0	0	0	0	0	1 (0.6)
Rash maculo-papular	0	0	0	0	0	1 (0.6)
Vascular disorders	0	0	0	0	0	1 (0.6)
Hypertension	0	0	0	0	0	1 (0.6)

Data Cutoff Dates: AG120-881-C-001 (30 May 2022); AG881-C-002 (17 October 2022); AG881-C-004 (06 September 2022).

Notes: The Safety Analysis Set for this table includes all subjects from AG881-C-004 who have received at least 1 dose of vorasidenib or placebo, and subjects from AG881-C-002 and AG120-881-C-001 who have received at least 1 dose of vorasidenib.
Treatment-emergent adverse events (TEAEs) presented in the summary tables include the AEs that begin or worsen from baseline during the on-treatment period.
A subject with multiple occurrences of an AE under one treatment is counted only once in the PT for that treatment.
A subject with multiple AEs within the same SOC is counted only once in the SOC.
System organ classes and preferred terms are coded from MedDRA v25.1.
Percentages are calculated based on N in each column.
a. 40 mg QD population includes subjects treated with vorasidenib 50 mg QD uncoated.
b. Includes data from subjects in Study AG881-C-004 who were randomized to and treated with vorasidenib 40 mg QD, those randomized to placebo but received at least one dose of vorasidenib without crossover, and pre-crossover data from subjects who received at least one dose of vorasidenib prior to cross over.
c. Includes data from subjects who were randomized to placebo who subsequently crossed over to receive vorasidenib 40 mg QD in Study AG881-C-004. Only data after crossover is included in this column.
d. Includes data from subjects treated with vorasidenib 40 mg QD in Study AG881-C-004, post crossover data from subjects 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 with glioma treated with vorasidenib 50 mg QD in Study AG881-C-002.

e. Includes data from subjects whose actual treatment was placebo in Study AG88

In patients with glioma who received vorasidenib any dose grade ≥3 related TEAE were consistent with the pivotal study results. Nevertheless, related PT of fatigue grade ≥3 was experienced by 2 patients.

Summary of grade ≥ 3 related TEAEs in all solid tumour patients who received vorasidenib 40 mg or any dose were consistent with already observed data with no additional PT was experienced by more than 1 patient.

2.6.8.3. Most Common Treatment-Related Adverse Events

Glioma Population Treated With Vorasidenib 40 mg QD

Table 4016. Summary of Most Common (≥10%) Related Treatment-Emergent Adverse Events by Preferred Term – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

	Vorasidenib 40 mg QD [a]					Placebo
Preferred Term (PT)	AG881-C-004 without crossover [b] N=167 n (%)	AG881-C-004 post-crossover [c] N=52 n (%)	AG881-C-002 N=11 n (%)	AG120-881-C-001 N=14 n (%)	Overall [d] N=244 n (%)	AG881-C-004 pre-crossover [e] N=163 n (%)
Subjects with any events	109 (65.3)	23 (44.2)	8 (72.7)	11 (78.6)	151 (61.9)	95 (58.3)
Alanine aminotransferase increased	61 (36.5)	10 (19.2)	5 (45.5)	5 (35.7)	81 (33.2)	18 (11.0)
Aspartate aminotransferase increased	41 (24.6)	7 (13.5)	4 (36.4)	3 (21.4)	55 (22.5)	9 (5.5)
Fatigue	35 (21.0)	6 (11.5)	4 (36.4)	4 (28.6)	49 (20.1)	29 (17.8)
Nausea	25 (15.0)	1 (1.9)	3 (27.3)	2 (14.3)	31 (12.7)	26 (16.0)
Gamma-glutamyltransferase increased	22 (13.2)	3 (5.8)	1 (9.1)	1 (7.1)	27 (11.1)	5 (3.1)

Data Cutoff Dates: AG120-881-C-001 (30 May 2022); AG881-C-002 (17 October 2022); AG881-C-004 (06 September 2022).
Notes: The Safety Analysis Set for this table includes all subjects from AG881-C-004 who have received at least 1 dose of vorasidenib or placebo, and subjects from AG881-C-002 and AG120-881-C-001 who have received at least 1 dose of vorasidenib.
Treatment-emergent adverse events (TEAEs) presented in the summary tables include the AEs that begin or worsen from baseline during the on-treatment period.
Most common related TEAEs are defined as the related TEAEs reported by ≥10% subjects overall under a PT.

A subject with multiple occurrences of an AE under one treatment is counted only once in the PT for that treatment.
Preferred terms are coded from MedDRA v25.1.
Percentages are calculated based on N in each column.
a. 40 mg QD population includes subjects treated with vorasidenib 50 mg QD uncoated.
b. Includes data from subjects in Study AG881-C-004 who were randomized to and treated with vorasidenib 40 mg QD, those randomized to placebo but received at least one dose of vorasidenib without crossover, and pre-crossover data from subjects who received at least one dose of vorasidenib prior to cross over.
c. Includes data from subjects who were randomized to placebo who subsequently crossed over to receive vorasidenib 40 mg QD in Study AG881-C-004. Only data after crossover is included in this column.
d. Includes data from subjects treated with vorasidenib 40 mg QD in Study AG881-C-004, post crossover data from subjects 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 with glioma treated with vorasidenib 50 mg QD in Study AG881-C-002.
e. 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.

2.6.8.4. Serious adverse event/deaths/other significant events

- On treatment deaths

There were no TEAEs leading to death in any subject with glioma in the vorasidenib (N=167) or placebo arms (N=163) in study AG881-C-004 or in the overall glioma cohort treated with vorasidenib 40 mg QD (N=244).

There were no TEAEs leading to death in subjects with glioma who received any dose of vorasidenib (N=295).

There were no TEAEs leading to death reported in the broader population with all solid tumours including glioma treated with vorasidenib 40 mg QD (N=251).

In the overall population with all solid tumors including glioma treated with any vorasidenib dose (N=336), one patient treated with > 40 mg vorasidenib died. The patient had signet cell adenocarcinoma and cause of death was a large intestine perforation that was reported as related to disease under study or its treatment and was not considered related to vorasidenib.

- Serious Adverse Events

Table 4117. Summary of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

	Vorasidenib 40 mg QD [a]					Placebo
System Organ Class (SOC) Preferred Term (PT)	AG881-C-004 without crossover [b] N=167 n (%)	AG881-C-004 post-crossover [c] N=52 n (%)	AG881-C-002 N=11 n (%)	AG120-881-C-001 N=14 n (%)	Overall [d] N=244 n (%)	AG881-C-004 pre-crossover [e] N=163 n (%)
Subjects with any events	11 (6.6)	4 (7.7)	1 (9.1)	7 (50.0)	23 (9.4)	8 (4.9)
Nervous system disorders	5 (3.0)	2 (3.8)	1 (9.1)	3 (21.4)	11 (4.5)	6 (3.7)
Seizure	5 (3.0)	1 (1.9)	1 (9.1)	1 (7.1)	8 (3.3)	3 (1.8)
Aphasia	0	0	0	1 (7.1)	1 (0.4)	0
Hydrocephalus	0	0	0	1 (7.1)	1 (0.4)	0
Partial seizures	0	1 (1.9)	0	0	1 (0.4)	1 (0.6)
Encephalopathy	0	0	0	0	0	1 (0.6)
Epilepsy	0	0	0	0	0	1 (0.6)
Toxic encephalopathy	0	0	0	0	0	1 (0.6)
Hepatobiliary disorders	2 (1.2)	0	0	1 (7.1)	3 (1.2)	0

Table 4117. Summary of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

System Organ Class (SOC) Preferred Term (PT)	Vorasidenib 40 mg QD [a]					Placebo
	AG881-C-004 without crossover [b] N=167 n (%)	AG881-C-004 post-crossover [c] N=52 n (%)	AG881-C-002 N=11 n (%)	AG120-881-C-001 N=14 n (%)	Overall [d] N=244 n (%)	AG881-C-004 pre-crossover [e] N=163 n (%)
Autoimmune hepatitis	1 (0.6)	0	0	0	1 (0.4)	0
Biliary dyskinesia	0	0	0	1 (7.1)	1 (0.4)	0
Hepatic failure	1 (0.6)	0	0	0	1 (0.4)	0
Infections and infestations	2 (1.2)	0	0	1 (7.1)	3 (1.2)	0
Brain abscess	0	0	0	1 (7.1)	1 (0.4)	0
Enterocolitis infectious	1 (0.6)	0	0	0	1 (0.4)	0
Post procedural infection	1 (0.6)	0	0	0	1 (0.4)	0
Investigations	1 (0.6)	1 (1.9)	0	1 (7.1)	3 (1.2)	0
Alanine aminotransferase increased	1 (0.6)	1 (1.9)	0	1 (7.1)	3 (1.2)	0
Cardiac disorders	0	1 (1.9)	0	0	1 (0.4)	1 (0.6)
Acute myocardial infarction	0	1 (1.9)	0	0	1 (0.4)	0
Myocardial ischaemia	0	0	0	0	0	1 (0.6)
Injury, poisoning and procedural complications	0	0	0	1 (7.1)	1 (0.4)	0
Toxicity to various agents	0	0	0	1 (7.1)	1 (0.4)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.6)	0	0	0	1 (0.4)	0
Lung neoplasm malignant	1 (0.6)	0	0	0	1 (0.4)	0
Renal and urinary disorders	0	0	0	1 (7.1)	1 (0.4)	0
Nephrolithiasis	0	0	0	1 (7.1)	1 (0.4)	0
Musculoskeletal and connective tissue disorders	0	0	0	0	0	1 (0.6)
Osteonecrosis	0	0	0	0	0	1 (0.6)
Psychiatric disorders	0	0	0	0	0	2 (1.2)
Suicidal ideation	0	0	0	0	0	2 (1.2)
Vascular disorders	0	0	0	0	0	1 (0.6)

Table 4117. Summary of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

System Organ Class (SOC) Preferred Term (PT)	Vorasidenib 40 mg QD [a]					Placebo
	AG881-C-004 without crossover [b] N=167 n (%)	AG881-C-004 post-crossover [c] N=52 n (%)	AG881-C-002 N=11 n (%)	AG120-881-C-001 N=14 n (%)	Overall [d] N=244 n (%)	AG881-C-004 pre-crossover [e] N=163 n (%)
Haematoma	0	0	0	0	0	1 (0.6)

Data Cutoff Dates: AG120-881-C-001 (30 May 2022); AG881-C-002 (17 October 2022); AG881-C-004 (06 September 2022).
Notes: The Safety Analysis Set for this table includes all subjects from AG881-C-004 who have received at least 1 dose of vorasidenib or placebo, and subjects from AG881-C-002 and AG120-881-C-001 who have received at least 1 dose of vorasidenib.
Treatment-emergent adverse events (TEAEs) presented in the summary tables include the AEs that begin or worsen from baseline during the on-treatment period.
A subject with multiple occurrences of an AE under one treatment is counted only once in the PT for that treatment.
A subject with multiple AEs within the same SOC is counted only once in the SOC.
System organ classes and preferred terms are coded from MedDRA version 25.1.
Percentages are calculated based on N in each column.
a. 40 mg QD population includes subjects treated with vorasidenib 50 mg QD uncoated.
b. Includes data from subjects in Study AG881-C-004 who were randomized to and treated with vorasidenib 40 mg QD, those randomized to placebo but received at least one dose of vorasidenib without crossover, and pre-crossover data from subjects who received at least one dose of vorasidenib prior to cross over.
c. Includes data from subjects who were randomized to placebo who subsequently crossed over to receive vorasidenib 40 mg QD in Study AG881-C-004. Only data after crossover is included in this column.
d. Includes data from subjects treated with vorasidenib 40 mg QD in Study AG881-C-004, post crossover data from subjects 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 with glioma treated with vorasidenib 50 mg QD in Study AG881-C-002.
e. 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.

In the population of glioma patients who received vorasidenib any dose, additional patients had serious TEAE of seizure, ALT and AST increase, and infection in consistency with the above findings. Furthermore, serious TEAE in the all tumours population who received vorasidenib any dose were consistent with the pivotal study, with additional serious TEAE of seizure (1 patient) and myelitis (1 patient).

Table 4218. Summary of Related, Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

System Organ Class (SOC) Preferred Term (PT)	Vorasidenib 40 mg QD [a]					Placebo
	AG881-C-004 without crossover [b] N=167 n (%)	AG881-C-004 post-crossover [c] N=52 n (%)	AG881-C-002 N=11 n (%)	AG120-881-C-001 N=14 n (%)	Overall [d] N=244 n (%)	AG881-C-004 pre-crossover [e] N=163 n (%)
Subjects with any events	3 (1.8)	2 (3.8)	0	1 (7.1)	6 (2.5)	0
Investigations	1 (0.6)	1 (1.9)	0	1 (7.1)	3 (1.2)	0
Alanine aminotransferase increased	1 (0.6)	1 (1.9)	0	1 (7.1)	3 (1.2)	0
Hepatobiliary disorders	2 (1.2)	0	0	0	2 (0.8)	0
Autoimmune hepatitis	1 (0.6)	0	0	0	1 (0.4)	0
Hepatic failure	1 (0.6)	0	0	0	1 (0.4)	0
Nervous system disorders	0	1 (1.9)	0	0	1 (0.4)	0

Table 4218. Summary of Related, Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

System Organ Class (SOC) Preferred Term (PT)	Vorasidenib 40 mg QD [a]					Placebo
	AG881-C-004 without crossover [b] N=167 n (%)	AG881-C-004 post-crossover [c] N=52 n (%)	AG881-C-002 N=11 n (%)	AG120-881-C-001 N=14 n (%)	Overall [d] N=244 n (%)	AG881-C-004 pre-crossover [e] N=163 n (%)
Seizure	0	1 (1.9)	0	0	1 (0.4)	0

Notes: The Safety Analysis Set for this table includes all subjects from AG881-C-004 who have received at least 1 dose of vorasidenib or placebo, and subjects from AG881-C-002 and AG120-881-C-001 who have received at least 1 dose of vorasidenib.
Treatment-emergent adverse events (TEAEs) presented in the summary tables include the AEs that begin or worsen from baseline during the on-treatment period.
A subject with multiple occurrences of an AE under one treatment is counted only once in the PT for that treatment.
A subject with multiple AEs within the same SOC is counted only once in the SOC.
System organ classes and preferred terms are coded from MedDRA version 25.1.
Percentages are calculated based on N in each column.
a. 40 mg QD population includes subjects treated with vorasidenib 50 mg QD uncoated.
b. Includes data from subjects in Study AG881-C-004 who were randomized to and treated with vorasidenib 40 mg QD, those randomized to placebo but received at least one dose of vorasidenib without crossover, and pre-crossover data from subjects who received at least one dose of vorasidenib prior to cross over.
c. Includes data from subjects who were randomized to placebo who subsequently crossed over to receive vorasidenib 40 mg QD in Study AG881-C-004. Only data after crossover is included in this column.
d. Includes data from subjects treated with vorasidenib 40 mg QD in Study AG881-C-004, post crossover data from subjects 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 with glioma treated with vorasidenib 50 mg QD in Study AG881-C-002.
e. 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

The summary of treatment related SAE in the subjects with glioma who received vorasidenib any dose are consistent with the above results. Additional patients had treatment related serious events of AST and ALT increase in the 40 mg and > 40 mg group. The overall population of patients with all solid tumour who receive vorasidenib 40 mg or any dose was consistent with the glioma cohort who received vorasidenib any dose. No additional PT were observed.

- Adverse Events of Special Interest (AESI)

Based on clinical findings during the conduct of study AG881-C-001 and study AG881-C-002, in addition to non-clinical liver findings, elevated liver transaminases were considered an identified risk for vorasidenib. To evaluate this risk further, elevated liver transaminases were included as AESIs in clinical protocols of vorasidenib.

The search strategy for hepatic enzyme elevations included PTs within the broad SMQ of liver-related investigations, signs, and symptoms. The search strategy for hepatotoxicity included the broad drug-related hepatic disorders comprehensive SMQ plus 2 additional PTs of blood albumin decreased (synonymous with hypoalbuminemia already contained in the SMQ) and immune-mediated cholestasis (biliary disorders already contained within the SMQ). This additional search strategy was used to identify clinically meaningful TEAEs that may have severe and serious outcomes associated with elevated liver enzymes that were not included in the SMQ of liver-related investigations, signs, and symptoms.

Hepatic Enzymes Elevation Search Strategy

Table 4319. Overall Summary of Treatment-Emergent Adverse Events From SMQ (Broad Search) Liver-Related Investigations, Signs, and Symptoms – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

Number (%) of subjects with	Vorasidenib 40 mg QD [a]					Placebo
	AG881-C-004 without crossover [b] N=167 n (%)	AG881-C-004 post-crossover [c] N=52 n (%)	AG881-C-002 N=11 n (%)	AG120-881-C-001 N=14 n (%)	Overall [d] N=244 n (%)	AG881-C-004 pre-crossover [e] N=163 n (%)
Any TEAEs	73 (43.7)	15 (28.8)	5 (45.5)	8 (57.1)	101 (41.4)	34 (20.9)
Grade ≥2 TEAEs	35 (21.0)	7 (13.5)	0	3 (21.4)	45 (18.4)	10 (6.1)
Grade ≥3 TEAEs	19 (11.4)	3 (5.8)	0	2 (14.3)	24 (9.8)	2 (1.2)
Treatment-related TEAEs	65 (38.9)	10 (19.2)	5 (45.5)	5 (35.7)	85 (34.8)	26 (16.0)
Grade ≥2 Treatment-related TEAEs	34 (20.4)	5 (9.6)	0	2 (14.3)	41 (16.8)	6 (3.7)
Grade ≥3 Treatment-related TEAEs	18 (10.8)	3 (5.8)	0	1 (7.1)	22 (9.0)	1 (0.6)
Serious TEAEs	1 (0.6)	1 (1.9)	0	1 (7.1)	3 (1.2)	0
Serious treatment-related TEAEs	1 (0.6)	1 (1.9)	0	1 (7.1)	3 (1.2)	0
TEAEs leading to study treatment discontinuation	5 (3.0)	1 (1.9)	0	1 (7.1)	7 (2.9)	0
TEAEs leading to study treatment interruption	28 (16.8)	7 (13.5)	0	3 (21.4)	38 (15.6)	5 (3.1)
TEAEs leading to study treatment dose reduction	14 (8.4)	2 (3.8)	1 (9.1)	1 (7.1)	18 (7.4)	2 (1.2)
TEAEs leading to death	0	0	0	0	0	0
Treatment-related TEAEs leading to death	0	0	0	0	0	0

Data Cutoff Dates: AG120-881-C-001 (30 May 2022); AG881-C-002 (17 October 2022); AG881-C-004 (06 September 2022).

Notes: The Safety Analysis Set for this table includes all subjects from AG881-C-004 who have received at least 1 dose of vorasidenib or placebo, and subjects from AG881-C-002 and AG120-881-C-001 who have received at least 1 dose of vorasidenib.

Treatment-emergent adverse events (TEAEs) presented in the summary tables include the AEs that begin or worsen from baseline during the on-treatment period.

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.

A subject with multiple occurrences of an AE is counted only once in the AE category. If a same AE appears more than once with different intensity or grade, then the event with the highest grade is considered.

Percentages are calculated based on N in each column.

Treatment-emergent AEs with relationship missing (unknown), probable, or possible are also considered as treatment-related.

a. 40 mg QD population includes subjects treated with vorasidenib 50 mg QD uncoated.

b. Includes data from subjects in Study AG881-C-004 who were randomized to and treated with vorasidenib 40 mg QD, those randomized to placebo but received at least one dose of vorasidenib without crossover, and pre-crossover data from subjects who received at least one dose of vorasidenib prior to cross over.
c. Includes data from subjects who were randomized to placebo who subsequently crossed over to receive vorasidenib 40 mg QD in Study AG881-C-004. Only data after crossover is included in this column.
d. Includes data from subjects treated with vorasidenib 40 mg QD in Study AG881-C-004, post crossover data from subjects 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 with glioma treated with vorasidenib 50 mg QD in Study AG881-C-002.
e. 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.

All PTs under the broad SMQ, except bilirubin conjugated increased, occurred more frequently in subjects in the vorasidenib arm than in the placebo arm. The PTs of blood alkaline phosphatase increased, blood bilirubin increased, and bilirubin conjugated increased were reported infrequently across both arms.

Table 44.20 Summary of Treatment-Emergent Adverse Events from SMQ (Broad search) of Hepatic enzymes elevation by Preferred Term-Glioma with Vorasidenib 40 mg QD.

	Vorasidenib 40 mg QD [1]					Placebo
Preferred Term (PT)	AG881-C-004 without crossover [2] N = 167 n (%)	AG881-C-004 post-crossover [3] N = 52 n (%)	AG881-C-002 N = 11 n (%)	AG120-881-C-001 N = 14 n (%)	Overall [4] N = 244 n (%)	AG881-C-004 pre-crossover [5] N = 163 n (%)
Subjects with any events	73 (43.7)	15 (28.8)	5 (45.5)	8 (57.1)	101 (41.4)	34 (20.9)
Alanine aminotransferase increased	65 (38.9)	14 (26.9)	5 (45.5)	7 (50.0)	91 (37.3)	24 (14.7)
Aspartate aminotransferase increased	48 (28.7)	9 (17.3)	4 (36.4)	4 (28.6)	65 (26.6)	13 (8.0)
Gamma-glutamyltransferase increased	26 (15.6)	4 (7.7)	1 (9.1)	2 (14.3)	33 (13.5)	8 (4.9)
Blood alkaline phosphatase increased	6 (3.6)	0	1 (9.1)	2 (14.3)	9 (3.7)	2 (1.2)
Blood bilirubin increased	6 (3.6)	0	0	0	6 (2.5)	4 (2.5)
Bilirubin conjugated increased	1 (0.6)	0	0	0	1 (0.4)	1 (0.6)

Table 45.21 Summary of Treatment-Emergent Adverse Events from SMQ (Broad search) of Hepatic enzymes elevation by Preferred Term and Worst CTCAE grade -Glioma with Vorasidenib 40 mg QD.

	Vorasidenib 40 mg QD [1]							
	AG881-C-004 without crossover [2] N = 167							
Preferred Term (PT)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Grade ≥3 n (%)	Missing n (%)	Any Grade n (%)
Subjects with any events	38 (22.8)	16 (9.6)	15 (9.0)	4 (2.4)	0	19 (11.4)	0	73 (43.7)
Alanine aminotransferase increased	35 (21.0)	14 (8.4)	12 (7.2)	4 (2.4)	0	16 (9.6)	0	65 (38.9)
Aspartate aminotransferase increased	34 (20.4)	7 (4.2)	5 (3.0)	2 (1.2)	0	7 (4.2)	0	48 (28.7)
Gamma-glutamyltransferase increased	15 (9.0)	6 (3.6)	5 (3.0)	0	0	5 (3.0)	0	26 (15.6)
Blood alkaline phosphatase increased	6 (3.6)	0	0	0	0	0	0	6 (3.6)
Blood bilirubin increased	5 (3.0)	0	1 (0.6)	0	0	1 (0.6)	0	6 (3.6)
Bilirubin conjugated increased	0	0	1 (0.6)	0	0	1 (0.6)	0	1 (0.6)

The median time to first event for TEAEs of any grade in the vorasidenib arm (N=167) was 57.0 (range: 1 – 451) days and most subjects had a time to first event ≤60 days following the first study treatment dose; subjects in the placebo arm had a median time to first event of 116.0 (range: 5 – 308) days.

The median TTR for Grade ≥3 TEAEs that occurred in ≥2 subjects in the vorasidenib arm is as follows:

- The median TTR for alanine aminotransferase increased (any grade) was longer for subjects in the vorasidenib arm than in the placebo arm (56.0 [range: 5 – 389] vs. 28.5 [range: 4 – 113]) days.
- The median TTR for aspartate aminotransferase increased (any grade), was the same in both arms at 29.0 days (range: 5 – 537 days for the vorasidenib arm and 6 – 162 days for the placebo arm).
- The median TTR for gamma-glutamyltransferase increased (any grade) was longer in the vorasidenib arm than placebo (57.0 [range: 8 – 337] vs. 29.0 [range: 27 – 112] days).

Results from pooled patients were consistent with the observations of the pivotal study.

Hepatotoxicity Search Strategy

Results from the analysis conducted using the search strategy composed of the comprehensive SMQ of drug-related hepatic disorders plus PTs of blood albumin decreased and immune-mediated cholestasis, unless otherwise stated are described below.

In study AG881-C-004, more subjects in the vorasidenib 40 mg QD arm (N=167) experienced TEAEs within the hepatotoxicity search strategy than subjects in the placebo arm (N=163) (73 [43.7%] vs. 34 [20.9%], respectively).

The additional PTs identified within the hepatotoxicity search strategy in the vorasidenib arm (N=167) that were not within the hepatic enzymes elevation SMQ included hepatic steatosis (2 [1.3%] subjects in the vorasidenib arm) and hypoalbuminemia, autoimmune hepatitis, benign hepatic neoplasm, hepatic failure, and hepatic necrosis that occurred in 1 (0.6%) subject each in the vorasidenib arm. No subjects in the placebo arm experienced events captured under the additional PTs.

The event of autoimmune hepatitis in 1 subject and the events of hepatic failure and hepatic necrosis in 1 subject were associated with laboratory values that met the ADR criteria.

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. The only TEAE that was identified in this cohort that was not in the AG881-C-004 study vorasidenib arm (N=167) was international normalised ratio increased, which occurred in 1 (0.4%) subject.

Overall, data in glioma patients who received vorasidenib any dose were consistent with the pivotal study. One additional event of hypoalbuminemia occurred at a dose > 40 mg and one event of INR decrease occurred at a dose < 40 mg occurred. In the solid tumour population treated by vorasidenib 40 mg and any dose, results of the hepatotoxicity search strategy were similar to the pivotal study. Additional PT included ascites in 5 patients treated with vorasidenib >40 mg. Other additional PTs identified in this pooled population were hyperbilirubinemia and prothrombin time prolonged (2 [0.6%] subjects each); and blood bilirubin unconjugated increased, and jaundice (1 [0.3%] subject each).

Laboratory Values for Liver Function Test

In addition, an assessment of laboratory values for liver function tests was meeting the following criteria: ALT or AST ≥3× ULN, total bilirubin ≥2× ULN, and ALP <2× ULN (or missing) within 10 days of each other. In study AG881 C 004, of the 167 patients treated with vorasidenib, 18.6% experienced elevations in ALT > 3 times the ULN and 8.4% experienced elevations in AST > 3 times the ULN. Among these patients, 1.2% had concurrent elevations in ALT or AST > 3 times the ULN and total bilirubin > 2 times the ULN. This assessment was overall consistent with the above observations.

- Other Events of Special Interest

Neurological Disturbances

A comprehensive search was conducted to identify potential clinically relevant TEAEs using the high-level term (HLT) tremor (excluding congenital) and the HLT coordination and balance disturbances, in addition to PTs of dystonic tremor and torticollis.

In study AG881-C-004, few subjects in the vorasidenib (4 [2.4%] subjects; N=167) and placebo arm (3 [1.8%] subjects; N=163) experienced TEAEs within the search strategy for neurological disturbances. TEAEs within the search strategy that occurred in subjects in the vorasidenib arm and placebo arm, respectively, were balance disorder (2 [1.2%] vs. 0 subjects), ataxia (1 [0.6%] subject each), dysdiadochokinesis (1 [0.6%] vs. 0 subjects), and tremor (0 vs. 2 [1.2%] subjects). All were non-

serious, and low grade (Grade 1 or Grade 2). One (0.6%) subject in each arm experienced treatment-related TEAEs within the search strategy; these treatment-related TEAEs were Grade 1 events of balance disorder (vorasidenib arm) and tremor (placebo arm).

There were no TEAEs within the search strategy that led to study treatment discontinuation or death in either arm. TEAEs within the search strategy leading to study treatment interruption or dose reduction occurred in 1 (0.6%) subject each in the vorasidenib arm, and no subjects in the placebo arm.

For TEAEs of any grade within the search strategy, the median time to first event following the first study treatment dose was shorter in the vorasidenib arm (246.5 [range: 41 – 265] days) than in the placebo arm (294.0 [range: 3 – 599] days).

In the overall glioma cohort treated with vorasidenib 40 mg QD (N=244), the proportion of subjects who experienced TEAEs within the search strategy (6 [2.5%]) was similar to the vorasidenib arm (N=167; 4 [2.4%]); there were no additional clinically meaningful TEAEs identified within this cohort.

In the pool of patients with glioma who received vorasidenib any dose, 5 additional patients experienced a TEAE within the neurological disturbances search strategy, of which one was grade ≥ 3 (balance disorders) and one was considered treatment-related. These patients received a dose > 40 mg. The PTs were one additional event of balanced disorder, 2 events of ataxia, 1 event of tremor and 1 event of coordination abnormal. PT within this search strategy occurred in 17.2% of patients who received vorasidenib > 40 mg. Although the number of patients who received vorasidenib > 40 mg is limited (n=29), these observations might suggest an increase of event with the dose.

In the all solid tumour including glioma population vorasidenib 40 mg and any dose, the search within neurological disorders was consistent with the overall glioma cohort vorasidenib 40 mg and any dose. In the 40 mg cohort, one additional event of balanced disorder occurred. In the > 40 mg group, 2 additional events were observed (1 tremor and 1 coordination abnormal).

Gastrointestinal Disorders

A comprehensive search using the search strategy that was composed of the high-level group term (HLGT) gastrointestinal signs and symptoms, along with HLGT gastrointestinal motility and defecation conditions based on MedDRA version 25.1.

In study AG881-C-004, a similar proportion of subjects experienced TEAEs within the search strategy of gastrointestinal disorders in the vorasidenib arm (76 [45.5%] subjects; N=167) and placebo arm (74 [45.4%] subjects; N=163). TEAEs within the search strategy that occurred in ≥5% of subjects in the vorasidenib arm or placebo, respectively, were diarrhoea (41 [24.6%] vs. 27 [16.6%] subjects), nausea (36 [21.6%] vs. 37 [22.7] subjects), constipation (21 [12.6%] subjects vs. 20 [12.3%] subjects), abdominal pain (14 [8.4%] vs. 14 [8.6%] subjects), and vomiting (11 [6.6%] vs. 16 [9.8%] subjects). Of the TEAEs listed, diarrhoea occurred in ≥2% more subjects in the vorasidenib arm than the placebo arm while vomiting occurred in ≥2% more subjects in the placebo arm than the vorasidenib arm. All TEAEs within the search strategy were non-serious and only 1 (0.6%) subject in each arm experienced Grade ≥3 TEAEs, which were treatment-related events of diarrhoea.

Within related TEAE, diarrhoea (12.0% and 9.8% respectively) and abdominal pain (6.0% and 3.1% respectively) occurred at a higher incidence in the vorasidenib arm than in the placebo arm.

There were no TEAEs within the search strategy that led to death. A similar proportion of subjects experienced TEAEs within the search strategy that led to dose modifications in the vorasidenib and placebo arms.

For TEAEs of any grade within the search strategy, the median time to first event following the first study treatment dose for the vorasidenib arm and the placebo arm was similar at 16.0 (range: 1 – 516) days

and 15.0 (range: 1 – 344) days, respectively. Most subjects in the vorasidenib arm (53 of 76) and the placebo arm (56 of 74) had a time to first event ≤60 days following the first study treatment dose.

In the overall glioma cohort treated with vorasidenib 40 mg QD (N=244), the proportion of subjects (105 [43.0%]) who experienced TEAEs within the search strategy was similar to the vorasidenib arm (N=167; 76 [45.5%]).

Data from the glioma patients who received vorasidenib any dose and patients with all solid tumours who received vorasidenib 40 mg or any dose were consistent with the pivotal study with similar incidences of nausea, diarrhoea, vomiting and abdominal pain.

Electrocardiogram QT Prolongation

A comprehensive search using the broad SMQ of torsade de pointes/QT prolongation based on MedDRA version 25.1 was conducted to identify potential clinically relevant TEAEs.

In study AG881-C-004, the proportion of subjects who experienced at least 1 TEAE within the broad SMQ of torsade de pointes/QT prolongation was low in both the vorasidenib 40 mg QD arm (6 [3.6%] subjects; N=167) and placebo arm (3 [1.8%] subjects; N=163). TEAEs within the SMQ that occurred in the vorasidenib arm and placebo, respectively, were electrocardiogram QT prolonged (2 [1.2%] subjects each), syncope (3 [1.8%] vs. 1 [0.6%] subject), and loss of consciousness (1 [0.6%] vs. 0 subjects); all were non-serious.

Grade ≥3 TEAEs within the SMQ were experienced by 3 (1.8%) subjects in the vorasidenib arm and 1 (0.6%) subject in the placebo arm; all events (in both arms) were Grade 3 syncope and were unrelated to study treatment. Of the 3 subjects in the vorasidenib arm, apart from underlying index disease, for which each subject concomitantly received antiepileptic medication:

- 1 subject had a prior medical history of syncope and on the same day as the Grade 3 event of syncope, experienced Grade 1 hypoglycemia.
- 1 subject had a prior medical history of hypotension and experienced several events of Grade 1 hyperglycemia; on the same day of the Grade 3 event of syncope the subject also received a COVID-19 vaccination.

Only 1 of the 3 subjects in the vorasidenib arm had a QTc value available on the same day as the syncope (study Day 351), which was 398 ms. Another subject had a QTc value of 446 ms available 2 days prior (study Day 169) to the syncope event (study Day 171).

Treatment-related TEAEs within the SMQ were experienced by 2 (1.2%) subjects in the placebo arm; all 3 events were non-serious Grade 1 TEAEs of electrocardiogram QT prolonged. No subjects experienced TEAEs within the SMQ leading to study treatment discontinuation or death; no TEAEs within the SMQ required treatment interruption or dose reduction.

For TEAEs of any grade within the SMQ, the median time to first event following the first study treatment dose was shorter in the vorasidenib arm (156.0 [range: 28 – 351] days) compared with the placebo arm (254 [range: 122 – 270] days.

In the overall glioma cohort treated with vorasidenib (N=244), the proportion of subjects who experienced TEAEs within the SMQ (7 [2.9%]) was similar to the vorasidenib arm (N=167; 6 [3.6%]) and does not demonstrate a safety concern. One additional subject experienced a TEAE within the SMQ that was a Grade 1 treatment-related event of electrocardiogram QT prolonged on study Day 114 that resolved without dose modification on study Day 142.

In the broader population with all solid tumours including glioma treated with vorasidenib 40 mg QD (N=251), the proportion of subjects (7 [2.8%]) who experienced TEAEs within the broad SMQ of torsade

de pointes/QT prolongation was consistent with the overall glioma cohort treated with vorasidenib 40 mg QD (N=244; 7 [2.8%].

In the overall population with all solid tumours including glioma treated with any vorasidenib dose (N=336), 11 (3.3%) subjects experienced at least 1 TEAE within the SMQ and 2 (0.6%) subjects experienced treatment-related TEAEs. The TEAEs within the SMQ that occurred were electrocardiogram QT prolonged (6 [1.8%] subjects), syncope (3 [0.9%] subjects), and loss of consciousness (2 [0.6%] subjects); all were non-serious. Only 1 subject experienced a Grade ≥3 TEAE within the SMQ.

Skin Disorders

A comprehensive search was conducted to identify potential clinically relevant TEAEs using a search strategy under the SOC of skin and subcutaneous tissue disorders. Additionally, a search strategy composed of HLT exfoliative conditions based on MedDRA version 25.1 was conducted; no TEAEs under this search strategy were reported for any subjects.

Table 4622. Summary of Treatment-Emergent Adverse Events Within the System Organ Class of Skin and Subcutaneous Disorders by Preferred Term – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

	Vorasidenib 40 mg QD [a]		Placebo
System Organ Class (SOC) Preferred Term (PT)	AG881-C-004 without crossover [b] N=167 n (%)	Overall [c] N=244 n (%)	AG881-C-004 pre-crossover [d] N=163 n (%)
Skin and subcutaneous tissue disorders	30 (18.0)	45 (18.4)	30 (18.4)
Pruritus	4 (2.4)	7 (2.9)	2 (1.2)
Hyperhidrosis	5 (3.0)	6 (2.5)	1 (0.6)
Alopecia	4 (2.4)	5 (2.0)	2 (1.2)
Rash	4 (2.4)	5 (2.0)	2 (1.2)
Photosensitivity reaction	2 (1.2)	4 (1.6)	4 (2.5)
Rash maculo-papular	3 (1.8)	4 (1.6)	5 (3.1)
Dermatitis contact	2 (1.2)	3 (1.2)	2 (1.2)
Dry skin	2 (1.2)	3 (1.2)	3 (1.8)
Acne	1 (0.6)	2 (0.8)	0
Dermatitis acneiform	1 (0.6)	2 (0.8)	1 (0.6)
Eczema	2 (1.2)	2 (0.8)	0
Night sweats	2 (1.2)	2 (0.8)	0
Dandruff	0	1 (0.4)	0
Dermatitis bullous	1 (0.6)	1 (0.4)	0
Drug eruption	0	1 (0.4)	0
Erythema	0	1 (0.4)	1 (0.6)
Hand dermatitis	1 (0.6)	1 (0.4)	1 (0.6)
Hyperkeratosis	0	1 (0.4)	0
Ingrowing nail	0	1 (0.4)	0
Onychoclasis	1 (0.6)	1 (0.4)	0
Rash macular	1 (0.6)	1 (0.4)	0
Rash papular	1 (0.6)	1 (0.4)	0

Table 4622. Summary of Treatment-Emergent Adverse Events Within the System Organ Class of Skin and Subcutaneous Disorders by Preferred Term – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

	Vorasidenib 40 mg QD [a]		Placebo
System Organ Class (SOC) Preferred Term (PT)	AG881-C-004 without crossover [b] N=167 n (%)	Overall [c] N=244 n (%)	AG881-C-004 pre-crossover [d] N=163 n (%)
Skin irritation	1 (0.6)	1 (0.4)	0
Skin odour abnormal	0	1 (0.4)	0
Blister	0	0	1 (0.6)
Dermal cyst	0	0	1 (0.6)
Psoriasis	0	0	1 (0.6)
Rash pruritic	0	0	2 (1.2)
Skin hypopigmentation	0	0	1 (0.6)
Telangiectasia	0	0	1 (0.6)
Urticaria	0	0	1 (0.6)

Data Cutoff Dates: AG120-881-C-001 (30 May 2022); AG881-C-002 (17 October 2022); AG881-C-004 (06 September 2022).
Notes: The Safety Analysis Set for this table includes all subjects from AG881-C-004 who have received at least 1 dose of vorasidenib or placebo, and subjects from AG881-C-002 and AG120-881-C-001 who have received at least 1 dose of vorasidenib.
Treatment-emergent adverse events (TEAEs) presented in the summary tables include the AEs that begin or worsen from baseline during the on-treatment period.
A subject with multiple occurrences of an AE under one treatment is counted only once in the PT for that treatment.
A subject with multiple AEs within the same SOC is counted only once in the SOC.
System organ classes and preferred terms are coded from MedDRA v25.1.
Percentages are calculated based on N in each column.
a. 40 mg QD population includes subjects treated with vorasidenib 50 mg QD uncoated.
b. Includes data from subjects in Study AG881-C-004 who were randomized to and treated with vorasidenib 40 mg QD, those randomized to placebo but received at least one dose of vorasidenib without crossover, and pre-crossover data from subjects who received at least one dose of vorasidenib prior to cross over.
c. Includes data from subjects treated with vorasidenib 40 mg QD in Study AG881-C-004, post crossover data from subjects 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 with glioma treated with vorasidenib 50 mg QD in Study AG881-C-002
d. 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.

In the vorasidenib arm, 9 (5.4%) subjects experienced treatment-related TEAEs within the SOC; all were Grade 1. In the placebo arm, 10 subjects experienced treatment-related TEAEs within the SOC; most events were Grade 1 or Grade 2. One subject in the placebo arm experienced a Grade 3 TEAE of rash maculo-papular. None of the events were serious.

In the overall glioma cohort treated with vorasidenib (N=244), the proportion of subjects who experienced TEAEs within the SOC (45 [18.4%]) was similar to the vorasidenib arm (N=167; 30 [18.0]) and does not demonstrate a safety concern (Table 46).

Overall, incidence of PT within SOC skin and subcutaneous tissue disorders in the pool of patients with all solid tumours who received vorasidenib 40 mg (18.3%) or any dose (17.9%), was similar to the incidence observed in the pivotal study.

- Other Adverse Events of Clinical Interest

Based on observations in other IDH inhibitors as well as common comorbidities observed in patients with gliomas, comprehensive search strategies were performed for other AEs of clinical interest of Guillain-Barré Syndrome, gastrointestinal disorders, seizures, rash, fatigue, and leukopenia/neutropenia.

Guillain-Barré Syndrome (GBS)

In study AG881-C-004, 4 subjects in the vorasidenib 40 mg QD arm (N=167) experienced at least 1 TEAE within the GBS search strategy, which included the following: peripheral motor neuropathy (1 subject), peripheral sensory neuropathy (2 subjects), and nerve compression (1 subject). All events were Grade 1 or Grade 2, non-serious, and none were considered treatment-related. In the placebo arm (N=163), 2 subjects experienced TEAEs within the search strategy, which included herpes zoster and peripheral sensory neuropathy. No events of GBS were reported in subjects in either arm.

In the overall glioma cohort treated with vorasidenib 40 mg QD (N=244), 1 subject each experienced a TEAE of diabetic neuropathy and neuropathy peripheral. Both events were Grade 1, non-serious, and unrelated to study treatment. In subjects with glioma treated at any dose (N=295), TEAEs of herpes zoster were reported in 3 subjects.

No events of GBS was observed in the all solid tumour population who received vorasidenib any dose.

Seizures

Seizures are the most common presenting symptom in patients with Grade 2 or 3 gliomas. In addition, 2-HG, the oncometabolite produced by IDH-mutant tumours, is a glutamate analogue which can activate the glutamate receptor that is implicated in seizure development, providing a mechanistic rationale for seizure activity in patients with IDH-mutant gliomas (Chen et al. 2017). Although no mechanistic non-clinical studies have been performed, the Irwin test in rodents showed no functional observational effect of vorasidenib with respect to seizures.

A comprehensive search using the broad SMQ of convulsions based on MedDRA version 25.1 was conducted to identify potential clinically relevant TEAEs.

Seven (4.2%) subjects in the vorasidenib arm and 6 (3.7%) subjects in the placebo arm experienced Grade ≥3 TEAEs within the SMQ.

- The 7 subjects in the vorasidenib arm experienced a total of 9 Grade 3 events of seizure that were unrelated to study treatment; 4 were considered serious. Four of the 7 subjects had a prior medical history of seizure.
    - Five events resolved without dose modification, 2 events resolved with sequelae without dose modification, and 1 event resolved following drug interruption; 1 event was unresolved as of the data cut-off and did not have a dose modification.
- The 6 subjects in the placebo arm experienced a total of 6 Grade 3 events. Four Grade 3 TEAEs of seizure occurred and none required dose modification; 2 events were serious and resolved, and 2 events were unresolved as of the data cut-off.
    - One Grade 3 SAE of partial seizure resolved with sequelae and did not require dose modification, and 1 Grade 3 SAE of epilepsy resolved following drug interruption.

Two (1.2%) subjects in each arm experienced at least 1 treatment-related TEAE within the SMQ; these treatment-related TEAEs were seizure in 2 (1.2%) subjects in the vorasidenib arm and seizure in 1 (0.6%) subject and aura in 1 (0.6%) subject in the placebo arm.

No subjects experienced any TEAEs within the SMQ leading to treatment discontinuation or death. Two (1.2%) subjects in the vorasidenib arm and 1 (0.6%) subject in the placebo arm experienced TEAEs within the SMQ leading to treatment interruption; there were no TEAEs within the SMQ leading to dose reduction.

For TEAEs of any grade within the SMQ, the median time to first event following the first study treatment dose was longer in the vorasidenib arm (141.0 [range: 13 – 731] days) than in the placebo arm (109.0 [range: 3 – 380] days).

In the overall glioma cohort treated with vorasidenib 40 mg QD (N=244), the proportion of subjects who experienced TEAEs within the SMQ (41 [16.8%]) was similar to the vorasidenib arm (N=167; 28 [16.8%]) and does not demonstrate a safety concern.

In the glioma population who received vorasidenib any dose, the incidence of any grade TEAE with SMQ of seizure was 19.3%.

In the all solid tumour population who receive vorasidenib any dose, one additional PT of seizure was observed at a dose > 40 mg.

Rash

Skin disorders were an important potential risk of vorasidenib during the clinical development program. Rash, the most commonly reported PT within the SOC of skin and subcutaneous tissue disorders, is also considered an AE of clinical interest based on non-clinical findings and the potential of a class effect of IDH inhibitors.

A comprehensive search was conducted to identify potential clinically relevant TEAEs using a search strategy composed of PTs from HLT rashes, eruptions, and exanthems not elsewhere classified based on MedDRA version 25.1.

Table 4723. Summary of Treatment-Emergent Adverse Events From SMQ (Broad Search) of Rash by Preferred Term – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

	Vorasidenib 40 mg QD [a]		Placebo
System Organ Class (SOC) Preferred Term (PT)	AG881-C-004 without crossover [b] N=167 n (%)	Overall [c] N=244 n (%)	AG881-C-004 pre-crossover [d] N=163 n (%)
Subjects with any events	9 (5.4)	11 (4.5)	9 (5.5)
Rash	4 (2.4)	5 (2.0)	2 (1.2)
Rash maculo-papular	3 (1.8)	4 (1.6)	5 (3.1)
Rash macular	1 (0.6)	1 (0.4)	0
Rash papular	1 (0.6)	1 (0.4)	0
Rash pruritic	0	0	2 (1.2)

Data Cutoff Dates: AG120-881-C-001 (30 May 2022); AG881-C-002 (17 October 2022); AG881-C-004 (06 September 2022).
Notes: The Safety Analysis Set for this table includes all subjects from AG881-C-004 who have received at least 1 dose of vorasidenib or placebo, and subjects from AG881-C-002 and AG120-881-C-001 who have received at least 1 dose of vorasidenib.
Treatment-emergent adverse events (TEAEs) presented in the summary tables include the AEs that begin or worsen from baseline during the on-treatment period.
A subject with multiple occurrences of an AE under one treatment is counted only once in the PT for that treatment.
Preferred terms are coded from MedDRA v25.1.
Percentages are calculated based on N in each column.
a. 40 mg QD population includes subjects treated with vorasidenib 50 mg QD uncoated.
b. Includes data from subjects in Study AG881-C-004 who were randomized to and treated with vorasidenib 40 mg QD, those randomized to placebo but received at least one dose of vorasidenib without crossover, and pre-crossover data from subjects who received at least one dose of vorasidenib prior to cross over.
c. Includes data from subjects treated with vorasidenib 40 mg QD in Study AG881-C-004, post crossover data from subjects 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 with glioma treated with vorasidenib 50 mg QD in Study AG881-C-002.
d. 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.

In study AG881-C-004, all events were non-serious. One (0.6%) subject in the placebo arm experienced one Grade 3 TEAE of rash maculo-papular. Two (1.2%) subjects in each arm experienced at least 1 treatment-related TEAE within the search strategy; these treatment-related TEAEs were Grade 1 rash

macular and Grade 1 rash papular in the vorasidenib arm and Grade 3 rash maculo-papular and Grade 1 rash maculo-papular in the placebo arm.

No TEAEs within the search strategy led to study treatment discontinuation or death. Two (1.2%) subjects in the placebo arm experienced 2 TEAEs within the search strategy that led to 2 instances of treatment interruption; there were no TEAEs within the search strategy leading to dose reduction.

In the overall glioma cohort treated with vorasidenib 40 mg QD (N=244), additional TEAEs within the search strategy that were observed compared with the vorasidenib arm (N=167) were: 1 subject that experienced Grade 1 events of rash maculo-papular and 1 subject that experienced a Grade 1 event of rash (Table 47).

In the pool of glioma patients who received vorasidenib any dose, results were consistent with the pivotal study observation.

In the all solid tumor population who received vorasidenib any dose, results were consistent with the above observations. Incidence of any TEAE was 4.8% in patients who received vorasidenib 40 mg and 5.4% any dose. Few events were considered treatment-related (1.6% at 40 mg and 1.8% at any dose). No events were of grade ≥3, serious or led to dose modification.

Consistently with the pivotal study, the most represented PT in the all solid tumour population who received vorasidenib any dose were Rash (2.4%) and rash maculo-papular (2.4%)

Fatigue

Fatigue has been characterized as an AE of clinical interest following vorasidenib treatment due to the prevalence of reported events during the pivotal study AG881-C-004. To further characterize fatigue in subjects during vorasidenib treatment, a comprehensive search was conducted to identify potential clinically relevant TEAEs using a search strategy composed of the PTs asthenia, cancer fatigue, and fatigue based on MedDRA version 25.1.

In study AG881-C-004, 61 (36.5%) subjects in the vorasidenib arm (N=167) and 58 (35.6%) subjects in the placebo arm (N=163) experienced at least 1 TEAE within the search strategy for fatigue. The proportion of subjects who experienced TEAEs within the search strategy was similar in the vorasidenib arm compared with the placebo arm, respectively, and included fatigue (54 [32.3%] vs. 52 [31.9%] subjects) and asthenia (9 [5.4%] vs. 6 [3.7%] subjects); all were non-serious. One (0.6%) subject in the vorasidenib arm and 2 (1.2%) subjects in the placebo arm experienced one TEAE each of Grade 3 fatigue. A similar proportion of subjects in the vorasidenib arm and placebo arm experienced at least 1 treatment-related TEAE within the search strategy (39 [23.4%] and 33 [20.2%] subjects, respectively); treatment-related TEAEs within the search strategy occurred in subjects in the vorasidenib arm and placebo arm, respectively, were fatigue (35 [21.0%] and 29 [17.8%] subjects) and asthenia (6 [3.6%] and 4 [2.5%] subjects).

No TEAEs within the search strategy led to death; 1 (0.6%) subject in the placebo arm experienced a TEAE within the search strategy that led to study treatment discontinuation. One (0.6%) subject in each arm experienced TEAEs within the search strategy that led to dose reduction; 1 (0.6%) subject in the vorasidenib arm and 3 (1.8%) subjects in the placebo arm experienced TEAEs that led to treatment interruption.

For TEAEs of any grade within the search strategy, the median time to first event following the first study treatment dose was longer in the vorasidenib arm (28.0 [range: 1 – 529] days) compared with the placebo arm (21.5 [range: 1 – 416] days). Most subjects in the vorasidenib arm (43 of 61), placebo arm (40 of 58), and overall (53 of 81) had a time to first event ≤60 days following the first study treatment dose.

In the overall glioma cohort treated with vorasidenib 40 mg QD (N=244), the proportion of subjects who experienced TEAEs within the search strategy (81 [33.2%]) was similar to the vorasidenib arm (N=167; 61 [36.5%]) and does not demonstrate a safety concern.

Overall, observations were consistent in the patient with glioma who received vorasidenib any dose and all solid tumor who received vorasidenib 40 mg and any dose.

Leukopenia/Neutropenia

Leukopenia/neutropenia has been characterized as an AE of clinical interest following vorasidenib treatment due to the potential class effect associated with other IDH inhibitors. To further characterize leukopenia/neutropenia in subjects during vorasidenib treatment, a comprehensive search was conducted to identify potential clinically relevant TEAEs using a search strategy composed of internal important risk event (IRE) list leukopenia including neutropenia based on MedDRA version 25.1.

In study AG881-C-004, events within the search strategy were reported in 11 (6.6%) subjects in the vorasidenib arm (N=167) and 15 (9.2%) subjects in the placebo arm (N=163).

- TEAEs of Grade 3 neutrophil count decreased were reported in 2 (1.2%) subjects in the vorasidenib arm and TEAEs of Grade 3 neutropenia and Grade 3 lymphocyte count decreased were reported in 1 (0.6%) subject (each) in the placebo arm.
- A similar proportion of subjects in the vorasidenib arm and placebo arm (4 [2.4%] and 8 [4.9%] subjects, respectively) experienced at least 1 treatment-related TEAE within the search strategy:

No TEAEs within the search strategy led to study treatment discontinuation, death, or dose reduction in subjects in either arm. One (0.6%) subject in the placebo arm experienced a TEAE within the search strategy that led to treatment interruption; no subjects experienced a TEAE within the search strategy that led to treatment interruption in the vorasidenib arm.

For TEAEs of any grade within the search strategy, the median time to first event following the first study treatment dose was longer in the vorasidenib arm (85.0 [range: 1 – 418] days) compared with the placebo arm (43.0 [range: 1 – 394] days).

In the overall glioma cohort treated with vorasidenib 40 mg QD (N=244), the number of subjects who experienced TEAEs within the search strategy (17 [7.0%]) was similar to the vorasidenib arm (N=167; 11 [6.6%] subjects). No additional Grade ≥3 TEAEs within the search strategy were reported in the overall glioma cohort treated with vorasidenib 40 mg QD (N=244) compared with in the vorasidenib arm (N=167).

In the population of patients with glioma who received vorasidenib any dose, a higher incidence of any TEAE within the search were observed in patients who received a dose > 40 mg (24.1%) and 20.7% were considered treatment related. In this population who received > 40 mg dosage, one event led to study treatment interruption.

In the all solid tumour population who received vorasidenib 40 mg and any dose, data were similar to the pivotal study. To be noted, the incidence of any TEAE in the > 40 mg dosage group was lower than in the glioma population who received > 40 mg (13.6%).

2.6.8.5. Laboratory findings

- Laboratory parameters

Hematology

In study AG881-C-004, among subjects in the vorasidenib 40 mg QD arm (N=167), any grade new or worsening hematologic parameters that occurred in ≥5% and in at least 2% more subjects than the placebo arm (N=163) included: high hemoglobin (21 [12.6%] vs. 4 [2.5%], respectively); low lymphocytes (18 [10.8%] vs. 13 [8.0%] subjects, respectively); low neutrophils (24 [14.4%] vs. 20 [12.3%] subjects, respectively); and low platelets (20 [12.0%] vs. 7 [4.3%] subjects, respectively). Low neutrophils was the only Grade 3-4 parameter that occurred in ≥2% of subjects in the vorasidenib arm regardless of the incidence in the placebo arm (4 [2.4%] subjects).

In the overall glioma cohort treated with vorasidenib 40 mg QD (N=244), the proportion of subjects with any grade new or worsening hematologic parameters was consistent with the subjects in the vorasidenib 40 mg QD arm (N=167).

Data from overall glioma patients who received vorasidenib 40 mg or any dose were consistent with findings of the pivotal study.

Clinical chemistry

In study AG881-C-004, among the subjects in the vorasidenib 40 mg QD arm (N=167), any grade new or worsening chemistry parameter that occurred in ≥5% and in at least 2% more subjects than the placebo arm (N=163) included: high ALT (99 [59.3%] vs. 41 [25.2%] subjects, respectively); high AST (76 [45.5%] vs. 33 [20.2%] subjects, respectively); high ALP (16 [9.6%] vs. 11 [6.7%] subjects, respectively); high calcium (10 [6.0%] vs. 3 [1.8%] subjects, respectively); low calcium (16 [9.6%] vs. 11 [6.7%] subjects, respectively); high creatinine (19 [11.4%] vs. 11 [6.7%] subjects, respectively); high ГGT (63 [37.7%] vs. 17 [10.4%] subjects, respectively); and high potassium (39 [23.4%] vs. 33 [20.2%] subjects, respectively). Grade 3-4 parameters which occurred in ≥2% of subjects in the vorasidenib arm regardless of the incidence in the placebo arm included high ALT (16 [9.6%] subjects), high AST (8 [4.8%] subjects), high γGT (5 [3.0%] subjects), and low glucose (4 [2.4%] subjects).

In the overall glioma cohort treated with vorasidenib 40 mg QD (N=244), the only Grade 3-4 new or worsening chemistry parameter that occurred in ≥2% of subjects was high ALT (21 [8.6%] subjects), high AST (11 [4.5%] subjects), and high γGT (5 [2.1%] subjects).

- Electrocardiograms

TEAEs of electrocardiogram QT prolonged occurred across all safety analysis populations. Events were non-serious and predominantly low-grade, requiring no action taken with vorasidenib dose to management the event.

In study AG881-C-004, among the subjects in the vorasidenib 40 mg QD arm (N=167) treated with vorasidenib 40 mg QD, categorical increases from baseline for QTcF >60 ms were reported in 4 (2.4%) subjects compared with 2 (1.2%) subjects in the placebo arm (N=163) (Table 48). One (0.6%) subject in each arm had a QTcF value >480 ms. A brief summary of the vorasidenib-treated subject is provided below.

1 subject in the vorasidenib arm experienced a pre-dose QTcF of 500 ms on study Day 229 (Cycle 9, Day 1). There was no treatment or any action taken with vorasidenib due to the QTcF value. Although the Investigator determined the reading to be abnormal, it was not deemed clinically significant; thus, it was not reported as a TEAE.

No subject in the vorasidenib or placebo arm experienced a QTcF value >500 ms.

In the overall glioma cohort treated with vorasidenib 40 mg QD (N=244), categorical increases from baseline with a QTcF having a >60 ms increase was reported in 5 (2.1%) subjects. Two (0.8%) subjects experienced a QTcF of >480 ms; details for the vorasidenib-treated subject are provided directly above. One (0.4%) subject experienced a QTcF of >500 ms; this event was not reported as a TEAE (Table 48).

Table 4824. Summary of Notable ECG Values During On-Treatment Period – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

	Vorasidenib 40 mg QD [a]					Placebo
ECG Parameter	AG881-C-004 without crossover [b] N=167 n/N1 (%)	AG881-C-004 post-crossover [c] N=52 n/N1 (%)	AG881-C-002 N=11 n/N1 (%)	AG120-881-C-001 N=14 n/N1 (%)	Overall [d] N=244 n/N1 (%)	AG881-C-004 pre-crossover [e] N=163 n/N1 (%)
QT (ms)						
>30 increase from baseline	61/167 (36.5)	8/51 (15.7)	6/11 (54.5)	7/14 (50.0)	82/243 (33.7)	58/163 (35.6)
>60 increase from baseline	7/167 (4.2)	0/51	1/11 (9.1)	1/14 (7.1)	9/243 (3.7)	5/163 (3.1)
>450	35/167 (21.0)	12/51 (23.5)	2/11 (18.2)	2/14 (14.3)	51/243 (21.0)	30/163 (18.4)
>480	12/167 (7.2)	2/51 (3.9)	0/11	1/14 (7.1)	15/243 (6.2)	5/163 (3.1)
>500	4/167 (2.4)	0/51	0/11	1/14 (7.1)	5/243 (2.1)	2/163 (1.2)
QTcF (ms)						
>30 increase from baseline	36/167 (21.6)	10/51 (19.6)	1/11 (9.1)	6/14 (42.9)	53/243 (21.8)	32/163 (19.6)
>60 increase from baseline	4/167 (2.4)	0/51	0/11	1/14 (7.1)	5/243 (2.1)	2/163 (1.2)
>450	21/167 (12.6)	9/51 (17.6)	0/11	2/14 (14.3)	32/243 (13.2)	15/163 (9.2)
>480	1/167 (0.6)	0/51	0/11	1/14 (7.1)	2/243 (0.8)	1/163 (0.6)
>500	0/167	0/51	0/11	1/14 (7.1)	1/243 (0.4)	0/163
QTcB (ms)						
>30 increase from baseline	65/167 (38.9)	17/51 (33.3)	2/11 (18.2)	7/14 (50.0)	91/243 (37.4)	63/163 (38.7)
>60 increase from baseline	14/167 (8.4)	2/51 (3.9)	1/11 (9.1)	1/14 (7.1)	18/243 (7.4)	11/163 (6.7)
>450	51/167 (30.5)	12/51 (23.5)	5/11 (45.5)	6/14 (42.9)	74/243 (30.5)	51/163 (31.3)
>480	9/167 (5.4)	1/51 (2.0)	0/11	2/14 (14.3)	12/243 (4.9)	9/163 (5.5)
>500	6/167 (3.6)	1/51 (2.0)	0/11	1/14 (7.1)	8/243 (3.3)	6/163 (3.7)
RR (ms)						
>200	167/167 (100)	51/51 (100)	11/11 (100)	14/14 (100)	243/243 (100)	163/163 (100)

Data Cutoff Dates: AG120-881-C-001 (30 May 2022); AG881-C-002 (17 October 2022); AG881-C-004 (06 September 2022).
Notes: The Safety Analysis Set for this table includes all subjects from AG881-C-004 who have received at least 1 dose of vorasidenib or placebo, and subjects from AG881-C-002 and AG120-881-C-001 who have received at least 1 dose of vorasidenib.
The denominator used to calculate percentages is N1, the number of subjects in the safety analysis set within each treatment group with at least one post-Baseline assessment during the on-treatment period or (for changes from Baseline only) both Baseline and at least one post-Baseline assessment during the on-treatment period.
Baseline is defined as the last assessment collected on or prior to the date of start of study treatment.
Each ECG value is counted in all qualifying categories.
QTcB (ms) = QT (ms)/[RR (sec)$^{0.5}$].
QTcF (ms) = QT (ms)/[RR (sec)$^{(1/3)}$].
a. 40 mg QD population includes subjects treated with vorasidenib 50 mg QD uncoated.
b. Includes data from subjects in Study AG881-C-004 who were randomized to and treated with vorasidenib 40 mg QD, those randomized to placebo but received at least one dose of vorasidenib without crossover, and pre-crossover data from subjects who received at least one dose of vorasidenib prior to cross over.
c. Includes data from subjects who were randomized to placebo who subsequently crossed over to receive vorasidenib 40 mg QD in Study AG881-C-004. Only data after crossover is included in this column.
d. Includes data from subjects treated with vorasidenib 40 mg QD in Study AG881-C-004, post crossover data from subjects 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 with glioma treated with vorasidenib 50 mg QD in Study AG881-C-002.
e. 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.

In the broader population with all solid tumours including glioma treated with vorasidenib 40 mg QD (N=251), the proportion of subjects (7 [2.8%]) who experienced TEAEs within the broad SMQ of torsade de pointe/QT prolongation was consistent with the overall glioma cohort treated with vorasidenib 40 mg QD (N=244; 7 [2.8%])

In the overall population with all solid tumours who received vorasidenib any dose (N=336), 11 (3.3%) subjects experienced at least 1 TEAE within the SMQ and 2 (0.6%) subjects experienced treatment-related TEAEs. The TEAEs within the SMQ that occurred were QTc prolongations (6 [1.8%] subjects), syncope (3 [0.9%] subjects), and loss of consciousness (2 [0.6%] subjects). Only 1 subject experienced a Grade ≥3 TEAE with glioma treated with vorasidenib 100 mg QD and was a Grade 3 loss of consciousness that was deemed unrelated to study treatment. The following subjects overall (N=336) experienced TEAEs of electrocardiogram QT prolonged in addition to the 3 (1.2%) subjects with glioma treated with vorasidenib 40 mg QD (N=251): 1 subject with glioma treated with vorasidenib 10 mg QD (Grade 1 treatment-related and Grade 2 unrelated to study treatment); 1 subject with glioma treated with vorasidenib 100 mg QD (Grade 1 event unrelated to study treatment); and 1 subject with non-glioma solid tumours treated with vorasidenib 200 mg BID.

- Overdose

A TEAE was considered possibly related to overdose if it occurred within 7 days following the overdose incident. A total of 5 TEAEs reported within 7 days following overdose occurred in subjects from the glioma population treated with vorasidenib 40 mg QD, and none were related to the study treatment.

One TEAE was reported within the 7 days following the overdose incident in study AG881-C-002. On Study Day 564, the subject took a dose of vorasidenib 400 mg over the course of one day. The subject experienced a TEAE of hyperglycemia on Study Day 568, which resolved on Study Day 590.

Three TEAEs were reported within 7 days following an overdose incident in study AG881-C-004. On Study Day 13, the subject took a dose of 80 mg of vorasidenib over the course of one day. The subject experienced 1 TEAE each of acute myocardial infarction on Study Day 15 (resolved on Study Day 17), essential hypertension on Study Day 16 (ongoing), and non-cardiac chest pain on Study Day 20 (resolved on Study Day 20). This subject had preexisting cardiac medical history including atypical hypertrophic cardiomyopathy, essential hypertension, hypercholesterolemia, and cardiac catheterization.

One TEAE reported within the 7 days after the overdose incidence in a subject receiving placebo.

All TEAEs reported within 7 days following the overdose incident did not show causality to the overdose and all were assessed as not related to vorasidenib.

2.6.8.6. Adverse drug reaction

Study AG881-C-004 was selected to serve as the basis for the selection of ADRs in the current proposed prescribing information given it was the only double-blind randomized placebo-controlled study. No additional ADRs were identified from the review of the other supportive studies.

The methodology for selection of ADRs to vorasidenib was conducted in accordance with 21 CFR 201.57(c)(7) and the US Food and Drug Administration (FDA) Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products (FDA, 2006), European Commission Guideline on Summary of Product Characteristics (European Commission, 2009), and European Medicines Agency (EMA) Guideline on the Evaluation of Anticancer Medicinal Products in Man (EMA, 2017).

ADRs were limited to those PTs for which there was some basis for believing that there was a causal relationship between the occurrence of a TEAE and the use of vorasidenib. Decisions on whether there is a reason to believe that there is a causal relationship are a matter of clinical judgment and are based on factors such as but not limited to the frequency, severity, and seriousness of reporting; whether the TEAE incidence for the drug exceeds the placebo incidence; the extent to which the TEAE is consistent with the pharmacology of the drug (mechanism of action) or similar drugs (eg, class effect); the Investigator's assessment of causality; the timing of the event relative to the time of drug exposure; whether the TEAE is known to be caused by concomitant medications, medical history, or disease under study; and/or assessment of other confounding factors.

All TEAEs, including laboratory TEAEs from Study AG881-C-004 regardless of frequency or Investigator-assigned causality, were reviewed in the process to determine ADRs. Initially, TEAEs of any grade reported at a frequency of ≥5% in the vorasidenib arm and with a ≥2% higher frequency compared to the placebo arm were identified and reviewed as possible ADRs. For the TEAEs that met these criteria, a qualitative review was conducted to determine a plausible causal relationship. In addition, severe TEAEs (ie, Grade ≥3 TEAEs) and SAEs that occurred in ≥2% of subjects in the vorasidenib arm, regardless of the incidence in the placebo arm were reviewed for evidence of a plausible causal relationship. Further review was conducted to identify rare but potentially serious events often causally associated with drugs across multiple pharmacological/therapeutic classes included within EMA's Designated Medical Event (DME) list (EMA, 2020) reported in ≥1 subject of any grade in the vorasidenib arm, regardless of the incidence in placebo. Additional TEAEs of relevance that did not meet the threshold incidence described above were selected for further review if they were previously considered to be a potential risk of vorasidenib or if, based on clinical judgment, they were deemed to be of clinical significance, irrespective of frequency.

Lastly, selection of new or worsening laboratory abnormalities followed a similar methodology as the selection of ADRs including any grade laboratory abnormality that occurred in ≥5% in the vorasidenib arm and with ≥2% difference as compared to placebo and Grade ≥3 laboratory abnormalities that occurred in ≥2% in the vorasidenib arm, regardless of the incidence in placebo. Further analysis of new or worsening laboratory abnormalities then focused on incidence of reported TEAEs corresponding to the identified laboratory abnormality.

The frequency of an ADR was determined by pooling PTs that represent that ADR. The incidence is calculated as subjects with any grade TEAE (or on-treatment newly occurring or worsening lab abnormality) in the Vorasidenib arm divided by N = 167 for the AG881-C-004 Vorasidenib arm. ADRs and laboratory abnormalities associated with vorasidenib identified from this study are reported in the table below including respective frequency data:

Table 49. Adverse drug reactions reported in patients treated with vorasidenib in the INDIGO trial (Study AG881-C-004) (N=167)

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Very common	Platelet count decreased (12%)
Metabolism and nutrition disorders	Common	Hyperglycaemia (9.6%)
		Decreased appetite (9.0%)
		Hypophosphataemia (8.4%)
Nervous system disorders	Very common	Dizziness (15.6%)
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea (3.6%)
Gastrointestinal disorders	Very common	Diarrhoea (24.6%)
		Abdominal pain (13.2%)
	Common	Gastro-oesophageal reflux disease (6.0%)

Hepatobiliary disorders	Very common	Alanine aminotransferase increased (59.3%)
		Aspartate aminotransferase increased (45.5%)
		Gamma-glutamyl transferase increased (37.7%)
	Common	Alkaline phosphatase increased (9.6%)
General disorders and administration site conditions	Very common	Fatigue (36.5%)

[a] Laboratory abnormality is defined as new or worsened by at least one grade from baseline, or baseline is unknown.

2.6.8.7. Safety in special populations

- Intrinsic Factors

Adverse Events by Sex

Glioma Population Treated With Vorasidenib 40 mg QD by Sex

Table 5025. Summary of Most Common (≥10%) Treatment-Emergent Adverse Events Overall (N=244) by Preferred Term and Sex – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

	Vorasidenib 40 mg QD [a]	
	Overall [b] N=244	
Preferred Term (PT)	Male N1=141 n (%)	Female N1=103 n (%)
Subjects with any events	131 (92.9)	92 (89.3)
Alanine aminotransferase increased	48 (34.0)	43 (41.7)
COVID-19	41 (29.1)	27 (26.2)
Fatigue	41 (29.1)	33 (32.0)
Headache	34 (24.1)	30 (29.1)
Diarrhoea	30 (21.3)	21 (20.4)
Aspartate aminotransferase increased	28 (19.9)	37 (35.9)
Nausea	24 (17.0)	25 (24.3)
Seizure	21 (14.9)	13 (12.6)
Gamma-glutamyltransferase increased	17 (12.1)	16 (15.5)
Dizziness	15 (10.6)	18 (17.5)
Insomnia	15 (10.6)	7 (6.8)
Constipation	14 (9.9)	13 (12.6)
Vomiting	11 (7.8)	11 (10.7)

Data Cutoff Dates: AG120-881-C-001 (30 May 2022); AG881-C-002 (17 October 2022); AG881-C-004 (06 September 2022).
Notes: The Safety Analysis Set for this table includes all subjects from AG881-C-004 who have received at least 1 dose of vorasidenib or placebo, and subjects from AG881-C-002 and AG120-881-C-001 who have received at least 1 dose of vorasidenib.
Treatment-emergent adverse events (TEAEs) presented in the summary tables include the AEs that begin or worsen from baseline during the on-treatment period.
A subject with multiple occurrences of an AE under one treatment is counted only once in the PT for that treatment.
System organ classes and preferred terms are coded from MedDRA v25.1.
The denominator used to calculate percentages is N1, the number of subjects in the safety analysis set in each treatment group and in each level of the subgroup variable.
a. The vorasidenib 40 mg QD population includes subjects treated with vorasidenib 50 mg QD uncoated.
b. Includes data from subjects treated with vorasidenib 40 mg QD in Study AG881-C-004, post crossover data from subjects 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 with glioma treated with vorasidenib 50 mg QD in Study AG881-C-002.

Adverse Events by Race

In Western Europe, collection of race is not permitted which limits comparisons across diverse racial subgroups. Some notable differences were observed for certain PTs; however, given the limited data available, no meaningful conclusions could be drawn based on comparisons across diverse racial subgroups. Therefore, the data are presented for the number of subjects within a subgroup for each safety analysis population.

Table 5126. Summary of Most Common (≥10 Subjects) Treatment-Emergent Adverse Events Overall (N=244) by Preferred Term and Race – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

	Vorasidenib 40 mg QD [a]				
	Overall [b] N=244				
Preferred Term	White N1=190 n (%)	Black or African American N1=2 n (%)	Asian N1=7 n (%)	Other N1=4 n (%)	Unknown N1=41 n (%)
Subjects with any events	173 (91.1)	2 (100)	7 (100)	4 (100)	37 (90.2)
Alanine aminotransferase increased	69 (36.3)	1 (50.0)	5 (71.4)	0	16 (39.0)
Fatigue	57 (30.0)	1 (50.0)	3 (42.9)	1 (25.0)	12 (29.3)
Headache	52 (27.4)	2 (100)	0	0	10 (24.4)
COVID-19	50 (26.3)	1 (50.0)	2 (28.6)	0	15 (36.6)
Aspartate aminotransferase increased	49 (25.8)	0	5 (71.4)	0	11 (26.8)
Nausea	39 (20.5)	1 (50.0)	0	1 (25.0)	8 (19.5)
Diarrhoea	36 (18.9)	1 (50.0)	1 (14.3)	1 (25.0)	12 (29.3)
Seizure	31 (16.3)	0	1 (14.3)	0	2 (4.9)
Dizziness	24 (12.6)	0	1 (14.3)	2 (50.0)	6 (14.6)
Gamma-glutamyltransferase increased	23 (12.1)	1 (50.0)	1 (14.3)	0	8 (19.5)
Vomiting	22 (11.6)	0	0	0	0
Constipation	19 (10.0)	0	1 (14.3)	1 (25.0)	6 (14.6)
Hyperglycaemia	18 (9.5)	0	0	1 (25.0)	3 (7.3)
Insomnia	18 (9.5)	0	1 (14.3)	0	3 (7.3)
Hypophosphataemia	15 (7.9)	0	2 (28.6)	0	0
Abdominal pain	15 (7.9)	1 (50.0)	0	1 (25.0)	2 (4.9)
Arthralgia	15 (7.9)	0	1 (14.3)	0	2 (4.9)
Decreased appetite	15 (7.9)	0	0	1 (25.0)	4 (9.8)
Back pain	11 (5.8)	2 (100)	1 (14.3)	0	1 (2.4)
Myalgia	11 (5.8)	1 (50.0)	0	0	3 (7.3)
Anxiety	11 (5.8)	0	0	0	2 (4.9)
Paraesthesia	10 (5.3)	0	0	1 (25.0)	1 (2.4)

Data cutoff dates: AG120-881-C-001 (30 May 2022); AG881-C-002 (17 October 2022); AG881-C-004 (06 September 2022).
Notes: The Safety Analysis Set for this table includes all subjects from AG881-C-004 who have received at least 1 dose of vorasidenib or placebo, and subjects from AG881-C-002 and AG120-881-C-001 who have received at least 1 dose of vorasidenib.
Treatment-emergent adverse events (TEAEs) presented in the summary tables include the AEs that begin or worsen from baseline during the on-treatment period.

A subject with multiple occurrences of an AE under one treatment is counted only once in the PT for that treatment.
System organ classes and preferred terms are coded from MedDRA v25.1.
The denominator used to calculate percentages is N1, the number of subjects in the safety analysis set in each treatment group and in each level of the subgroup variable.
a. The vorasidenib 40 mg QD population includes subjects treated with vorasidenib 50 mg QD uncoated.
b. Includes data from subjects treated with vorasidenib 40 mg QD in Study AG881-C-004, post crossover data from subjects 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 with glioma treated with vorasidenib 50 mg QD in Study AG881-C-002.

Adverse Events by Ethnicity

In Western Europe, the collection of ethnicities is not permitted, which limits comparisons across diverse ethnicity subgroups. Some notable differences were observed for certain PTs; however, given the limited data available, no meaningful conclusions could be drawn based on comparisons across diverse ethnic subgroups. Therefore, the data are presented by percentage and number of subjects within each subgroup for each safety analysis population.

Table 2752. Summary of Most Common (≥10%) Treatment-Emergent Adverse Events Overall (N=244) by Preferred Term and Ethnicity – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

	Vorasidenib 40 mg QD [a]		
	Overall [b] N=244		
Preferred Term	Not Hispanic or Latino N1=186 n (%)	Hispanic or Latino N1=15 n (%)	Unknown N1=43 n (%)
Subjects with any events	170 (91.4)	15 (100)	38 (88.4)
Alanine aminotransferase increased	70 (37.6)	9 (60.0)	12 (27.9)
Fatigue	58 (31.2)	2 (13.3)	14 (32.6)
Headache	53 (28.5)	5 (33.3)	6 (14.0)
Aspartate aminotransferase increased	51 (27.4)	5 (33.3)	9 (20.9)
COVID-19	49 (26.3)	4 (26.7)	15 (34.9)
Nausea	38 (20.4)	4 (26.7)	7 (16.3)
Diarrhoea	35 (18.8)	6 (40.0)	10 (23.3)
Seizure	28 (15.1)	1 (6.7)	5 (11.6)
Gamma-glutamyltransferase increased	27 (14.5)	2 (13.3)	4 (9.3)
Dizziness	25 (13.4)	3 (20.0)	5 (11.6)
Vomiting	21 (11.3)	1 (6.7)	0
Constipation	20 (10.8)	1 (6.7)	6 (14.0)
Hyperglycaemia	20 (10.8)	1 (6.7)	1 (2.3)
Insomnia	19 (10.2)	1 (6.7)	2 (4.7)
Arthralgia	14 (7.5)	2 (13.3)	2 (4.7)
Back pain	12 (6.5)	2 (13.3)	1 (2.3)
Anxiety	11 (5.9)	2 (13.3)	0
Depression	5 (2.7)	2 (13.3)	1 (2.3)
Blood lactate dehydrogenase increased	3 (1.6)	2 (13.3)	0

Data Cutoff Dates: AG120-881-C-001 (30 May 2022); AG881-C-002 (17 October 2022); AG881-C-004 (06 September 2022).
Notes: The Safety Analysis Set for this table includes all subjects from AG881-C-004 who have received at least 1 dose of vorasidenib or placebo, and subjects from AG881-C-002 and AG120-881-C-001 who have received at least 1 dose of vorasidenib.
Treatment-emergent adverse events (TEAEs) presented in the summary tables include the AEs that begin or worsen from baseline during the on-treatment period.
A subject with multiple occurrences of an AE under one treatment is counted only once in the PT for that treatment.

System organ classes and preferred terms are coded from MedDRA v25.1.
The denominator used to calculate percentages is N1, the number of subjects in the safety analysis set in each treatment group and in each level of the subgroup variable.
a. The vorasidenib 40 mg QD population includes subjects treated with vorasidenib 50 mg QD uncoated.
b. Includes data from subjects treated with vorasidenib 40 mg QD in Study AG881-C-004, post crossover data from subjects 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 with glioma treated with vorasidenib 50 mg QD in Study AG881-C-002.

Adverse Events by Age

Table 5328. Summary of Most Common (≥2 Subjects) Treatment-Emergent Adverse Events Overall (N=244) by Preferred Term and Age – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

	Vorasidenib 40 mg QD [a]		
	Overall [b] N=244		
Preferred Term	18-<40 years N1=119 n (%)	40-<65 years N1=123 n (%)	≥65 years N1=2 n (%)
Subjects with any events	106 (89.1)	115 (93.5)	2 (100)
Alanine aminotransferase increased	41 (34.5)	49 (39.8)	1 (50.0)
Headache	32 (26.9)	32 (26.0)	0
Fatigue	31 (26.1)	42 (34.1)	1 (50.0)
Aspartate aminotransferase increased	29 (24.4)	36 (29.3)	0
Nausea	27 (22.7)	22 (17.9)	0
COVID-19	27 (22.7)	40 (32.5)	1 (50.0)
Diarrhoea	23 (19.3)	28 (22.8)	0
Dizziness	18 (15.1)	15 (12.2)	0
Constipation	16 (13.4)	11 (8.9)	0
Seizure	14 (11.8)	20 (16.3)	0
Gamma-glutamyltransferase increased	12 (10.1)	21 (17.1)	0
Hyperglycaemia	7 (5.9)	15 (12.2)	0

Data Cutoff Dates: AG120-881-C-001 (30 May 2022); AG881-C-002 (17 October 2022); AG881-C-004 (06 September 2022).
Notes: The Safety Analysis Set for this table includes all subjects from AG881-C-004 who have received at least 1 dose of vorasidenib or placebo, and subjects from AG881-C-002 and AG120-881-C-001 who have received at least 1 dose of vorasidenib.
Treatment-emergent adverse events (TEAEs) presented in the summary tables include the AEs that begin or worsen from baseline during the on-treatment period.
A subject with multiple occurrences of an AE under one treatment is counted only once in the PT for that treatment.
System organ classes and preferred terms are coded from MedDRA v25.1.
The denominator used to calculate percentages is N1, the number of subjects in the safety analysis set in each treatment group and in each level of the subgroup variable.
a. The vorasidenib 40 mg QD population includes subjects treated with vorasidenib 50 mg QD uncoated.
b. Includes data from subjects treated with vorasidenib 40 mg QD in Study AG881-C-004, post crossover data from subjects 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 with glioma treated with vorasidenib 50 mg QD in Study AG881-C-002.

Adverse Events by Baseline Renal Function

- Creatinine Clearance

Given the limited data available, no meaningful conclusions could be drawn based on comparisons across renal function (creatinine clearance) subgroups; however, some notable differences were observed for certain PTs. Therefore, the data are presented by percentage and number of subjects within each subgroup for each safety analysis population.

Table 5429. Summary of Most Common (≥10 Subjects) Treatment-Emergent Adverse Events Overall (N=244) by Preferred Term and Baseline Renal Function Based on Creatinine Clearance – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

	Vorasidenib 40 mg QD [a]		
	Overall [b] N=244		
	Normal N1=225	Mild N1=18	Moderate N1=1
Preferred Term	n (%)	n (%)	n (%)
Subjects with any events	205 (91.1)	17 (94.4)	1 (100) [c]
Alanine aminotransferase increased	83 (36.9)	8 (44.4)	0
Fatigue	67 (29.8)	7 (38.9)	0
COVID-19	62 (27.6)	6 (33.3)	0
Headache	57 (25.3)	7 (38.9)	0
Aspartate aminotransferase increased	57 (25.3)	8 (44.4)	0
Diarrhoea	47 (20.9)	4 (22.2)	0
Nausea	45 (20.0)	4 (22.2)	0
Dizziness	30 (13.3)	3 (16.7)	0
Gamma-glutamyltransferase increased	30 (13.3)	3 (16.7)	0
Seizure	28 (12.4)	6 (33.3)	0
Constipation	25 (11.1)	2 (11.1)	0
Vomiting	19 (8.4)	3 (16.7)	0
Hyperglycaemia	19 (8.4)	3 (16.7)	0
Decreased appetite	18 (8.0)	2 (11.1)	0
Arthralgia	16 (7.1)	2 (11.1)	0
Back pain	11 (4.9)	4 (22.2)	0
Hypertension	11 (4.9)	3 (16.7)	0
Cough	10 (4.4)	4 (22.2)	0

Data Cutoff Dates: AG120-881-C-001 (30 May 2022); AG881-C-002 (17 October 2022); AG881-C-004 (06 September 2022).
Notes: The Safety Analysis Set for this table includes all subjects from AG881-C-004 who have received at least 1 dose of vorasidenib or placebo, and subjects from AG881-C-002 and AG120-881-C-001 who have received at least 1 dose of vorasidenib.
Treatment-emergent adverse events (TEAEs) presented in the summary tables include the AEs that begin or worsen from baseline during the on-treatment period.
A subject with multiple occurrences of an AE under one treatment is counted only once in the PT for that treatment.
System organ classes and preferred terms are coded from MedDRA v25.1.
The denominator used to calculate percentages is N1, the number of subjects in the safety analysis set in each treatment group and in each level of the subgroup variable.
a. The vorasidenib 40 mg QD population includes subjects treated with vorasidenib 50 mg QD uncoated.
b. Includes data from subjects treated with vorasidenib 40 mg QD in Study AG881-C-004, post crossover data from subjects 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 with glioma treated with vorasidenib 50 mg QD in Study AG881-C-002.
c. The single subject with moderate renal dysfunction experienced TEAEs of neutropenia, dry mouth, and parotitis.

- Estimated Glomerular Filtration Rate

Table 5530. Summary of Most Common (≥10 Subjects) Treatment-Emergent Adverse Events Overall (N=244) by Preferred Term and Baseline Renal Function Based on eGFR – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

	Vorasidenib 40 mg QD [a]		
	Overall [b] N=244		
Preferred Term	Normal N1=172 n (%)	Mild N1=67 n (%)	Moderate N1=5 n (%)
Subjects with any events	156 (90.7)	62 (92.5%)	5 (100)
Alanine aminotransferase increased	58 (33.7)	29 (43.3)	4 (80.0)
Fatigue	51 (29.7)	20 (29.9)	3 (60.0)
COVID-19	45 (26.2)	22 (32.8)	1 (20.0)
Headache	41 (23.8)	20 (29.9)	3 (60.0)
Aspartate aminotransferase increased	40 (23.3)	22 (32.8)	3 (60.0)
Nausea	38 (22.1)	9 (13.4)	2 (40.0)
Diarrhoea	36 (20.9)	14 (20.9)	1 (20.0)
Gamma-glutamyltransferase increased	25 (14.5)	7 (10.4)	1 (20.0)
Seizure	22 (12.8)	11 (16.4)	1 (20.0)
Dizziness	21 (12.2)	12 (17.9)	0
Constipation	17 (9.9)	10 (14.9)	0
Vomiting	16 (9.3)	4 (6.0)	2 (40.0)
Insomnia	14 (8.1)	7 (10.4)	1 (20.0)
Decreased appetite	13 (7.6)	6 (9.0)	1 (20.0)
Hypophosphataemia	13 (7.6)	3 (4.5)	1 (20.0)
Hyperglycaemia	11 (6.4)	11 (16.4)	0

Data Cutoff Dates: AG120-881-C-001 (30 May 2022); AG881-C-002 (17 October 2022); AG881-C-004 (06 September 2022).
Notes: The Safety Analysis Set for this table includes all subjects from AG881-C-004 who have received at least 1 dose of vorasidenib or placebo, and subjects from AG881-C-002 and AG120-881-C-001 who have received at least 1 dose of vorasidenib.
Treatment-emergent adverse events (TEAEs) presented in the summary tables include the AEs that begin or worsen from baseline during the on-treatment period.
A subject with multiple occurrences of an AE under one treatment is counted only once in the PT for that treatment.
System organ classes and preferred terms are coded from MedDRA v25.1.
The denominator used to calculate percentages is N1, the number of subjects in the safety analysis set in each treatment group and in each level of the subgroup variable.
a. The vorasidenib 40 mg QD population includes subjects treated with vorasidenib 50 mg QD uncoated.
b. Includes data from subjects treated with vorasidenib 40 mg QD in Study AG881-C-004, post crossover data from subjects 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 with glioma treated with vorasidenib 50 mg QD in Study AG881-C-002.

Adverse Events by Baseline Hepatic Function

Table 5631. Summary of Most Common (≥10%) Treatment-Emergent Adverse Events Overall (N=244) by Preferred Term and Baseline Hepatic Function – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

	Vorasidenib 40 mg QD [a]	
	Overall [b] N=244	
Preferred Term	Normal N1=217 n (%)	Mild N1=27 n (%)
Subjects with any events	197 (90.8)	26 (96.3)
Alanine aminotransferase increased	82 (37.8)	9 (33.3)
Fatigue	67 (30.9)	7 (25.9)
COVID-19	61 (28.1)	7 (25.9)
Headache	57 (26.3)	7 (25.9)
Aspartate aminotransferase increased	56 (25.8)	9 (33.3)
Nausea	45 (20.7)	4 (14.8)
Diarrhoea	43 (19.8)	8 (29.6)
Seizure	33 (15.2)	1 (3.7)
Gamma-glutamyltransferase increased	30 (13.8)	3 (11.1)
Dizziness	28 (12.9)	5 (18.5)
Constipation	24 (11.1)	3 (11.1)
Anxiety	10 (4.6)	3 (11.1)
Hyperglycaemia	19 (8.8)	3 (11.1)
Abdominal Pain	16 (7.4)	3 (11.1)
Decreased appetite	15 (6.9)	5 (18.5)
Arthralgia	15 (6.9)	3 (11.1)
Tinnitus	6 (2.8)	3 (11.1)
Nasal congestion	5 (2.3)	3 (11.1)
Hepatic steatosis	0	3 (11.1)

Data Cutoff Dates: AG120-881-C-001 (30 May 2022); AG881-C-002 (17 October 2022); AG881-C-004 (06 September 2022).
Notes: The Safety Analysis Set for this table includes all subjects from AG881-C-004 who have received at least 1 dose of vorasidenib or placebo, and subjects from AG881-C-002 and AG120-881-C-001 who have received at least 1 dose of vorasidenib.
Treatment-emergent adverse events (TEAEs) presented in the summary tables include the AEs that begin or worsen from baseline during the on-treatment period.
A subject with multiple occurrences of an AE under one treatment is counted only once in the PT for that treatment.
System organ classes and preferred terms are coded from MedDRA v25.1.
The denominator used to calculate percentages is N1, the number of subjects in the safety analysis set in each treatment group and in each level of the subgroup variable.
a. The vorasidenib 40 mg QD population includes subjects treated with vorasidenib 50 mg QD uncoated.
b. Includes data from subjects treated with vorasidenib 40 mg QD in Study AG881-C-004, post crossover data from subjects 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 with glioma treated with vorasidenib 50 mg QD in Study AG881-C-002.

- Mild to Moderate Hepatic Impairment Population

Adverse Events by Histological Subtype

In study AG881-C-004, among subjects in the vorasidenib arm (N=167) and the placebo arm (N=163), the proportion of subjects with TEAEs was similar between arms for subjects with astrocytomas (95.0% [76 of 80 subjects] vs. 93.7% [74 of 79 subjects], respectively) and subjects with oligodendrogliomas

(94.3% [82 of 87 subjects] vs. 92.9% [78 of 84 subjects], respectively). No subjects had other tumour types in either arm.

In the overall glioma cohort treated with vorasidenib 40 mg QD (N=244), the proportion of subjects with TEAEs was similar between subjects with astrocytoma (89.3% [109 of 122]) and those with oligodendroglioma (93.3% [112 of 120]). Only 2 subjects had other glioma tumours; both (100%) experienced at least 1 TEAE. No meaningful conclusions can be drawn for comparison to subjects with other glioma tumours due to the limited number of subjects in this subgroup. No TEAEs occurred at a ≥10% higher incidence in subjects with astrocytoma compared with subjects with oligodendroglioma. A higher incidence (≥10%) of subjects with oligodendroglioma compared with astrocytoma experienced TEAEs of COVID-19 (33.3% [40 of 120] vs. 23.0% [28 of 122] subjects) and diarrhoea (26.7% [32 of 120] vs. 14.8% [18 of 122] subjects).

- Extrinsic Factors

Adverse Events by Geographical Region

Clinical studies were conducted globally for study AG881-C-004 and study AG881-C-001.

Table 5732. Summary of Most Common (≥10%) Treatment-Emergent Adverse Events Overall (N=244) by Preferred Term and Geographic Region – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

	Vorasidenib 40 mg QD [a]		
	Overall [b] N=244		
Preferred Term	**North America N1=147 n (%)**	**Western Europe N1=63 n (%)**	**Rest of the World N1=34 n (%)**
Subjects with any event	135 (91.8)	57 (90.5)	31 (91.2)
Alanine aminotransferase increased	62 (42.2)	21 (33.3)	8 (23.5)
Fatigue	48 (32.7)	16 (25.4)	10 (29.4)
Aspartate aminotransferase increased	45 (30.6)	15 (23.8)	5 (14.7)
Headache	42 (28.6)	11 (17.5)	11 (32.4)
Nausea	38 (25.9)	7 (11.1)	4 (11.8)
COVID-19	38 (25.9)	21 (33.3)	9 (26.5)
Diarrhoea	33 (22.4)	13 (20.6)	5 (14.7)
Dizziness	22 (15.0)	5 (7.9)	6 (17.6)
Gamma-glutamyltransferase increased	21 (14.3)	6 (9.5)	6 (17.6)
Hyperglycaemia	20 (13.6)	2 (3.2)	0
Seizure	18 (12.2)	9 (14.3)	7 (20.6)
Vomiting	18 (12.2)	1 (1.6)	3 (8.8)
Constipation	15 (10.2)	7 (11.1)	5 (14.7)
Insomnia	15 (10.2)	4 (6.3)	3 (8.8)
Oropharyngeal pain	6 (4.1)	0	4 (11.8)

Data Cutoff Dates: AG120-881-C-001 (30 May 2022); AG881-C-002 (17 October 2022); AG881-C-004 (06 September 2022).
Notes: The Safety Analysis Set for this table includes all subjects from AG881-C-004 who have received at least 1 dose of vorasidenib or placebo, and subjects from AG881-C-002 and AG120-881-C-001 who have received at least 1 dose of vorasidenib.
Treatment-emergent adverse events (TEAEs) presented in the summary tables include the AEs that begin or worsen from baseline during the on-treatment period.
A subject with multiple occurrences of an AE under one treatment is counted only once in the PT for that treatment.
System organ classes and preferred terms are coded from MedDRA v25.1.

The denominator used to calculate percentages is N1, the number of subjects in the safety analysis set in each treatment group and in each level of the subgroup variable.
a. The vorasidenib 40 mg QD population includes subjects treated with vorasidenib 50 mg QD uncoated.
b. Includes data from subjects treated with vorasidenib 40 mg QD in Study AG881-C-004, post crossover data from subjects 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 with glioma treated with vorasidenib 50 mg QD in Study AG881-C-002.

2.6.8.8. Immunological events

N/A

2.6.8.9. Safety related to drug-drug interactions and other interactions

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 metabolised or transported by enzymes or transporters whose expression is mediated by PXR.

In an in vivo drug-drug interaction study, co-administration of 20 mg vorasidenib with a strong CYP1A2 inhibitor (500 mg ciprofloxacin twice daily for 14 days) increased vorasidenib maximum plasma concentration (Cmax) by 29% and area under the plasma time-concentration curve (AUC) by 153%.

Co-administration of vorasidenib with moderate CYP1A2 inducers (phenytoin and rifampicin) reduced steady-state vorasidenib Cmax and AUC by around 30% and 40% respectively.

Co-administration of vorasidenib with CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4 substrates has been shown to decrease, at different extents the plasma concentrations of these medicinal products.

In vitro, vorasidenib is an inhibitor of breast cancer resistance protein (BCRP). Further information on drug interaction for Voranigo are reported in section 2.6.2.1. Pharmacokinetics.

2.6.8.10. Discontinuation due to adverse events

- Adverse Events Leading to Study Treatment Discontinuation

Table 5833. Summary of Treatment-Emergent Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

System Organ Class (SOC) Preferred Term (PT)	Vorasidenib 40 mg QD [a]					Placebo
	AG881-C-004 without crossover [b] N=167 n (%)	AG881-C-004 post-crossover [c] N=52 n (%)	AG881-C-002 N=11 n (%)	AG120-881-C-001 N=14 n (%)	Overall [d] N=244 n (%)	AG881-C-004 pre-crossover [e] N=163 n (%)
Subjects with any events	6 (3.6)	1 (1.9)	0	1 (7.1)	8 (3.3)	2 (1.2)
Investigations	5 (3.0)	1 (1.9)	0	1 (7.1)	7 (2.9)	0
Alanine aminotransferase increased	5 (3.0)	1 (1.9)	0	1 (7.1)	7 (2.9)	0
Aspartate aminotransferase increased	3 (1.8)	0	0	1 (7.1)	4 (1.6)	0
Gamma-glutamyltransferase increased	1 (0.6)	0	0	0	1 (0.4)	0

Table 5833. Summary of Treatment-Emergent Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

System Organ Class (SOC) Preferred Term (PT)	Vorasidenib 40 mg QD [a]					Placebo
	AG881-C-004 without crossover [b] N=167 n (%)	AG881-C-004 post-crossover [c] N=52 n (%)	AG881-C-002 N=11 n (%)	AG120-881-C-001 N=14 n (%)	Overall [d] N=244 n (%)	AG881-C-004 pre-crossover [e] N=163 n (%)
Hepatobiliary disorders	1 (0.6)	0	0	0	1 (0.4)	0
Autoimmune hepatitis	1 (0.6)	0	0	0	1 (0.4)	0
Gastrointestinal disorders	0	0	0	0	0	1 (0.6)
Diarrhoea	0	0	0	0	0	1 (0.6)
General disorders and administration site conditions	0	0	0	0	0	1 (0.6)
Fatigue	0	0	0	0	0	1 (0.6)

Data Cutoff Dates: AG120-881-C-001 (30 May 2022); AG881-C-002 (17 October 2022); AG881-C-004 (06 September 2022).
Notes: The Safety Analysis Set for this table includes all subjects from AG881-C-004 who have received at least 1 dose of vorasidenib or placebo, and subjects from AG881-C-002 and AG120-881-C-001 who have received at least 1 dose of vorasidenib.
Treatment-emergent adverse events (TEAEs) presented in the summary tables include the AEs that begin or worsen from baseline during the on-treatment period.
A subject with multiple occurrences of an AE under one treatment is counted only once in the PT for that treatment.
A subject with multiple AEs within the same SOC is counted only once in the SOC.
System organ classes and preferred terms are coded from MedDRA v25.1.
Percentages are calculated based on N in each column.
a. 40 mg QD population includes subjects treated with vorasidenib 50 mg QD uncoated.
b. Includes data from subjects in Study AG881-C-004 who were randomized to and treated with vorasidenib 40 mg QD, those randomized to placebo but received at least one dose of vorasidenib without crossover, and pre-crossover data from subjects who received at least one dose of vorasidenib prior to cross over.
c. Includes data from subjects who were randomized to placebo who subsequently crossed over to receive vorasidenib 40 mg QD in Study AG881-C-004. Only data after crossover is included in this column.
d. Includes data from subjects treated with vorasidenib 40 mg QD in Study AG881-C-004, post crossover data from subjects 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 with glioma treated with vorasidenib 50 mg QD in Study AG881-C-002.
e. 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.

The median time to first event for TEAEs of any grade that led to study treatment discontinuation was earlier in the vorasidenib arm (N=167) compared with the placebo arm (N=163), and most subjects in the vorasidenib arm had a time to first event ≤60 days following the first study treatment dose. The median TTR was similar across both treatment arms.

Among subjects in the vorasidenib arm (N=167), the most common (≥2 subjects) TEAEs leading to study treatment discontinuation were alanine aminotransferase increased (5 [3.0%] subjects) and aspartate aminotransferase increased (3 [1.8%] subjects).

- The median time to first event was 57.0 (range: 15 – 170) days following the first study treatment dose for alanine aminotransferase increased and 57.0 (range: 30 – 201) days for aspartate aminotransferase increased.
- The median TTR was 75.0 (range: 45 – 155) days following TEAE onset for alanine aminotransferase increased and 56.0 (range: 50 – 100) days for aspartate aminotransferase increased.

Among subjects in the placebo arm (N=163), a total of 2 (1.2%) subjects experienced TEAEs of any grade that led to study treatment discontinuation.

- The median time to first event was 151.5 (range: 7 – 296) days following the first study treatment dose.
- The median TTR was 57.0 (range: 42 – 72) days following TEAE onset.

In the overall glioma population who received vorasidenib 40 mg, 2 additional events of ALT increase and one ALT increase led to treatment discontinuation.

In the all solid tumours population, events that led to treatment discontinuation were consistent with the above observations. In addition, in patients who received a dose > 40 mg one additional event that led to discontinuation was large intestine perforation.

- Adverse Events Leading to Study Treatment Interruption

Table 5934. Summary of Treatment-Emergent Adverse Events Leading to Treatment Interruption by System Organ Class and Preferred Term – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

	Vorasidenib 40 mg QD [a]					Placebo
System Organ Class (SOC) Preferred Term (PT)	AG881-C-004 without crossover [b] N=167 n (%)	AG881-C-004 post-crossover [c] N=52 n (%)	AG881-C-002 N=11 n (%)	AG120-881-C-001 N=14 n (%)	Overall [d] N=244 n (%)	AG881-C-004 pre-crossover [e] N=163 n (%)
Subjects with any events	50 (29.9)	11 (21.2)	2 (18.2)	4 (28.6)	67 (27.5)	37 (22.7)
Investigations	28 (16.8)	7 (13.5)	0	3 (21.4)	38 (15.6)	5 (3.1)
Alanine aminotransferase increased	24 (14.4)	7 (13.5)	0	3 (21.4)	34 (13.9)	3 (1.8)
Aspartate aminotransferase increased	10 (6.0)	3 (5.8)	0	1 (7.1)	14 (5.7)	3 (1.8)
Gamma-glutamyltransferase increased	4 (2.4)	0	0	0	4 (1.6)	0
Platelet count decreased	0	1 (1.9)	0	0	1 (0.4)	0
Infections and infestations	18 (10.8)	1 (1.9)	0	1 (7.1)	20 (8.2)	16 (9.8)
COVID-19	15 (9.0)	1 (1.9)	0	0	16 (6.6)	12 (7.4)
Breast abscess	1 (0.6)	0	0	0	1 (0.4)	0
Conjunctivitis	1 (0.6)	0	0	0	1 (0.4)	0
Enterocolitis infectious	1 (0.6)	0	0	0	1 (0.4)	1 (0.6)
Post procedural infection	1 (0.6)	0	0	0	1 (0.4)	0
Tooth infection	0	0	0	1 (7.1)	1 (0.4)	0
Asymptomatic COVID-19	0	0	0	0	0	2 (1.2)
Pharyngotonsillitis	0	0	0	0	0	1 (0.6)

Table 5934. Summary of Treatment-Emergent Adverse Events Leading to Treatment Interruption by System Organ Class and Preferred Term – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

System Organ Class (SOC) Preferred Term (PT)	Vorasidenib 40 mg QD [a]					Placebo
	AG881-C-004 without crossover [b] N=167 n (%)	AG881-C-004 post-crossover [c] N=52 n (%)	AG881-C-002 N=11 n (%)	AG120-881-C-001 N=14 n (%)	Overall [d] N=244 n (%)	AG881-C-004 pre-crossover [e] N=163 n (%)
Nervous system disorders	4 (2.4)	2 (3.8)	1 (9.1)	0	7 (2.9)	2 (1.2)
Seizure	2 (1.2)	1 (1.9)	1 (9.1)	0	4 (1.6)	0
Dizziness	2 (1.2)	0	0	0	2 (0.8)	0
Aphasia	1 (0.6)	0	0	0	1 (0.4)	0
Balance disorder	1 (0.6)	0	0	0	1 (0.4)	0
Disturbance in attention	1 (0.6)	0	0	0	1 (0.4)	0
Dural arteriovenous fistula	1 (0.6)	0	0	0	1 (0.4)	0
Headache	0	0	1 (9.1)	0	1 (0.4)	1 (0.6)
Partial seizures	0	1 (1.9)	0	0	1 (0.4)	0
Epilepsy	0	0	0	0	0	1 (0.6)
Gastrointestinal disorders	4 (2.4)	0	1 (9.1)	0	5 (2.0)	6 (3.7)
Diarrhoea	2 (1.2)	0	0	0	2 (0.8)	3 (1.8)
Nausea	2 (1.2)	0	0	0	2 (0.8)	5 (3.1)
Abdominal pain	1 (0.6)	0	0	0	1 (0.4)	1 (0.6)
Oral dysaesthesia	0	0	1 (9.1)	0	1 (0.4)	0
Vomiting	1 (0.6)	0	0	0	1 (0.4)	2 (1.2)
Metabolism and nutrition disorders	3 (1.8)	0	0	0	3 (1.2)	1 (0.6)
Hypophosphataemia	2 (1.2)	0	0	0	2 (0.8)	0
Hyperglycaemia	1 (0.6)	0	0	0	1 (0.4)	0
Hypocalcaemia	1 (0.6)	0	0	0	1 (0.4)	0
Hypoglycaemia	0	0	0	0	0	1 (0.6)
Cardiac disorders	0	1 (1.9)	0	0	1 (0.4)	2 (1.2)
Acute myocardial infarction	0	1 (1.9)	0	0	1 (0.4)	0
Atrial fibrillation	0	0	0	0	0	1 (0.6)
Myocardial ischaemia	0	0	0	0	0	1 (0.6)
Eye disorders	1 (0.6)	0	0	0	1 (0.4)	0
Cataract	1 (0.6)	0	0	0	1 (0.4)	0
General disorders and administration site conditions	1 (0.6)	0	0	0	1 (0.4)	6 (3.7)
Fatigue	1 (0.6)	0	0	0	1 (0.4)	3 (1.8)
Influenza like illness	0	0	0	0	0	1 (0.6)
Pyrexia	0	0	0	0	0	2 (1.2)

Table 5934. Summary of Treatment-Emergent Adverse Events Leading to Treatment Interruption by System Organ Class and Preferred Term – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

System Organ Class (SOC) Preferred Term (PT)	Vorasidenib 40 mg QD [a]					Placebo
	AG881-C-004 without crossover [b] N=167 n (%)	AG881-C-004 post-crossover [c] N=52 n (%)	AG881-C-002 N=11 n (%)	AG120-881-C-001 N=14 n (%)	Overall [d] N=244 n (%)	AG881-C-004 pre-crossover [e] N=163 n (%)
Hepatobiliary disorders	1 (0.6)	0	0	0	1 (0.4)	0
Hepatic steatosis	1 (0.6)	0	0	0	1 (0.4)	0
Injury, poisoning and procedural complications	0	1 (1.9)	0	0	1 (0.4)	1 (0.6)
Toxicity to various agents	0	1 (1.9)	0	0	1 (0.4)	0
Fall	0	0	0	0	0	1 (0.6)
Musculoskeletal and connective tissue disorders	1 (0.6)	0	0	0	1 (0.4)	2 (1.2)
Intervertebral disc protrusion	1 (0.6)	0	0	0	1 (0.4)	0
Arthralgia	0	0	0	0	0	1 (0.6)
Osteonecrosis	0	0	0	0	0	1 (0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.6)	0	0	0	1 (0.4)	0
Chordoma	1 (0.6)	0	0	0	1 (0.4)	0
Respiratory, thoracic and mediastinal disorders	1 (0.6)	0	0	0	1 (0.4)	0
Dyspnoea	1 (0.6)	0	0	0	1 (0.4)	0
Vascular disorders	1 (0.6)	0	0	0	1 (0.4)	1 (0.6)
Deep vein thrombosis	1 (0.6)	0	0	0	1 (0.4)	0
Hypertension	0	0	0	0	0	1 (0.6)
Blood and lymphatic system disorders	0	0	0	0	0	1 (0.6)
Neutropenia	0	0	0	0	0	1 (0.6)
Psychiatric disorders	0	0	0	0	0	5 (3.1)
Anxiety	0	0	0	0	0	3 (1.8)
Suicidal ideation	0	0	0	0	0	2 (1.2)
Skin and subcutaneous tissue disorders	0	0	0	0	0	2 (1.2)
Rash maculo-papular	0	0	0	0	0	2 (1.2)

Data Cutoff Dates: AG120-881-C-001 (30 May 2022); AG881-C-002 (17 October 2022); AG881-C-004 (06 September 2022).
Notes: The Safety Analysis Set for this table includes all subjects from AG881-C-004 who have received at least 1 dose of vorasidenib or placebo, and subjects from AG881-C-002 and AG120-881-C-001 who have received at least 1 dose of vorasidenib.
Treatment-emergent adverse events (TEAEs) presented in the summary tables include the AEs that begin or worsen from baseline during the on-treatment period.
A subject with multiple occurrences of an AE under one treatment is counted only once in the PT for that treatment.
A subject with multiple AEs within the same SOC is counted only once in the SOC.
System organ classes and preferred terms are coded from MedDRA v25.1.
Percentages are calculated based on N in each column.
a. 40 mg QD population includes subjects treated with vorasidenib 50 mg QD uncoated.

b. Includes data from subjects in Study AG881-C-004 who were randomized to and treated with vorasidenib 40 mg QD, those randomized to placebo but received at least one dose of vorasidenib without crossover, and pre-crossover data from subjects who received at least one dose of vorasidenib prior to cross over.
c. Includes data from subjects who were randomized to placebo who subsequently crossed over to receive vorasidenib 40 mg QD in Study AG881-C-004. Only data after crossover is included in this column.
d. Includes data from subjects treated with vorasidenib 40 mg QD in Study AG881-C-004, post crossover data from subjects 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 with glioma treated with vorasidenib 50 mg QD in Study AG881-C-002.
e. 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.

The median time to first event for TEAEs that led to study treatment interruption was earlier in the vorasidenib arm (N=167) than in the placebo arm (N=163). The median TTR was longer in the vorasidenib arm than in the placebo arm; the range was similar across the treatment arms.

Data in the overall glioma patients who received vorasidenib 40 mg were consistent with the pivotal study. Data in the all solid tumour patients who received vorasidenib 40 mg were consistent with the pivotal study, although it is noted than one additional event of seizure led to treatment interruption in a patient with a non glioma solid tumour at a dose > 40 mg.

- Adverse Events Leading to Study Treatment Dose Reduction

Table 6035. Summary of Treatment-Emergent Adverse Events Leading to Treatment Dose Reduction in ≥2 Subjects by System Organ Class and Preferred Term – Glioma With Vorasidenib 40 mg QD (Safety Analysis Set)

System Organ Class (SOC) Preferred Term (PT)	Vorasidenib 40 mg QD [a]					Placebo
	AG881-C-004 without crossover [b] N=167 n (%)	AG881-C-004 post-crossover [c] N=52 n (%)	AG881-C-002 N=11 n (%)	AG120-881-C-001 N=14 n (%)	Overall [d] N=244 n (%)	AG881-C-004 pre-crossover [e] N=163 n (%)
Subjects with any events	18 (10.8)	2 (3.8)	1 (9.1)	1 (7.1)	22 (9.0)	5 (3.1)
Investigations	14 (8.4)	2 (3.8)	1 (9.1)	1 (7.1)	18 (7.4)	3 (1.8)
Alanine aminotransferase increased	13 (7.8)	2 (3.8)	1 (9.1)	1 (7.1)	17 (7.0)	1 (0.6)
Aspartate aminotransferase increased	2 (1.2)	0	1 (9.1)	0	3 (1.2)	0
Gastrointestinal disorders	2 (1.2)	0	0	0	2 (0.8)	1 (0.6)
Abdominal pain	2 (1.2)	0	0	0	2 (0.8)	1 (0.6)
Diarrhoea	2 (1.2)	0	0	0	2 (0.8)	1 (0.6)
Nervous system disorders	2 (1.2)	0	0	0	2 (0.8)	1 (0.6)
Aphasia	2 (1.2)	0	0	0	2 (0.8)	0
Dizziness	2 (1.2)	0	0	0	2 (0.8)	0

Data Cutoff Dates: AG120-881-C-001 (30 May 2022); AG881-C-002 (17 October 2022); AG881-C-004 06 September 2022).
Notes: The Safety Analysis Set for this table includes all subjects from AG881-C-004 who have received at least 1 dose of vorasidenib or placebo, and subjects from AG881-C-002 and AG120-881-C-001 who have received at least 1 dose of vorasidenib.
Treatment-emergent adverse events (TEAEs) presented in the summary tables include the AEs that begin or worsen from baseline during the on-treatment period.
A subject with multiple occurrences of an AE under one treatment is counted only once in the PT for that treatment.
A subject with multiple AEs within the same SOC is counted only once in the SOC.
System organ classes and preferred terms are coded from MedDRA v25.1.
Percentages are calculated based on N in each column.
a. 40 mg QD population includes subjects treated with vorasidenib 50 mg QD uncoated.

b. Includes data from subjects in Study AG881-C-004 who were randomized to and treated with vorasidenib 40 mg QD, those randomized to placebo but received at least one dose of vorasidenib without crossover, and pre-crossover data from subjects who received at least one dose of vorasidenib prior to cross over.
c. Includes data from subjects who were randomized to placebo who subsequently crossed over to receive vorasidenib 40 mg QD in Study AG881-C-004. Only data after crossover is included in this column.
d. Includes data from subjects treated with vorasidenib 40 mg QD in Study AG881-C-004, post crossover data from subjects 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 with glioma treated with vorasidenib 50 mg QD in Study AG881-C-002.
e. 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.

The median time to first event for TEAEs that led to dose reduction was earlier in the vorasidenib arm than in placebo arm, and most subjects in the vorasidenib arm (N=167) and overall (N=244) had a time to first event ≤60 days following the first study treatment dose. The median TTR was longer in the vorasidenib arm than in the placebo arm.

Pooled safety dataset was consistent with observations of the pivotal study

2.6.8.11. Post marketing experience

Not Applicable

2.6.9. Discussion on clinical safety

The assessment of safety vs placebo presented in the dossier is adequate to isolate TEAEs, and as basis for discussion of potential ADRs.

Overall, the safety data from the pooled populations were consistent with the pivotal study dataset. The safety profile of vorasidenib in subjects with haematologic malignancies is expected to differ from that in subjects with solid tumours due to fundamental differences in disease characteristics and response to mutant IDH-directed therapy, therefore data in patients with hematologic malignancies have been commented in this section when adding a relevant information to the assessment. Furthermore, differences in safety data for glioma and non-glioma solid tumour treated with vorasidenib dosage below 40 mg (N=26, of which 22 with glioma), at 40 mg (N= 251 of which 244 with glioma) and above 40 mg (N= 59 of which 29 with glioma) are discussed where needed.

Extent of exposure

In the pivotal study AG881-C-004, 167 patients received vorasidenib 40 mg and 163 patients received placebo. In addition, 52 patients crossed over from placebo to vorasidenib. Median exposure to vorasidenib 40mg in the pivotal study was 12.65 (range: 1.0 – 29.9) months vs 11.17 (range: 0.6 – 26.2) months in the placebo arm, thus exposure can be considered similar in both treatment arms.

Overall, 107 patients with glioma, including patients of supportive studies, were treated with vorasidenib 40 mg > 12 months (of which, 53 patients from the pivotal study). Relative dose intensity was >90% in all groups, with 93.6% in the vorasidenib arm of the pivotal study vs 91.2% in the placebo arm.

Median treatment duration in patients with all solid tumours treated with vorasidenib 40 mg (n=251) was 10.58 (range: 0 – 80.5) months and 109 patients were treated for > 12 months. This meets the ICH E1 guideline requirements and is considered acceptable. Relative dose intensity was > 99% in all groups even in patients who received > 40 mg (although median duration was 3.52 months). Nevertheless, long term safety data on deschloro-methyl sulfone product (AGI-69460), the main metabolite of vorasidenib, are currently not available. Long term safety>12 months has been included as missing information in the list of safety concerns in the RMP. This will allow to collect safety information regarding this metabolite in addition to the ER and PPK modelling that the applicant committed to provide for Q1 2026 (REC).

Haematologic malignancies population provide limited supportive data, not only because of the different expected sensitivity of the population, but also because the median treatment duration was 2.15 months, eight subjects exposed to > 6 months and 5 subjects ≥ 12 months.

Subjects disposition

At the DCO 06 September 2022 of pivotal study AG881-C-004, more patients remained on treatment in the vorasidenib (131 [78.4%]) arm than in the placebo arm (95 [58.3%]). The main reason for treatment discontinuation was progressive disease in both arms. This was more commonly reported in patients in the placebo arm (60 [36.8%]) than in patients in the vorasidenib arm (24 [14.4%]). Discontinuation due to an adverse event in the vorasidenib arm was higher than in the placebo arm (3.6% vs 1.2% respectively), however, both incidences were low.

Demographics and other characteristics

In the pivotal study, mean and median age were similar in the vorasidenib (both 41.0 years) and in the placebo arm (39.8 years and 39.0 years respectively). Consistent data was observed in overall glioma patients who received vorasidenib 40mg.

Considering that the intended indication is for patients from 12 years of age, it must be highlighted that no patient under 21 years old was included in the vorasidenib arm. The provided PIP mentioned that a minimal number of 1 or 2 patients would be acceptable if a model allowing extrapolation was proposed. One adolescent, aged 16 years received vorasidenib in study AG881-C-002. The PK data for this subject were generally similar to those observed in the adult population (see section 2.6.2.1. Pharmacokinetics).

There were notably more male patients in the vorasidenib arm than in the placebo arm, and the pooling of all patients with glioma who received vorasidenib 40 mg do not allow to balance this observation. Nevertheless, additional analyses requested (data not shown) did not suggest an impact on the observed safety profile, and the provided recommendations for monitoring and management of adverse reactions are acceptable. In both treatment groups as in the overall glioma population who received vorasidenib 40 mg, the vast majority of patients were white, with less than 5% of Asian. Demographics in patient with haematological malignancies differ mostly by a higher median age (68 years). Baseline characteristics and prior therapy were generally balanced between both treatment arms of the pivotal study.

Adverse events

In the pivotal study, any TEAE was experienced by 94.6% and 93.3% of patients in vorasidenib and placebo arm respectively. Nevertheless, treatment related TEAEs were more frequent in the vorasidenib arm (65.3%) than in the placebo arm (58.3%).

While most TEAEs were grade 1-2, a higher incidence of grade ≥3 TEAEs was observed in the vorasidenib arm (22.8%) than in the placebo arm (13.5%) as well as treatment-related grade ≥3 TEAEs (13.2% and 3.7% in the vorasidenib arm and the placebo respectively). In addition, a higher frequency for dose interruption and reduction and a higher incidence of AESI of hepatic events was observed in the vorasidenib arm compared to the placebo arm and for serious TEAE.

No TEAE leading to death was observed in the study or in the broader population with all solid tumours treated with 40 mg vorasidenib (N=251). In the overall population with all solid tumours including glioma treated with any vorasidenib dose (N=336), one patient treated with > 40 mg vorasidenib died. The patient had signet cell adenocarcinoma and the cause of death was a large intestine perforation that was reported as related to disease under study or its treatment, but was not considered related to vorasidenib.

Overall, the summary of overall TEAEs for all subjects with glioma who received 40 mg or any dose of vorasidenib were consistent with the one described. Nevertheless, additional observations by dose suggest that the incidence of treatment related TEAEs, serious TEAEs, TEAE leading to dose modification (discontinuation, interruption, or reduction) and AESI (including serious AESI) increased with the dose.

The summary of TEAEs in the overall solid tumours in patients who received vorasidenib at any dose was consistent with data of the pivotal study with 93.8% of TEAEs (63.4% treatment related), 25.6% of grade ≥ 3 TEAEs. Serious TEAEs were observed at an incidence of 12.2% thus higher than in the pivotal study. This discrepancy is due to the incidence of serious TEAEs in alternative doses of vorasidenib (higher and lower doses). Similarly, the incidence of any AESI increased with the dose as previously observed in the pool of patients with glioma who received vorasidenib at any dose.

Common Adverse Events

In the pivotal study AG881-C-004, the most frequent TEAEs by SOC in the vorasidenib arm were Nervous system disorders (55.7%), Investigations (50.9%), gastrointestinal disorders (50.9%), infections and infestations (47.3%) and General disorders and administration site conditions (32.3%). Incidences in the overall glioma pool who received vorasidenib 40mg were consistent with vorasidenib arm in the pivotal study.

When compared to placebo, notable difference in TEAEs by SOC was observed for Investigations (30.1%), while SOC of nervous system disorders (51.5%), Gastrointestinal disorders (48.5%) Infections and infestations (46.6%) and General disorders and administration site conditions (31.9%) had similar incidences.

At the PT level, the main differences between the vorasidenib and the placebo arm were within SOC investigation, for PTs of ALT increased (38.9% vs 14.7% respectively), AST increased (28.7% vs 8.0% respectively) and γGT increased (15.6% vs 4.9% respectively).

The most common PTs within SOC of nervous system disorders had similar incidences in the vorasidenib and the placebo arm: headache 26.9% and 27.0% respectively, dizziness: 15.0% and 16.0% respectively. Furthermore, based on the criteria from the applicant's quantitative ADR criteria (all grade TEAEs with a ≥5% incidence and ≥2% difference compared to placebo), a difference in the PT seizure between vorasidenib arm (13.8%) and placebo arm (11.7%) can be highlighted. The inclusion as ADR was ultimately not considered warranted following additional analyses per patients/years and confounding factors for the majority of the patients.

Regarding the TEAEs which occurred at an incidence < 10%, PTs of disturbance in attention (4.8%), blood alkaline phosphatase increased (3.6%), gastro-oesophageal reflux disease (3.6%), oedema peripheral (3.6%), hyperglycaemia (9.6%), decreased appetite (9.0%), hypophosphatemia (7.8%), hyperkalaemia (3.6%), oropharyngeal pain (5.4%), dyspnoea (3.6%), tinnitus (4.2%) occurred >2% higher frequency in the vorasidenib arm compared to the placebo arm (data not shown). The applicant provided an acceptable justification for not including PT of oedema peripheral, hypophosphatemia, hyperkalaemia, oropharyngeal pain, and tinnitus. Nevertheless, from the provided data, blood alkaline phosphatase increased, hyperglycaemia, decreased appetite, gastro-oesophageal reflux disease, dyspnoea have at least a reasonable possibility of a causal relationship to vorasidenib based on comparative incidence, evaluation of causality from individual case reports and non-clinical findings and are included as ADRs in section 4.8 of the SmPC.

Data in the glioma and all solid tumours populations who received vorasidenib any dose was overall consistent with the findings of the pivotal study. In addition, an increase in incidence of AST, ALT increase and oropharyngeal pain with the dose was observed.

In the haematological malignancies population, most commonly reported TEAEs were fatigue, ALT increase, blood alkaline phosphatase, and diarrhoea and vomiting, thus overall consistent with the solid tumour population although blood alkaline phosphatase was more frequent.

In the broader population with all solid tumours the most commonly (≥20%) reported TEAEs of any grade were alanine aminotransferase increased (91 [36.3%] patients), fatigue (78 [31.1%] patients), COVID-19 (68 [27.1%] patients), aspartate aminotransferase increased (67 [26.7%] patients), headache (64 [25.5%] patients), diarrhoea (53 [21.1%] patients), and nausea (51 [20.3%] patients).

The grade ≥ 3 TEAEs which occurred at least in 2% of the patients (>3 patients) in the vorasidenib arm of the pivotal study were ALT increase (9.6% vs 0 in the placebo arm), AST increase (4.2% vs 0 in placebo arm), γGT increased (3.0% vs 1.2% in the placebo arm) and seizure (4.2% vs 2.5% in the placebo arm). In addition, grade ≥3 syncope occurred at 1.8% in vorasidenib vs 0.6 in the placebo arm.

In the broader population with all solid tumors, the Grade ≥3 TEAEs were reported that occurred in ≥2 patients were alanine aminotransferase increased (20 [8.0%]), aspartate aminotransferase increased (9 [3.6%]), and γGT increased (4 [1.6%]).

The most frequent related TEAE in the pivotal study were ALT increased (65.3%), AST increased (36.5%), fatigue (21.0%), nausea (15.0%) and γGT increased (13.2%). All, except nausea, occurred at a higher frequency in vorasidenib arm than in placebo arm. In addition, for related TEAEs that occurred at a lower incidence, blood alkaline phosphatase increased (3.6%), diarrhoea (12.0%), abdominal pain (6.0%) and dizziness (6.6%) occurred at a higher incidence in the vorasidenib arm than in the placebo arm (blood alkaline phosphatase increased at 1.2%, diarrhoea at 9.8%, abdominal pain at 3.1%, dizziness 4.3%). Blood alkaline phosphatase increased and diarrhoea are included as ADRs in section 4.8 of the SmPC, however, it was considered that a causal relationship between vorasidenib and abdominal pain and dizziness is at least a reasonable possibility based on the comparative incidence of treatment related events, the recognized ADR of diarrhoea, non-clinical findings (for abdominal pain), and potential class effect. Both PT of abdominal pain and dizziness have been included as ADRs in section 4.8 of the SmPC.

Serious Adverse events

In the pivotal study, serious TEAEs occurred at an incidence of 6.6% in the vorasidenib arm and 4.9% in the placebo arm. Half of the serious TEAEs occurred within SOC Nervous system disorders in the vorasidenib arm (3.0%, i.e. 5 patients with the PT of seizure) and more than half in placebo arm (3.7%, 6 patients of which 5 patients experienced serious events of seizure, partial seizure and epilepsy).

Hepatobiliary disorders was the second most common SOC represented in the vorasidenib arm with one PT each of autoimmune hepatitis and hepatic failure (which was associated with a non-serious event of hepatic necrosis). A warning has been included in section 4.4 reporting those events. In addition, one serious TEAE of ALT increase occurred in the vorasidenib arm (and 2 additional in the overall glioma population who received vorasidenib 40mg).

Furthermore, 3 related serious TEAEs were experienced by 2 patients (1.8%) in the vorasidenib arm versus none in the placebo arm. All 3 events were related to hepatotoxicity (above mentioned events of ALT increase, autoimmune hepatitis and hepatic failure). In the population of patients with glioma who received vorasidenib 40 mg, 2 additional serious related TEAEs of ALT increase occurred, and one event of serious seizure was considered related to study treatment.

Adverse events of special interest

Hepatotoxicity

In the pivotal study, the incidence of TEAEs from SMQ liver related investigations, signs and symptoms was twice higher in the vorasidenib arm (43.7%) than in the placebo arm (20.9%) and 10 times higher for events of grade ≥ 3 (11.4% vs 1.2% respectively). Most of the events in the vorasidenib and in the placebo arms were considered treatment related (38.9% and 16.0% respectively). Nevertheless, events were rarely considered serious.

Dose modifications were mainly treatment interruption (16.8% and 3.1% in the vorasidenib and placebo arm respectively). Treatment dose reduction occurred in 8.4% of patients of the vorasidenib arm and 1.2% in the placebo arm. Few events led to drug discontinuation (3.0%, i.e. 5 patients in the vorasidenib arm vs none in the placebo arm).

The analyses by PT within this broad search were overall consistent with the prior observations. The most frequent PTs in vorasidenib arm of the pivotal study were ALT increased (38.9%), AST increased (28.7%) and γGT increased (15.6%) and were higher than in the placebo arm (17.4%, 8.0% and 4.9% respectively). In addition, blood alkaline phosphatase increase (3.6%) and blood bilirubin increase (3.6%) were also higher than in the placebo arm (1.2% and 2.5% respectively). Most PTs identified across both arms were Grade 1 or Grade 2 and non-serious. Grade ≥3 TEAEs that occurred in ≥2 patients in the vorasidenib arm were alanine aminotransferase increased (16 [9.6%] patients), aspartate aminotransferase increased (7 [4.2%] patients), and γGT increased (5 [3.0%] patients). Two events of ALT increased were of grade 4. Events of blood alkaline phosphatase increased were all of grade ≤ 2. The only grade ≥3 TEAE in placebo arm was γGT increase in 2 patients (1.2%).

The median time to first event in the vorasidenib arm was 57.0 days (range 1-451) and 116 days (range 5-308) in the placebo arm. Although most events occurred within the first 60 days, 41% of events occurred > 60 days. Thus, hepatic enzyme elevation may occur any time during treatment, and the recommendation of monitoring in the SmPC has been adapted following this observation.

The median time to resolution was longer in the vorasidenib arm than in the placebo arm for ALT (56.0 vs 28.5 days respectively) and γGT increased (57.0 vs 29.0 days respectively), while similar median TTR was observed in both treatment groups for AST increased (29.0 days).

The hepatotoxicity search strategy allowed to capture additional events. Two subjects with a hepatic steatosis, and 1 subject each with hypoalbuminemia, autoimmune hepatitis, benign hepatic neoplasm, hepatic failure, and hepatic necrosis (same subject for the last two events). No additional PT was observed in the placebo arm. In the overall glioma patients who received vorasidenib 40 mg, one additional PT of hepatic steatosis, one event of hypoalbuminemia and one event of INR ratio increased were observed. All events were grade 1, non-serious, and not considered related to vorasidenib according to the investigator. Moreover, 2/3 patients had a BMI > 30 (considered obese) and the last patient had the event at D4 with baseline increase of AST. Nevertheless, considering the observed hepatotoxicity in non-clinical and clinical studies, and the observation of these 3 cases of hepatic steatosis, the applicant will closely monitor the events of hepatic steatosis in the PSURs.

During the clinical development of vorasidenib, 4 patients met Hy's law laboratory criteria, of which 2 events in patients with a glioma were considered related to study treatment by the investigator. The 2 other patients (one with a cholangiocarcinoma and one with an AML) had events not considered related to study treatment. Since the events considered related to study treatment resolved, that hepatotoxicity is already included as an important identified risk in the RMP (with FU questionnaire to collect post-authorisation information), that routine risk minimization measures are proposed (monitoring and management of hepatoxicity in SmPC sections 4.2, 4.4 and 4.8 and PL sections 2 and 4), it has been considered that the risk is sufficiently mitigated at this stage.

The hepatotoxicity search strategy in the solid tumour population treated by vorasidenib 40 mg and any dose was overall similar to the pivotal study. Overall, laboratory values for liver test function support the above observations.

Altogether, data from the pivotal study raise concerns whether vorasidenib has a potential for severe DILI, which is difficult to ascertain since the number of patients who received vorasidenib during clinical development is somewhat limited (244 patients). Overall, the provided analysis did not bring additional concerns, the safety profile remains consistent with a manageable hepatotoxicity. In addition, since hepatotoxicity is included as an important identified risk in the list safety concerns in the RMP, it will be closely monitored.

Neurological disturbances

Neuropathy peripheral is included as an ADR in section 4.8 of the SmPC of ivosidenib, an IDH1 inhibitor authorized in cholangiocarcinoma. A total of 6 patients in the overall safety population experienced a peripheral neuropathy (motor and sensory) The analyses of the cases showed that all events except one were considered not related to vorasidenib. Due to confounding factors for most of the patients, it is agreed that inclusion of peripheral neuropathy as an ADR of vorasidenib is not warranted at the present time.

Gastro-intestinal disorders

The most frequent PT in the vorasidenib and the placebo arms were diarrhoea (24.6% and 16.6% respectively), nausea (21.6% and 22.7% respectively), constipation (12.6% and 12.3% respectively), vomiting (6.6% and 9.8% respectively) and abdominal pain (8.4% and 8.6% respectively).

Within related TEAEs, diarrhoea (12.0% and 9.8% respectively) and abdominal pain (6.0% and 3.1% respectively) had a higher incidence in the vorasidenib arm than in the placebo arm. Both PTs are included as ADRs in section 4.8 of the SmPC.

Guillain barré syndrome (GBS)

Because GBS has been observed with other IDH inhibitor in hematologic malignancies (although not in solid tumours), a search strategy was conducted under HLTs: acute polyneuropathies, chronic polyneuropathies, mononeuropathies, or peripheral neuropathies not elsewhere classified. No case of GBS was observed in the all solid tumour population who received vorasidenib any dose.

Rash

Rash is reported as very common in other IDH inhibitors for the use in other clinical settings. In the pivotal study, incidences of any TEAE within the search strategy composed of PTs from HLT rashes, eruptions, and exanthems NEC were similar in both vorasidenib arm (5.4%) and placebo arm (5.5 %) and in treatment related TEAE (1.2% in both arms). All events were grade 1/2 in vorasidenib and one event was grade ≥ 3 in placebo arm. In the vorasidenib arm, no event was serious or led to dose modification, while 2 events led to treatment interruption in the placebo arm. The most frequent PTs were rash (2.4%, 4 patients) and rash maculo-papular (1.8%, 3 patients). In the placebo arm, the most frequent PT was rash papulo-macular (5 patients 3.1%).

Fatigue

In the pivotal study AG881-C-004**,** incidences of any TEAE within the broad search of fatigue (PTs asthenia, cancer fatigue, and fatigue) were similar between the vorasidenib (36.5%) and the placebo arm (35.6%). In both arms, the majority of events were considered related although the incidence of treatment related fatigue was higher in the vorasidenib arm (23.4%) than in the placebo arm (20.2%). Only one event was grade ≥ 3 in the vorasidenib arm (vs 2 patients in the placebo arm) and was considered treatment related. No event of fatigue was considered serious. Only one event in the

vorasidenib arm required study treatment interruption and dose reduction and no event led to study treatment discontinuation. Considering the higher incidence of treatment related event within the broad search of fatigue, it has been included as ADR in section 4.8 of the SmPC.

Dose modifications:

In the pivotal study, the incidence of events leading to treatment discontinuation was higher in the vorasidenib arm (3.6%) than in the placebo arm (1.2%). All PTs which led to discontinuation in the vorasidenib arm were related to hepatic function (ALT increase, AST increase, γGT increase and autoimmune hepatitis). In the placebo arm, the two events which led to study treatment discontinuation were not related to hepatic function (diarrhoea and fatigue).

There were more events leading to treatment interruption in the vorasidenib arm (29.9%) than in the placebo arm (22.7%). The SOC with the highest difference between vorasidenib and placebo arm was investigation (16.8% and 3.1% respectively), with AST increase, ALT increase and γGT increase as main reasons for interruption. Although of low incidence, events that led to treatment interruption within the SOC nervous system disorders were twice higher in the vorasidenib arm (2.4%) than in the placebo arm (1.2%). Seizure and dizziness were the only PT In vorasidenib arm that led to treatment interruption in more than one patient (2 patients each) while none in the placebo arm. It is noted than one additional event of seizure led to treatment interruption in a patient with non glioma solid tumour at a dose > 40 mg.

There were more subjects with any event that led to dose reduction in the vorasidenib arm (10.8%) than in the placebo arm (3.1%). The majority of events occurred within the SOC investigations and were PT of ALT increase (8.4%) and AST increase (7.8%). Other events that led to dose reduction in ≥2 subjects were within the SOC gastrointestinal disorders (2 patients in the vorasidenib arm and 1 patient in the placebo arm) and nervous system disorders (2 patients in the vorasidenib arm and 1 patient in the placebo arm).

Incidence of most TEAEs was not related to dosage (patients treated with > 40 mg, 40 mg or < 40 mg), only higher incidence of alanine aminotransferase increased (19.2% vs 36.3% vs 42.4%), aspartate aminotransferase increase (19.2% vs 26.7% vs 42.4%) vomiting (7.7% vs 10.4% vs 27.1%) and decrease appetite (7.7% vs 9.6% vs 18.6%), were observed with increasing dosages.

Safety in special population

Although the applicant states that AST increased was the only TEAE that occurred with a ≥10% higher incidence in females (35.9%) than males (19.9%), based on the provided data for the pivotal study, also ALT increased, nausea, dizziness can be considered different between males and females. Overall, the provided table for study AG881-C-004 comparing incidence of all TEAEs by frequency in male and females did not add any concerns.

The toxicity profile in adolescents cannot be established as only one patient younger than 18 years of age (16 years) was treated with vorasidenib in the studies. The lack of long-term safety data might, especially for adolescents, be problematic as some safety concerns related to vorasidenib may impact this population: these include a possible irreversible effect on fertility, and concerns regarding carcinogenicity based on findings in the repeat-dose toxicity studies. The issues have been included as missing information in the list of safety concerns in the RMP and a study in paediatric patients 12 years of age and older to assess the safety of vorasidenib has been included as a post authorisation measure (MEA).

Given the findings from animal studies and the lack of data in pregnant women exposed to vorasidenib, a risk in humans is possible according to the "Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling" (EMEA/CHMP/203927/2005). As a

consequence vorasidenib is not recommended during pregnancy and contraception in women of childbearing potential is recommended during the treatment and for a period of 5 elimination half-lives after stopping treatment, i.e 2 months after cessation of treatment.

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.

Laboratory and other findings

In the pivotal study, haematological laboratory parameters reported with higher incidence in the vorasidenib arm compared to the placebo arm were high haemoglobin (12.6% and 2.5% respectively), low lymphocytes (10.8% and 8.0% respectively), low neutrophils (14.4% and 12.3% respectively), low platelets (12.0% and 4.3% respectively), high eosinophils (4.2% vs 0.6% respectively). Incidence of grade ≥3 events were low in general. Nevertheless, the incidence of grade ≥ 3 events was high for low neutrophils (2.4% in the vorasidenib arm vs 1.8% in the placebo arm) and low lymphocytes (1.8% and 0.6% respectively).

Regarding chemistry parameters, consistently with the analysis of TEAEs, high ALT, high AST and high γGT were more frequent in the vorasidenib arm than in the placebo arm. In addition, other parameters with a higher incidence in the vorasidenib arm than in the placebo arm were high alkaline phosphatase (9.6% and 6.7%, respectively); high calcium (6.0% and 1.8%, respectively); low calcium (16 and 6.7% respectively); high creatinine (11.4% and 6.7% respectively) and high potassium (23.4% and 20.2% respectively). In addition, grade ≥3 were higher in the vorasidenib arm for high ALT, high AST, high γGT, and low glucose.

Creatinine high was not considered as an ADR based on the fact that the TEAE of blood creatinine increased did not meet quantitative ADR criteria. Nevertheless, non-clinical findings suggest that kidney is a target organ. It has been clarified that, in the pivotal study, 1 (0.6%) patient in the vorasidenib arm vs. 2 (1.2%) patients in the placebo arm had a TEAE of blood creatinine increased. Although one patient in each arm had a confounding factor, TEAE of blood creatinine increased was assessed as related to treatment by the Investigator for 1 subject in each arm. No TEAEs associated with renal failure were reported. Therefore, events of renal impairment will be closely monitored in the PSURs.

Electrocardiogram

Considering all available non-clinical and in vitro data and based on a comprehensive review across all glioma, solid tumours, and haematological malignancies, no information or recommendation related to electrocardiogram QTc prolongation is included in the SmPC. However, because of the class of drug, the possibility of co-prescription of drugs susceptible to prolong the QTc in these indications, the slight observed imbalance of TEAES from the SMQ Torsades and of the categorical QTc prolongations in patients treated with vorasidenib as compared with placebo, the risk management plan of vorasidenib include QTc prolongation as an important potential risk and clinical signs pertaining to that issue are described.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

Overall, the safety profile is mainly related to hepatotoxicity issues, events which were manageable in accordance with the proposed dose modifications. Other adverse reactions include low grade diarrhoea,

hyperglycemia, decreased appetite, hypophosphatemia, dizziness, dyspnoea, and gastro-oesophageal reflux disease, all considered manageable.

The safety database and the described profile as presented above for the use of vorasidenib in glioma patients is acceptable.

2.7. Risk Management Plan

2.7.1. 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

2.7.2. Pharmacovigilance plan

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	Identify a tumorigenic potential in animals and assess the relevant risk in humans: statistical analysis of	Carcinogenic potential	Final report	04/2027

Oral Gavage to CB6F1/TgrasH2 Hemizygous Mice Planned	mortality and tumor histomorphological data (spontaneous and induced) vs absolute controls and positive reference compound-dosed animals			
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

2.7.3. Risk minimisation measures

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

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 06 August 2024. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

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

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Voranigo (Vorasidenib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic context

3.1.1. Disease or condition

The final indication is:

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 are not in immediate need of radiotherapy or chemotherapy.

3.1.2. Available therapies and unmet medical need

There are no approved therapies for Grade 2 IDH-mutant diffuse gliomas, and most treatments used are adopted from the higher-grade setting (Dietrich and Wen, 2022; van den Bent et al. 2021). The current treatment approach for IDH-mutant diffuse gliomas at the time of initial diagnosis includes maximal safe resection of the tumour followed by either radiotherapy (RT) and/or chemotherapy or an alternative active observation approach with serial magnetic resonance imaging (MRI) (NCCN, 2021; Weller et al. 2021).

Post-operative active observation is a standard of care option for patients with Grade 2 IDH-mutant gliomas who are not in immediate need of chemoradiotherapy. The goal of this approach is to defer the need for more toxic regimens (e.g., RT and chemotherapy) until there is evidence of progression and/or evidence of clinical deterioration.

There is an unmet need for alternative therapies that target IDH-mutant gliomas early in their development. As IDH mutations are early genetic drivers of the disease, a targeted approach suppressing the mutant enzyme may offer an opportunity to intervene early (before radiotherapy or chemotherapy) in the disease course, delaying disease progression, development of contrast enhancement, and malignant transformation and therefore the need for more aggressive therapies.

3.1.3. Main clinical studies

The pivotal study supporting the current application is the INDIGO study, an ongoing phase 3, global, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of vorasidenib (n = 168) compared to placebo (n = 163) in subjects with residual or recurrent predominantly non-enhancing Grade 2 oligodendroglioma or astrocytoma with an IDH1 or IDH2 mutation who were considered to be appropriate candidates for a watch-and-wait approach.

Subjects had at least 1 prior surgery and had not received any other treatment, including systemic chemotherapy or radiotherapy, and did not have any high-risk features and or need of immediate chemotherapy or radiotherapy in the opinion of the Investigator. Adolescent patients (12 years of age and older) weighing at least 40 kg were eligible for inclusion in the pivotal trial.

Randomisation was stratified based on chromosome 1p19q co-deletion status (co-deleted or not co-deleted) and baseline tumour size per local assessment (longest diameter of ≥2 cm or <2 cm).

Patients with confirmed radiographic progression and randomised to placebo had the option to crossover to receive open-label vorasidenib if they were still not in need of immediate chemotherapy or radiotherapy, or other treatment in the opinion of the Investigator.

The primary objective was to demonstrate the superior efficacy of AG-881 (Vorasidenib) based on radiographic PFS per BIRC compared with placebo in subjects with residual or recurrent Grade 2 as their only treatment. The key secondary objective was to demonstrate the superiority efficacy of vorasidenib based on Time to Next Intervention (TTNI) compared with placebo.

3.2. Favourable effects

Vorasidenib improved statistically and significantly rPFS per the BIRC compared with the placebo arm with an HR of 0.39 (95% CI, 0.27, 0.56; one-sided P=0.000000067, one-sided alpha-level = 0.000359).

The median rPFS was 27.7 months (95% CI, 17.0, not estimable) for the vorasidenib arm and 11.1 months (95% CI, 11.0, 13.7) for the placebo arm (Δ rPFS gain 16.6 months). All events were PD (88/163 [54.0%] in the placebo arm and 47/168 [28.0] in the vorasidenib arm); no death events occurred in either arm.

As of the second interim analysis (IA2) data cut-off date (06 September 2022), the observed information fraction was 82% (135/164 PFS events) for the primary endpoint.

With longer follow up, vorasidenib continued to demonstrate a clinically meaningful benefit compared to placebo. As of 07 March 2023 (study unblinding date), an additional 23 PFS events by BIRC have occurred (7 for vorasideninb arm and 16 for placebo arm), representing an observed information fraction of 96.3% (158 out of 164 events). All events were progressive disease (PD), and there were no deaths in either arm. Consistent with previously presented results, PFS by BIRC was improved in the vorasidenib arm compared with that in the placebo arm, with a HR of 0.35 (95% CI, 0.25, 0.49). The median PFS was not estimable (NE) (95% CI: 22.1, NE) in the vorasidenib arm and was 11.4 (95% CI: 11.1, 13.9) months in the placebo arm. At 24 months, the PFS rate was 58.8% (95% CI: 48.4, 67.8) in the vorasidenib arm and 26.2% (17.9, 35.3) in the placebo arm.

Vorasidenib showed an alteration in the dynamics of tumour growth, as evidenced by a mean decrease in tumour volume of 2.5% (TGR of -2.5%; 95% CI, -4.7%, -0.2%) every 6 months in subjects randomized to vorasidenib. In comparison, tumour volume increased in subjects randomized to the placebo arm by a mean percentage of 13.9% (TGR of 13.9%; 95% CI, 11.1%, 16.8%) every 6 months.

3.3. Uncertainties and limitations about favourable effects

No evidence of symptomatic benefit has been shown despite the CHMP's recommendation to consider other measures of patient benefit such as cognition, symptom burden, and seizure activity (EMA/CHMP/SAWP/398727/2019).

3.4. Unfavourable effects

The safety database for vorasidenib in glioma comprises 167 patients in the vorasidenib 40 mg arm included in the pivotal study AG-881-C-001 (INDIGO). In addition, supportive safety dataset allows to increase the population who received the intended dosage of vorasidenib 40 mg in all solid tumours to 295 patients. A total of 109 patients were treated > 12 months with vorasidenib 40 mg. The safety database could be considered acceptable.

In the pivotal study, the incidence of TEAEs was similar in the vorasidenib (94.6%) and placebo (93.3%) arms. Nevertheless, treatment related TEAEs were more frequent in vorasidenib arm (65.3%) than in placebo arm (58.3%). A higher incidence of grade ≥3 TEAEs was also observed in vorasidenib arm (22.8%) than in placebo arm (13.5%) as well as treatment-related grade ≥3 TEAEs (13.2% and 3.7% in vorasidenib and placebo arms respectively).

The most frequent TEAEs by SOC in the vorasidenib arm were nervous system disorders (55.7%), investigations (50.9%), gastrointestinal disorders (50.9%), infections and infestations (47.3%) and General disorders and administration site conditions (32.3%). When compared to placebo, a notable difference in TEAEs by SOC was observed only for investigations (30.1%).

At the PT level, the main differences between vorasidenib and placebo arm were within SOC Investigations, regarding PTs of ALT increase (38.9% vs 14.7% respectively), AST increase (28.7% vs 8.0% respectively) and γGT (15.6% vs 4.9% respectively).

The most common ADR within SOC of nervous system disorders had similar incidence in vorasidenib and placebo arm: dizziness: 15.0% and 16.0% respectively.

PTs occurring at a frequency >2% in vorasidenib arm compared to placebo arm and considered as ADRs were blood alkaline phosphatase increase (3.6%), gastro-oesophageal reflux disease (3.6%), hyperglycaemia (9.6%), decreased appetite (9.0%), hypophosphatemia (7.8%) and dyspnoea (3.6%).

The grade ≥ 3 TEAEs which occurred at least in 2% of the patients (>3 patients) in the vorasidenib arm of the pivotal study and considered as ADRs were ALT (9.6% vs 0 in placebo arm), AST (4.2% vs 0 in placebo arm) and γGT (3.0% vs 1.2% in placebo arm).

Adverse event of special interest based on non-clinical findings was hepatotoxicity which is confirmed as an ADR of vorasidenib according to above clinical data. Hepatic enzymes increased were frequent, were observed at high grade severity and resolved with dose modifications (see section 4.2 of the SmPC). Accordingly, AST, ALT, γGt and alkaline blood phosphatase increase are included in section 4.8 of the SmPC and a warning in section 4.4 includes serious events of hepatic failure and auto-immune hepatitis.

In addition, gastro-toxicity observed in non-clinical studies, translated into a higher incidence of diarrhoea in the vorasidenib (12.0%) arm compared to the placebo arm (9.8%). Diarrhoea is included as an ADR in section 4.8 of the SmPC. Events were grade 1 and 2 and the absence of dose modification in the SmPC is endorsed.

Finally, haematological laboratory findings allowed to observe a platelet count decrease which is included in section 4.8 of the SmPC.

3.5. Uncertainties and limitations about unfavourable effects

Human relevance of testicular toxicity (tubular degeneration) cannot be excluded and measures to manage this potential risk are implemented in SmPC 4.6.

Carcinogenicity concerns are identified. Since no animal carcinogenicity studies are available yet (PASS category 3 studies are requested post approval as per the RMP pharmacovigilance plan see section 2.7.2 above) and long-term clinical safety data are insufficient to characterize this risk, a warning that a carcinogenicity risk in humans could not be excluded has been added in the SmPC 4.4.

The safety in the paediatric population > 12 years old relies mainly on the similarity between paediatric and adult disease and a PK model. Use of vorasidenib in patients aged 12 years to less than 18 years with IDH1 or IDH2 mutant astrocytoma or oligodendroglioma is supported by pharmacokinetic data demonstrating 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. Only one paediatric patient received vorasidenib 40mg in a supportive study.

Due to the short duration of the study submitted for the application, no long term safety data are available yet and they will be collected post authorisation in order to receive further characterisation of the long term safety profile (Category 3 study in the RMP see section 2.7.2 Pharmacovigilance plan)

3.6. Effects table

Table 61. Effects table for vorasidenib in predominantly non-enhancing astrocytoma or oligodendroglioma with a susceptible IDH1 or IDH2 mutation in adult and adolescent patients 12 years and older following surgical intervention (data cut-off: 30 May 2022).

Effect	Short Description	Unit	Vorasidenib 40 mg (n=168)	Control Placebo (n=163)	Uncertainties/ Strength of evidence	References
Favourable Effects						
rPFS	Median (95% CI)	months	27.7 (17.0, NE)	11.1 (11.0, 13.7)	HR of 0.39 (95% CI, 0.27, 0.56; one-sided P=0.000000067, one-sided alpha-level = 0.000359)	
Unfavourable Effects						
TEAE Grade ≥3	Regardless causality (drug related)	%	22.8 (13.2)	13.5 (3.7)		
Serious TEAEs	Regardless causality	%	6.6	4.9		
TEAE leading to death	Regardless causality	%	0	0		
TEAE leading to discontinuation	Regardless causality	%	3.6	1.2		
ALT increase	Incidence of ALT increase	%	38.9	14.7		
AST increase	Incidence of AST increase	%	28.7	8.0		
γGT increase	Incidence of γGT increase	%	15.6	4.9		
diarrhoea	Incidence of diarrhoea	%	24.2	16.6		

Abbreviations: rPFS=radiological progression free survival; TEAE: Treatment emergent adverse event

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The INDIGO study met its primary endpoint and showed a statistically significant improvement of radiographic PFS per the BIRC with vorasidenib compared to placebo with a gain of rPFS which may represents up to 16.6 months (~1.4 years). With longer follow up, vorasidenib continued to demonstrate a clinically meaningful benefit compared to placebo.

The standard of care in this clinical setting is currently an active observation because there is no other therapeutic option for this population of young patients, and the only option consists of aggressive therapies (chemotherapy and radiotherapy) associated with neurocognitive effect and functional decline which aim is to postpone their use as long as possible. Radiographic progression is considered as a major driver of initiation of next therapy and thus its delay represents a clinical benefit for this patient population.

As IDH mutations are early genetic drivers of the disease, targeting IDH-mutant gliomas early in their development may delay the malignant transformation. Vorasidenib has shown to have a preferential activity in non-enhancing IDH-mutant gliomas than in subjects with enhancing Grade 3 tumours who experienced inferior outcomes (studies AG881-C-002 and AG120-881-C-001) and thus may represent a good candidate.

Although the disease similarity across populations in terms of similar biology, disease behaviour and clinical prognosis in adolescents with 'adult-type' IDH1/2 mutant low grade gliomas is endorsed, the similar vorasidenib exposures in adolescents >40 kg with proposed 40 mg QD and adolescents < 40 kg with the proposed 20 mg QD has not been demonstrated and thus, the recommendation of vorasidenib for patients weighing less than 40kg at a dose of 20 mg QD is not supported and will be further explored in the post authorisation setting through a PopPK study committed by the applicant (REC).

Overall, the safety profile of vorasidenib is mainly related to hepatotoxicity with grade ≥ 3 events at a common frequency and serious events that may occur as well. Nevertheless, all events resolved to grade 1 or baseline according to recommendations which are reported in the SmPC. Diarrhoea occurred frequently but were mainly low grade.

Uncertainties remained on TEAEs observed at a lower incidence in the pivotal study regarding events related to hepatotoxicity or other findings, therefore, additional data will be collected post authorisation. In addition, although non-clinical studies did not suggest any neurological events, uncertainties remain for the paediatric population since no paediatric patient >12 years received vorasidenib 40 mg. Finally, although ICH-E1 requirements are fulfilled, and given the potential treatment duration of several years, and the lack of characterization of the main metabolite AGI-69460, longer term safety data are lacking and will be provided in the post authorisation setting as per the long term follow up requested in the context of the RMP.

Toxic effects on reproductive organs were observed in rat studies, indicating potential infertility in males (degeneration of seminiferous tubules), and in females (vacuolation of ovarian interstitial cells). These effects are mentioned in SmPC section 4.4, 4.6 and 5.3 and impairment of male and female fertility is considered an important potential risk in the RMP and will be followed as a safety concern.

Based on available non-clinical data a carcinogenic risk including a risk for liver tumour formation cannot be excluded. Considering the unmet medical need and the clinical benefit of vorasidenib in the intended indication, it is considered acceptable to provide the result of the carcinogenicity studies post authorisation. The applicant has therefore committed to conduct and submit the results of a 2-year rat and a 6-month transgenic mouse carcinogenicity studies post-approval (PASS category 3 for carcinogenicity as reported in the RMP - see section 2.7.2 pharmacovigilance plan). Current carcinogenicity concerns and the missing results of carcinogenicity studies are mentioned in the SmPC sections 4.4 and 5.3 and in the RMP.

3.7.2. Balance of benefits and risks

The robustness of rPFS by BIRC results is not questioned and the magnitude of the effect observed is considered important and acceptable. The toxicity of vorasidenib appears manageable, and a number

of uncertainties on the safety profile of vorasidenib in astrocytoma and oligodendroglioma will be closely monitored and further characterised in the near future through relevant studies.

3.7.3. Additional considerations on the benefit-risk balance

Patient and healthcare provider engagement

A methodology of engaging with patient organisations at the start of evaluation of new MAAs has been agreed by CHMP (for more details see the dedicated process and FAQs document: https://www.ema.europa.eu/en/documents/other/chmp-early-contact-patient-and-healthcare-professional-organisations-process-and-faqs_en.pdf). In this context the CHMP invited healthcare professional societies as well as patient organisations to share their perspectives regarding the assessment of vorasidenib for the applied indication on behalf of its members. The response received from such organization are summarised below sharing their expectations:

- Related to the impact of vorasidenib in the natural history of early-stage IDH mutant lower (i.e. grade 2-3) gliomas with a prolongation of the time to malignant transformation and a delay to the initiation of further treatments (such as radio-chemotherapy),
- For a better seizure control, with improvement of quality of life
- For postponing the appearance of intense or debilitating symptoms of disease or avoiding the adverse effects of radiation or chemotherapy
- For showing evidence of efficacy and safety of new treatment in the paediatric population
- In case vorasidenib is administered in paediatric patients assess safety and efficacy first.
- Given the mechanistic cause of many symptoms caused by low-grade glioma (in other words, infiltration by the tumour), delayed tumour growth should lead to delayed symptoms or reduced symptom intensity.
- A delay to the initiation of further treatments (such as radio-chemotherapy), with favourable medical and socioeconomic consequences (reduced incidence of delayed radio- and chemotherapy-associated adverse events).

3.8. Conclusions

The overall benefit /risk balance of Voranigo is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Voranigo is not similar to Finlee and Spexotras within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Voranigo is favourable in the following indication:

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

are not in immediate need of radiotherapy or chemotherapy.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

New active substance status

Based on the CHMP review of the available data, the CHMP considers that vorasidenib is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0007/2022 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.