

A Phase IV, Prospective, Open Label, Multi-Centre Study of Vorasidenib in Indian Adult and Paediatric Participants 12 Years and Older with Grade 2 Astrocytoma and Oligodendroglioma with a Susceptible IDH1 or IDH2 Mutation following Surgery including Biopsy, Sub-Total Resection, or Gross Total Resection

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALK	Anaplastic Lymphoma Kinase
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CDSCO	Central Drugs Standard Control Organization
CDM	Clinical Data Management
CI	Confidence Interval
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DCGI	Drug Controller General of India
DCR	Disease Control Rate
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Forms
eGFR	Estimated Glomerular Filtration Rate
EOT	End of Treatment
FAS	Full Analysis Set
FLAIR	Fluid-Attenuated Inversion Recovery
GCP	Good Clinical Practice

HCG	Human Chorionic Gonadotropin
ICF	Informed Consent Form
ICH	International Council on Harmonization-Good Clinical Practice
IDH	Isocitrate Dehydrogenase
IEC	Institutional Ethics Committee
IUD	Intrauterine Device
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent to Treat
IV	Intravenous
IWRS	Interactive Web Response System
LAR	Legally Acceptable Representative
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
MeDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
PD	Progressive Disease
PFS	Progression Free Survival
PI	Principal Investigator
PPS	Per Protocol Set
PR	Partial Response
PT	Preferred Term
PTT	Partial Thromboplastin Time
QD	quaque die; everyday
RANO	Response Assessment in Neuro-Oncology
RBC	Red Blood Cell
RT-CT	Radiotherapy and/or Chemotherapy

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Stable Disease
SEC	Subject Expert Committee
SFU	Safety Follow-up
SOA	Schedule of Assessments
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Events
TESAE	Treatment Emergent Serious Adverse Events
TRAE	Treatment Related Adverse Events
ULN	Upper Limit of Normal
WBC	White Blood Cells
WHODD	WHO Drug Dictionary
WHO-UMC	World Health Organization- Uppsala Monitoring Centre
WOCBP	Women of Childbearing Potential

STUDY SYNOPSIS

Title	A Phase IV, Prospective, Open Label, Multi-Centre Study of Vorasidenib in Indian Adult and Paediatric Participants 12 Years and Older with Grade 2 Astrocytoma and Oligodendroglioma with a Susceptible IDH1 or IDH2 Mutation following Surgery including Biopsy, Sub-Total Resection, or Gross Total Resection
Protocol Number	SER-VOR-001
Phase	IV
Rationale	Vorasidenib is a dual inhibitor of isocitrate dehydrogenase-1 (IDH1) and isocitrate dehydrogenase-2 (IDH2). It is indicated for the treatment of adult and paediatric patients aged 12 years and older with Grade 2 astrocytoma or oligodendroglioma harbouring a susceptible IDH1 or IDH2 mutation, following surgical intervention including biopsy, subtotal resection, or gross total resection. In August 2025, Servier India received a positive recommendation from the Subject Expert Committee (SEC) under the Central Drugs Standard Control Organization (CDSCO) to import and market Vorasidenib tablets (10 mg and 40 mg) in India for this indication. The SEC granted a waiver for local Phase III trials, considering the drug's orphan status internationally and the unmet medical need in India. However, the committee mandated the conduct of a Phase IV interventional clinical trial in Indian patients and required submission of the protocol within three months of approval. This Phase IV study is therefore being conducted as part of the regulatory requirement to evaluate the safety and effectiveness of vorasidenib in Indian adults and paediatric patients (≥ 12 years) with Grade 2 IDH-mutant diffuse glioma (astrocytoma or oligodendroglioma) following surgery.
Study Design	This Phase IV, prospective, open-label, multi-centre clinical study is designed to evaluate the safety and effectiveness of vorasidenib in Indian adult and paediatric participants 12 years and older with grade 2 astrocytoma and oligodendroglioma with a susceptible IDH1 or IDH2 mutation. The primary objective of the study is to evaluate the safety of vorasidenib, with the key primary endpoint of analysing the incidence of Treatment Emergent Adverse Events (TEAEs). All participants with a confirmed diagnosis of Grade 2 Astrocytoma and Oligodendroglioma with a susceptible IDH1 Or IDH2 mutation following surgery including biopsy, sub-total resection, or gross total resection will undergo screening procedures within 28 days before enrollment. Upon enrolment, participants will begin treatment with oral vorasidenib once daily, starting on Cycle 1 Day 1 (C1D1). Each treatment cycle will last 28 days, with continuous daily dosing throughout the cycle. Participants will be treated for six cycles (with no planned inter cycle rest periods), unless discontinued earlier due to any adverse event, disease progression or death, TEAEs resulting in discontinuation, confirmed pregnancy, or withdrawal of consent. A window period of ± 3 days will be allowed for all Treatment visits. The End of Treatment (EOT) visit will be conducted within +3 days from the last study treatment dose of Cycle 6. The safety follow-up (SFU) visit will be conducted within 7 weeks from the last study treatment dose. Safety assessments will be conducted at each visit and will include ECGs, vital signs, physical examinations and laboratory tests. AE monitoring will be done throughout the study, especially the Adverse Event of Special Interest (AESI) of LFT derangement will be noted. Tumor assessments to evaluate the disease or the response to treatment will be performed as per RANO 2.0 Criteria at screening, C3 and at the C6/ EOT visit.

	Post Trial Access to Drug: Post-trial access to the investigational new drug will be provided by the Sponsor free of cost when recommended by the Investigator and approved by the Ethics Committee. Such access will be granted to subject till the drug demonstrates clinical benefit (even after completion of extension phase) for the subject as per the treating investigator. The subject or legal heir must provide written consent to continue post-trial use, and both the Investigator and the subject or legal heir must submit written declarations confirming that the Sponsor shall have no liability arising from post-trial use of the investigational product. Extension Phase: All participants who complete the study treatment will be invited to participate in an extension phase for a duration of up to 18 months following completion of the safety follow-up visit. The extension phase is non-interventional and observational in nature. Participants receiving post-trial access to vorasidenib may continue to be followed during the extension phase till 18 months post receipt of informed consent. Treatment provided under extension phase and post-trial access will be considered outside the interventional study period (refer Section 3.1.2).
Study Center(s)	Approximately 10 study centres across India
Objectives and Endpoints	
Objectives	Endpoints
PRIMARY	
1. To evaluate the safety of vorasidenib	1. Key Primary Endpoint: Incidence of Treatment Emergent Adverse events (TEAEs) 2. Co-Primary Endpoints: - Incidence of Treatment Emergent Serious Adverse events (TESAEs) - Incidence of AE of Special Interest (AESI) i.e. LFT derangement - Incidence of TEAEs leading to dose interruption, reduction or discontinuation - Incidence of TEAEs leading to death - Incidence of Treatment Related Adverse Events (TRAEs)
SECONDARY	
1. To evaluate the effectiveness of Vorasidenib	Response Rates as per RANO 2.0 Criteria
<u>Note:</u> - The severity of AEs will be assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 6.0. - Causality will be assessed using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) system.	
Study Population	The study will enrol a total of 15 participants from India aged 12 years and older with grade 2 astrocytoma or oligodendroglioma with a susceptible IDH1 or IDH2 mutation following surgery including biopsy, sub-total resection, or gross total resection.
Eligibility Criteria	Inclusion Criteria: 1. Participants willing to provide informed consent or assent (whichever applicable) and comply with protocol requirements

	2. Age ≥ 12 years at the time of enrolment 3. Histologically confirmed WHO Grade 2 Astrocytoma or Oligodendroglioma 4. Male or Non-Pregnant, Non-Lactating Female 5. Females of childbearing potential must be willing to use any one highly effective contraception method with null to minimal failure rate (either of non-hormonal IUDs, or Sexual abstinence or bilateral tubal occlusion or sterilization) during treatment with VORANIGO and for 3 months after the last dose; they must have a negative serum pregnancy test within 72 hours prior to the first dose of study drug. 6. Male patients with female partners of reproductive potential to use effective contraception during treatment with VORANIGO and for 3 months after the last dose. 7. VORANIGO is indicated for the treatment of adult and pediatric patients 12 years and older with Grade 2 astrocytoma or oligodendroglioma with a susceptible isocitrate dehydrogenase-1 (IDH1) or isocitrate dehydrogenase-2 (IDH2) mutation following surgery including biopsy, sub-total resection, or gross total resection 8. Have confirmed any type of IDH1 (IDH1 R132H/C/G/S/L mutation variants tested) or IDH2 (IDH2 R172K/M/W/S/G mutation variants tested) gene mutation status 9. Have adequate hepatic function as defined by: a. Serum total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN) unless considered due to Gilbert's disease after approval by the Medical Monitor, and b. Aspartate aminotransferase at or below ULN and alanine aminotransferase at or below ULN, and c. Alkaline phosphatase $\leq 2.5 \times$ ULN. 10. Planned to initiate vorasidenib as per approved label Exclusion criteria: 1. Any contraindications to vorasidenib treatment as per the latest approved India Prescribing Information (PI) 2. Prior or ongoing radiotherapy and/or chemotherapy (RT-CT) for glioma, including adjuvant or concurrent treatment. 3. Any condition deemed unfit as per the investigator
Study Intervention	All participants will receive an oral daily dose of vorasidenib as mentioned below: a. For adult participants: 40 mg orally once daily b. For paediatric participants (12 years of age and older): Dosage will be based on body weight: • ≥ 40 kg: 40 mg orally once daily • < 40 kg: 20 mg orally once daily Participants will undergo treatment for six consecutive cycles, each consisting of 28 days. Dosing will be continuous, with no planned inter-cycle rest periods.
Study Duration and Phases	The total study duration for a study participant will be approximately 8 months from the date of screening for the interventional phase of the study, followed by an extension phase of up to 18 months. The interventional study period includes Screening Phase, Treatment Phase and Safety follow up phase. The extension phase is observational in nature and is intended for long-term safety follow-up.

	Study Phases: <i>Screening phase:</i> Up to 28 days prior to Cycle 1 Day 1 <i>Treatment phase:</i> Up to 6 cycles (approximately 6 months) <i>Safety follow up phase:</i> 7 weeks from last study dose administration <i>Extension phase (Optional):</i> Up to 18 months after completion of the safety follow-up phase Note: <i>Treatment will be continued until completion of 6 cycles, unless discontinued earlier due to any treatment emergent adverse event, disease progression or death, TEAEs resulting in discontinuation, confirmed pregnancy, or withdrawal of consent.</i> <i>Participants demonstrating clinical benefit at the end of 6 cycles may continue treatment beyond six months, based on the Investigator's clinical judgment and with the participant's informed consent (refer Section 3.1.1).</i>
Statistical Analysis	
Sample Size Estimation	A total of 15 participants will be enrolled in the study. A formal power-based sample size calculation was not performed due to the rarity of Grade 2 astrocytoma and oligodendroglioma harbouring susceptible IDH1 or IDH2 mutations, particularly within the Indian population. Vorasidenib has demonstrated safety and effectiveness in global clinical studies, and this study is being conducted as a post-marketing, real-world evaluation to further characterize the safety profile of vorasidenib in Indian adult and paediatric participants (≥12 years) following surgical intervention. From a statistical perspective, a sample size of 15 participants allows for the detection of common adverse events (AEs) occurring at a rate of approximately 20% with a high probability (approximately 96%). Specifically, the probability of at least one AE when the true AE rate is 20% is given by: $P(\geq 1 \text{ AE}) = 1 - (1 - p)^n = 1 - (0.8)^{15} \approx 0.96$ In addition, if no AEs are observed in 15 participants, the upper bound of the confidence interval for the true AE rate depends on the method used. Using the exact binomial approach: - The one-sided 95% upper confidence bound is approximately 18.1% - The two-sided exact 95% confidence interval upper bound is approximately 21.8% This distinction is important for interpretation. The two-sided confidence interval is typically preferred for regulatory reporting; therefore, in the context of 0 observed events among 15 participants, the true AE rate cannot be ruled out to be as high as approximately 21.8%. Overall, this sample size is considered appropriate for a feasibility-driven, descriptive Phase IV safety study in a rare, molecularly defined population, and provides clinically meaningful bounds for post-marketing safety surveillance. This provides a clinically meaningful statistical boundary for post-marketing safety surveillance in this rare molecularly defined population. Therefore, the selected sample size of 15 participants is considered adequate to meet the primary objective of estimating the incidence of adverse events associated with vorasidenib in the real-world Indian clinical setting, while remaining feasible given the rarity of the target population. In pivotal trials of vorasidenib in adult and pediatric patients with Grade 2 IDH-mutant glioma, common adverse events (e.g., fatigue, headache, diarrhea, elevated liver enzymes) occurred at rates of approximately 15–40%, and Grade 3 or higher adverse events were

	reported in approximately 22–23% of patients, demonstrating that a 20% threshold aligns with observed clinical safety data.
Statistical Analysis Plan and Data Handling/Management	A Statistical Analysis Plan (SAP) will be prepared as a separate document and finalized before the database lock. Any deviation from the original statistical plan will be described and justified in the final report, as appropriate. The procedure for accounting for missing, unused, and spurious data will be included in the Statistical Analysis Plan. All statistical analysis will be conducted using SAS®, Version 9.4 or higher. Electronic Case Report Forms (eCRFs) will be used to collect information required for statistical analysis. The eCRF will be designed as per protocol and protocol amendment(s). CDM team will set up the study database/application as specified in Data Management Plan. Data will be cleaned through query generation and resolution. Medical coding, handling of external data etc. will be done as per the Data Management Plan. Medical coding will be done by using standard medical dictionaries like Med-DRA and WHODD.
Statistical Methods	The following analysis sets will be evaluated and used for the presentation of the data. Only subjects who sign informed consent will be included in the analyses: <u>Full Analysis Set (FAS)</u>: The Full Analysis Set will include all subjects who are enrolled into the study. The FAS will be the default analysis set for all effectiveness analyses. <u>Per-Protocol Set (PPS)</u>: The Per-Protocol Set will include all enrolled subjects from the Full Analysis Set who completed the study without major protocol violations and adhered sufficiently to key protocol requirements. The PPS will be used as a supportive analysis population to evaluate the consistency and robustness of effectiveness. <u>Safety Analysis Set</u>: The Safety Analysis Set will include all subjects who receive at least one dose of the study treatment, regardless of their protocol compliance. The safety analysis set will be the primary analysis set for all safety analyses.
Primary Analysis	<u>Key Primary Endpoint:</u> <i>Incidence of Treatment Emergent Adverse events (TEAEs)</i> <u>Co-Primary Endpoints:</u> <i>Incidence of Treatment Emergent Serious Adverse Events (TESAEs)</i> <i>Incidence of AE of Special Interest (AESI) i.e. LFT derangement</i> <i>Incidence of TEAEs leading to dose interruption, reduction or discontinuation</i> <i>Incidence of TEAEs leading to death</i> <i>Incidence of Treatment Related Adverse Events (TRAEs)</i> The primary endpoint and co-primary endpoints will be analysed by using safety analysis set. The incidence of TEAE will be reported as the number and percentage of subjects experiencing at least one TEAE overall and will be further tabulated by System Organ Class (SOC) and Preferred Term (PT) using MedDRA coding v28.1, 01SEP2025 or higher. For each SOC and PT, a subject will be counted only once, regardless of the number of occurrences, and the highest severity grade recorded will be used in the summary. Additional descriptive summaries will include TEAEs by severity level and by relationship to study treatment (related vs unrelated), as assessed by the investigator. Electrocardiograms (ECGs), vital signs, physical examination findings, and clinical laboratory test results will be analyzed descriptively. For ECGs, vital signs, and laboratory parameters, observed values and changes from baseline will be summarized by study visit using descriptive statistics. Values will also be classified relative to normal reference ranges, and the incidence of clinically significant abnormalities and worst post-baseline values will

	be summarized. Physical examination findings will be summarized descriptively, with abnormal findings tabulated by visit and by body system. Serious TEAEs, AESI, treatment-related TEAEs, and TEAEs leading to study drug discontinuation, dose modification, or interruption, death will also be tabulated separately. Adverse events will be coded according to the NCI CTCAE version 6.0 grading system.
Secondary Analysis	• <i>Response Rates as per RANO 2.0 Criteria</i> The Response Assessment in Neuro-Oncology for Low-Grade Glioma (RANO 2.0) criteria will be analyzed using the Full Analysis Set (FAS). The Response Assessment in Neuro-Oncology for Low-Grade Glioma (RANO 2.0) criteria will be used to evaluate radiographic tumor response and progression based on changes in MRI measurements [T1-weighted sequences (pre- and post-contrast) and T2/FLAIR sequences], with progression defined as a $\geq 25\%$ increase in lesion size or appearance of new lesions according to RANO 2.0 standards. Response outcomes (e.g., complete response, partial response, minor response, stable disease, progressive disease) will be summarized descriptively as the number and percentage of subjects in each category at prespecified timepoints. Response rates will be reported with exact confidence intervals. No formal hypothesis testing will be performed for RANO-based categories; results will support interpretation of treatment effect on imaging-based outcomes.
Ethics	This study will be conducted according to the principles of the Declaration of Helsinki, International Conference of Harmonization-Good Clinical Practices [ICH-GCP] and New Drug and Clinical Trials, 2019 and Indian regulatory laws governing biomedical research in human participants. Each institution will have an ethics committee approval before initiating the study. Participant's written informed consent/ assent (whichever applicable) will be taken prior to any study procedure being conducted.

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1 INTRODUCTION

This document is a protocol for a human research study. This study will be conducted according to the international standards of Good Clinical Practice (CFR Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations, and institutional research policies and procedures.

1.1 Background

Diffuse gliomas are primary brain tumors arising from glial cells and are a major cause of morbidity in young adults. Grade 2 gliomas—astrocytoma and oligodendroglioma—tend to be slow growing yet ultimately progressive and are now defined molecularly by IDH status in the WHO 2021 classification, with oligodendroglioma further requiring 1p/19q codeletion [2].

1.1.1 Epidemiology

Population-based registry data indicate that gliomas comprise roughly one quarter of primary brain and other CNS tumors in the United States, with overall malignant and non-malignant brain/CNS tumor incidence ~24–25 per 100,000; Grade 2 diffuse gliomas account for a minority of these but present disproportionately in younger adults [3].

Across large datasets, Grade 2 “low-grade” gliomas typically present between ages 20–45 and frequently with seizures; historical estimates place diffuse low-grade glioma incidence near 1 per 100,000 person-years, though exact rates vary by registry and classification era [4,5].

In India, national cancer registry infrastructure (ICMR-NCRP/PBCR) documents CNS tumor incidence broadly consistent with global patterns; GLOBOCAN 2022 shows India’s overall cancer burden without CNS tumors among top sites, underscoring the need for improved ascertainment of brain tumor subtypes in national reporting [6,7].

1.1.2 IDH1/ IDH2 Mutation Prevalence and Prognosis

IDH1/IDH2 mutations are the defining molecular feature of adult-type diffuse Grade 2 astrocytomas and oligodendrogliomas; oligodendroglioma requires IDH1/2 mutation plus 1p/19q codeletion [2].

Across cohorts and consensus reviews, the majority of Grade 2 diffuse gliomas harbor IDH mutations, with IDH1-R132H being the most frequent alteration; IDH mutation is consistently associated with improved survival relative to IDH-wildtype gliomas [8, 9, 10].

IDH-mutant gliomas (astrocytoma grades 2–4; oligodendroglioma grades 2–3) constitute the principal adult glioma subset occurring before age 50, reflecting distinct biology driven by the oncometabolite D-2-hydroxyglutarate and epigenetic dysregulation [11].

1.1.3 Treatment Modalities

Standard management begins with maximal safe resection, followed by observation or adjuvant therapy (radiotherapy ± temozolomide/PCV), tailored to molecular subtype, extent of resection, and clinical risk [9].

The INDIGO Phase 3 trial demonstrated that vorasidenib (40 mg daily) significantly prolonged progression-free survival (median 27.7 vs 11.1 months, HR 0.39) and delayed time to next intervention compared with placebo in treatment-naïve, post-surgical Grade 2 IDH-mutant glioma, supporting integration of targeted IDH inhibition in contemporary care algorithms [12, 13, 14].

1.2 Vorasidenib

Vorasidenib is an oral, brain-penetrant, dual mutant IDH1/IDH2 inhibitor that suppresses 2-HG production, aiming to reverse differentiation block and favourably alter tumor kinetics. Clinical evidence from INDIGO confirms disease-control benefit with a manageable safety profile, including hepatic transaminase elevations as the principal Grade ≥ 3 adverse event [12, 13].

1.3 Study Rationale

Given the high prevalence of IDH mutations in Grade 2 diffuse gliomas and their prognostic significance, targeted inhibition with vorasidenib offers a mechanism-based approach to delay progression and defer cytotoxic therapies that carry neurocognitive risks.

Servier India received a positive recommendation from the SEC (CDSCO) to import and market vorasidenib tablets (10 mg, 40 mg) for eligible patients ≥ 12 years with Grade 2 astrocytoma or oligodendroglioma. This Phase IV interventional study is being conducted as a condition of the marketing authorization approval.

This study is being conducted by Servier India Private Limited as part of this mandate.

2 STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
PRIMARY	
1. To evaluate the safety of vorasidenib	1. Key Primary Endpoint: Incidence of Treatment Emergent Adverse events (TEAEs) 2. Co-Primary Endpoints: • Incidence of Treatment Emergent Serious Adverse Events (TESAEs) • Incidence of AE of Special Interest (AESI) i.e. LFT derangement • Incidence of TEAEs leading to dose interruption, reduction or discontinuation • Incidence of TEAEs leading to death • Incidence of Treatment Related Adverse Events (TRAEs)
SECONDARY	
1. To evaluate the effectiveness of vorasidenib	• Response Rates as per RANO 2.0 Criteria
<u>Note:</u> a. The severity of AEs will be assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 6.0. b. Causality will be assessed using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) system.	

3 STUDY DESIGN

3.1 General Design

This Phase IV, prospective, open-label, multi-centre clinical study is designed to evaluate the safety and effectiveness of vorasidenib in Indian adult and paediatric participants 12 years and older with grade 2 astrocytoma or oligodendroglioma with a susceptible IDH1 or IDH2 mutation.

A total of 15 participants will be enrolled in the study.

All participants with a confirmed diagnosis of Grade 2 Astrocytoma or Oligodendroglioma with a Susceptible IDH1 or IDH2 mutation will undergo screening procedures within 28 days before enrollment. Upon enrolment, participants will begin treatment with oral vorasidenib once daily starting on Cycle 1 Day 1 (C1D1). Adult participants will receive vorasidenib 40 mg orally once daily. For paediatric participants (12 to <18 years), the dose will be weight-based: those weighing ≥ 40 kg will receive 40 mg orally once daily, while those weighing < 40 kg will receive 20 mg orally once daily.

Each treatment cycle will last 28 days, with continuous daily dosing throughout the cycle and no planned intercycle rest periods. Participants will be treated for six cycles, unless discontinued earlier due to any treatment emergent adverse event, disease progression or death, TEAEs resulting in discontinuation, confirmed pregnancy, or withdrawal of consent. A window period of ± 3 days will be allowed for all Treatment visits. The End of Treatment (EOT) visit will be conducted within +3 days from the last study treatment dose of Cycle 6. The Safety follow-up (SFU) visit will be conducted within 7 weeks from the EOT.

Safety assessments will be conducted at each visit and will include ECGs, vital signs, physical examinations and laboratory tests. AE monitoring will be done throughout the study, especially the Adverse Event of Special Interest (AESI) of LFT derangement will be noted. Tumor assessments to evaluate the disease or the response to treatment will be performed as per RANO 2.0 Criteria at multiple visits as indicated in schedule of assessments.

Participants demonstrating clinical benefit may receive Post Trial Access to vorasidenib, to continue treatment beyond six cycles at the investigator's discretion (refer [Section 3.1.1](#)).

All participants who complete the study treatment will be invited to participate in a non-interventional extension phase (refer [Section 3.1.2](#)) for a duration of up to 18 months following completion of the safety follow-up visit.

3.1.1 Post Trial Access to Drug

Participants responding to the study drug at the end of the 6 cycles may be provided the study drug till progression or TEAEs requiring dose discontinuation, as per Investigator's discretion and the package insert (label in India).

Post-trial access to the investigational new drug may be provided by the Sponsor free of cost when recommended by the Investigator and approved by the Ethics Committee. Such access may be granted only if no alternative therapy is available for the indication and the drug has demonstrated clinical benefit

for the subject. Post trial access, if approved, will continue until disease progression or unacceptable adverse events (as deemed by the investigator).

The subject or legally acceptable representative (LAR) must provide written consent to continue post-trial use, and both the Investigator and the subject or legal heir must submit written declarations confirming that the Sponsor shall have no liability arising from post-trial use of the investigational product. Participants qualifying for continued treatment beyond the initial six cycles must complete all protocol-defined assessments and study requirements—including the SFU evaluations—prior to initiating any subsequent cycles of therapy.

3.1.2 Extension Phase

All participants who complete the study treatment will be invited to participate in the extension phase, which will be non-interventional and observational in nature.

This extension phase will be for a maximum duration of 18 months and will:

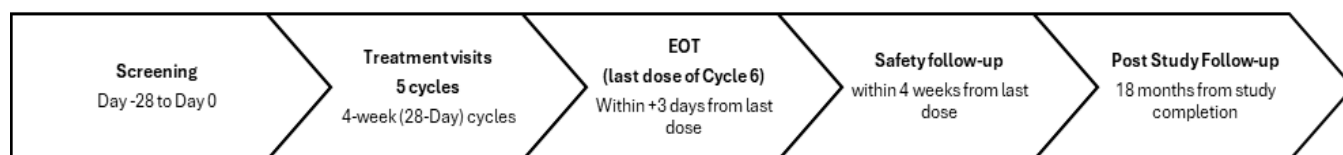
- Evaluate effectiveness & response rates
- Assess adverse events

Treatment provided under post-trial access will be considered outside the interventional study period.

Separate written informed consent will be obtained from participants or their legally acceptable representatives (LAR) prior to participation in the extension phase. During the extension phase, participants will continue to receive routine clinical care. Liver function tests (LFTs) are commonly performed monthly in clinical practice for patients receiving the investigational product and may be conducted accordingly, at the Investigator's discretion. Tumour assessments (e.g., MRI) may be performed approximately every 6 months, as clinically indicated. These evaluations are conducted independent of study requirements and are not considered protocol-mandated procedures.

Data collected during the extension phase will not be considered part of the primary interventional study analyses. The Clinical Study Report (CSR) for this study will be finalized based on data collected up to the end of the safety follow-up phase. Data from the extension phase may be reported separately or included as an addendum to the CSR, as applicable.

Figure 1 Study Design



3.2 Study Procedures

The participants will undergo a comprehensive physical examination and appropriate laboratory investigations to confirm eligibility prior to enrolment. Fifteen eligible participants will be enrolled in the study after providing informed consent.

The study will be conducted in accordance with the Schedule of Assessments (SOA) ([Appendix 1](#)). The SOA provides an indicative overview of the tests and evaluations to be performed during the various phases of the study. Additional tests and procedures may be performed based on individual participant needs, at the Investigator's discretion. For detailed guidance on study procedures and specific assessment methods, refer to the relevant subsections within [Section 3.3](#) and [Section 4](#).

3.2.1 Screening Phase (Day -28 to Day 0)

The following study procedures must be completed in the screening phase (Day -28 to Day 0) to ensure participant eligibility:

- Written informed consent/ assent (as applicable)
- Eligibility criteria assessment
- Medical/ surgical history and concomitant illnesses
- Demographics
- IDH1 or IDH2 mutation analysis
- Enrolment
- Prior medications
- Concomitant medications
- AE monitoring
- Height and weight
- Vital signs
- Physical examination including neurological exam (Comprehensive)
- 12-lead ECG
- Pregnancy tests (for WOCBP only)
- Hematology and Serum chemistry
- Evaluate Disease - Tumor Assessments (MRI Brain)
- LFT Monitoring
- Coagulation studies

3.2.2 Treatment Phase Visits

The study procedures to be completed at each visit in the treatment phase are shown below.

3.2.2.1 Cycle 1 Day 1 (C1D1), Cycle 2 Day 1 (C2D1), Cycle 3 Day 1 (C3D1), Cycle 4 Day 1 (C4D1), Cycle 5 Day 1 (C5D1), Cycle 6 Day 1 (C6D1)

- Concomitant medications
- AE monitoring
- Weight
- Vital signs
- Physical examination (refer [Section 4.1.2](#))

- 12-lead ECG
- Pregnancy tests (for WOCBP only)
- Hematology and serum chemistry
- Evaluate Disease/ Response - Tumor Assessments (MRI Brain) – C3D1 and C6D1 only
- LFT Monitoring
- Coagulation studies
- Vorasidenib administration
- Study diary and study medication accountability

3.2.2.2 Cycle 1 Day 8 (C1D8), Cycle 1 Day 15 (C1D15), Cycle 1 Day 22 (C1D22), Cycle 2 Day 15 (C2D15), Cycle 3 Day 15 (C3D15) and Cycle 4 Day 15 (C4D15)

- Concomitant medications
- AE monitoring
- LFT Monitoring – C1D15 and C2D15 only
- Coagulation studies – C1D15 and C2D15 only
- Vorasidenib Administration
- Study diary and Study medication accountability

3.2.3 End of Treatment Visit

An End of Treatment (EOT) visit is required within +3 days following the final dose of study treatment in the treatment phase.

The procedures involved are as below:

- Concomitant medications
- AE monitoring
- Height and Weight
- Vital signs
- Physical examination (refer [Section 4.1.2](#))
- 12-lead ECG
- Pregnancy tests (for WOCBP only)
- Hematology and Serum chemistry
- Evaluate Response - Tumor Assessments (MRI Brain) at either C6/ EOT, as per Investigator's discretion
- LFT Monitoring
- Coagulation Studies
- Vorasidenib Administration
- Study diary and Study medication accountability

3.2.4 Safety Follow-up Visit

A Safety Follow-up (SFU) visit is required within 7 weeks from the final dose of study treatment in the treatment phase.

The procedures involved are as below:

- Concomitant medications
- AE monitoring

3.2.5 Extension Phase

Assessments during the extension phase may include:

- Concomitant medications
- AE monitoring
- LFT – Monthly
- Evaluate response rate through 2D MRI every 6 months as per RANO 2.0 criteria

3.3 Study Assessments

3.3.1 Demographics

Demographic information including gender, date of birth (age), race, and ethnicity, and relevant lifestyle habits will be collected for all participants during screening according to applicable regulations.

3.3.2 Medical/ Surgical History and Concomitant Illness

A complete medical and surgical history, including the primary histological subtype of glioma, primary site of disease, and the date of confirmation of the histologic diagnosis of the underlying glioma, will be obtained during screening. The medical history will include all relevant past medical history and current medical conditions.

Preexisting conditions present at the time when informed consent is taken till the time of first dosing will be regarded as medical history but considered ongoing (concomitant).

Illnesses first occurred or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF.

3.3.3 Prior and Concomitant Medication & Procedures

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the participant over the counter. Concomitant medication is not provided by the sponsor. At each study visit, participants will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

Participant's prior medications— including alternative or supplemental therapies and procedures— taken within 4 weeks (28 days) prior to C1D1 will be recorded in the eCRF.

3.3.4 IDH1/ IDH2 Mutation Analysis

A banked tumor sample (preferably from the most recent surgery) or fresh tumor biopsy (if banked tumor sample is not available) is required to confirm IDH1 gene mutation status and IDH2 gene mutation status. Samples will be analyzed by an accredited laboratory as part of the subject's eligibility for enrollment.

4 CRITERIA FOR EVALUATION

4.1 Safety Assessments

4.1.1 Vital Signs, Weight and Height

Assessment of vitals: body temperature, pulse, respiratory rate, systolic and diastolic blood pressure. Any clinically significant changes in the vitals as compared to the baseline parameters, will be reported as AEs and duly recorded in the eCRF.

The actual dose will be calculated based on the body weight on the scheduled day of dosing or the day before it. Height will only be measured at the first visit.

4.1.2 Physical Examination

A comprehensive physical examination will be conducted and should include assessment of major body systems, including but not limited to the skin, musculoskeletal system, gastrointestinal system, respiratory system, cardiovascular system, central nervous system, urogenital system, ear/nose/throat (ENT), and lymphatic system.

A limited physical examination may be performed at subsequent visits based on clinical judgment. This should focus on specific body systems or organs relevant to ongoing safety concerns, reported symptoms, or adverse events (e.g., respiratory and gastrointestinal systems in the case of cough or diarrhea).

Documentation of the physical examination must be maintained in the eCRF at the study site. Any clinically significant abnormalities identified during the study should be evaluated by the investigator. Based on clinical judgment, the investigator may initiate appropriate medical management and/or refer the participant to a qualified healthcare provider for further evaluation or treatment.

4.1.3 Electrocardiogram (ECG)

The 12-lead ECGs are to be obtained at timepoints mentioned in the SOA ([Appendix 1](#)).

4.1.4 Safety Laboratory Assessments

Laboratory tests, including pregnancy tests (for WOCBP only), haematology, serum chemistry, and other parameters, will be performed during safety assessments as per the SOA. Any laboratory test result considered by the investigator to be clinically significant should be considered an AE (clinically significant AEs include those that require an intervention).

The following laboratory parameters will be evaluated by the Investigator:

Pregnancy Test: All women of reproductive potential must have a negative pregnancy test to be eligible. A serum β -hCG pregnancy test will be performed at screening and confirmed negative within 72 hours prior to study treatment administration. A urine pregnancy test will be conducted on C1D1 and on Day 1 of each subsequent cycle, with a confirmed negative result prior to dosing. Urine pregnancy test should be conducted at EOT.

Hematology: Hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count and differential (% neutrophils, % bands) and platelet count

Chemistry: Sodium, potassium, calcium, magnesium, phosphorus, albumin, glucose, blood urea nitrogen (BUN)/urea, creatinine, uric acid and lactate dehydrogenase (LDH).

Liver Function Tests (LFTs): Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, and serum albumin.

Coagulation Studies: aPTT, prothrombin time and INR.

All blood samples for laboratory tests must be drawn prior to administration of study drugs. All samples will be used only for the tests specified and destroyed after those tests are completed or at the end of the study, as applicable.

4.1.5 Adverse Events

Each participant will be evaluated by the investigator or a qualified designee for the presence of new or worsening adverse events, as outlined in the SOA. These assessments will be conducted at scheduled visits and may occur more frequently if clinically indicated. Adverse events will be graded and recorded according to NCI CTCAE (Version 6.0) during the study and follow-up.

Requirements for collecting, recording, and reporting of AEs are described in [Section 8](#). Each participant will be evaluated from the time of signing of informed consent form till the SFU.

4.2 Effectiveness Assessments

4.2.1 Tumor Response Evaluation

Tumor response evaluation (MRI Brain) will be performed at Screening, C3D1 and at C6D1/EOT, as per Investigator's discretion. MRI scans will be submitted for central, independent radiologic assessment, which will be performed by qualified central reviewers blinded to clinical information, in accordance with the modified RANO-LGG 2.0 criteria. Central review assessments will be used to support consistency and standardization of tumor response evaluations across study sites.

All tumor response data will be captured in the electronic case report form (eCRF), and source documentation will be maintained to support all assessments.

At Screening, MRI scans obtained as part of standard of care are preferred to include 2D T1-weighted MRI pre- and post-contrast enhancement, 2D T2-weighted MRI, and 2D fluid-attenuated inversion recovery (FLAIR) scans, or may be performed in accordance with the Investigator's routine treatment practice. Where feasible, similar MRI sequences should preferably be used for subsequent assessments to allow for consistent longitudinal evaluation. MRI images obtained will be transferred to the central imaging vendor in accordance with the study imaging manual.

- Patients must have at least one **measurable non-enhancing lesion** identified on MRI images. Any contrast enhancement, if present, must be minimal, non-nodular, and non-measurable, consistent with imaging characteristics of low-grade gliomas.

- If the most recent MRI scan was obtained as part of routine clinical care within 28 days (± 7 days) prior to study entry, it may be used as the Screening scan, provided the image quality and sequences are sufficient for assessment in accordance with the protocol and applicable RANO criteria.
- In addition, if available, up to three pretreatment (historical) MRI scans obtained as part of standard of care prior to Screening may be submitted.

Central Imaging Review and Data Handling:

Radiological assessment of tumour response will be performed using Response Assessment in Neuro-Oncology (RANO) 2.0 criteria for low-grade gliomas. To ensure consistency and minimise inter-observer variability across participating sites, imaging evaluations will be conducted through a centralised review process coordinated by a designated central imaging review facility.

Participating sites will perform MRI scans as per standard institutional practice, ensuring inclusion of, at a minimum, T1-weighted sequences (pre- and post-contrast) and T2/FLAIR sequences. Wherever feasible, imaging acquisition parameters should be kept consistent across timepoints for each participant. Baseline imaging will be defined as the most recent MRI performed within 28 days prior to initiation of study treatment. Subsequent assessments will be conducted at protocol-defined timepoints (e.g., Cycle 3, Cycle 6, and end of treatment), and additional scans will be performed in the extension phase at 6-month intervals till completion of therapy with vorasidenib.

All imaging data will be shared and transferred through a secure, access-controlled electronic platform. The selected platform will comply with applicable data protection regulations and institutional policies, and access will be restricted to authorised study personnel involved in image review and data management.

Prior to transfer, all imaging data will be anonymised at the site level in accordance with applicable regulatory requirements. Direct patient identifiers (including name, medical record number, and date of birth) will be removed or masked, and each dataset will be labelled using a unique study-specific subject identification number.

Central review will be performed by qualified neuroradiologists with experience in neuro-oncology imaging. Two independent reviewers will assess each time point, and tumour response will be categorised as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) based on RANO 2.0 criteria.

5 PARTICIPANT SELECTION AND WITHDRAWAL

5.1 Study Population

Participants who meet all the inclusion and none of the exclusion criteria will be enrolled in this trial:

Inclusion Criteria:

1. Participants willing to provide informed consent or assent (whichever applicable) and comply with protocol requirements
2. Age ≥ 12 years at the time of enrolment
3. Histologically confirmed WHO Grade 2 Astrocytoma or Oligodendroglioma
4. Male or Non-Pregnant, Non-Lactating Female
5. Females of childbearing potential must be willing to use any highly effective contraception method with null to minimal failure rate (either of non-hormonal IUDs, and/or Sexual abstinence and/or bilateral tubal occlusion or sterilization) during treatment with VORANIGO and for 3 months after the last dose; they must have a negative serum pregnancy test within 72 hours prior to the first dose of study drug.
6. Male patients with female partners of reproductive potential to use effective contraception during treatment with VORANIGO and for 3 months after the last dose.
7. VORANIGO is indicated for the treatment of adult and pediatric patients 12 years and older with Grade 2 astrocytoma or oligodendroglioma with a susceptible isocitrate dehydrogenase-1 (IDH1) or isocitrate dehydrogenase-2 (IDH2) mutation following surgery including biopsy, sub-total resection, or gross total resection
8. Have confirmed any type of IDH1 (IDH1 R132H/C/G/S/L mutation variants tested) or IDH2 (IDH2 R172K/M/W/S/G mutation variants tested) gene mutation status
9. Have adequate hepatic function as evidenced by:
 - a. Serum total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN) unless considered due to Gilbert's disease after approval by the Medical Monitor, and
 - b. Aspartate aminotransferase at or below ULN and alanine aminotransferase at or below ULN, and
 - c. Alkaline phosphatase $\leq 2.5 \times$ ULN.
10. Planned to initiate vorasidenib as per approved label

Exclusion criteria:

1. Any contraindications to vorasidenib treatment as per the latest approved India Prescribing Information (PI)
2. Prior or ongoing radiotherapy and/or chemotherapy (RT-CT) for glioma, including adjuvant or concurrent treatment.

3. Any condition deemed unfit as per the investigator

5.2 Study Withdrawal, Removal, and Replacement of Participants

Participants have the right to withdraw from the study at any time for any reason. A participant's withdrawal from treatment or the study will not jeopardize the relationship with their healthcare providers or affect their future care. This decision must be recorded in writing by the study site.

Should a participant decide to withdraw, the date and primary reason for discontinuation or withdrawal must be recorded in the appropriate section of the electronic case report form (eCRF) and all efforts will be made to complete and report final study observations as thoroughly as possible.

In the event a participant is withdrawn from study treatment or the study, the Medical Monitor must be informed. If there is a medical reason for withdrawal, the participant will remain under the supervision of the Investigator until satisfactory health status has been restored.

Participants who discontinue early from the study will be asked to return to the study site within 1 week from the last administration of study drug to complete assessments at the withdrawal visit intended to document the reason for withdrawal/ discontinuation, assess safety, and collect any remaining study data. Safety assessments will be conducted as per the EOT of the applicable SOA ([Appendix 1](#)).

Once a participant is withdrawn from the study, the participant must not re-enter the study.

5.2.1 Withdrawal from the Study

Participants will be terminated from the study for the following reasons:

- Death
- Withdrawal of consent: at any time, a participant's participation in the study may be terminated at their request or on the basis of the investigator's clinical judgment. The reason for participant withdrawal will be noted on the eCRF
- Treatment failure
- TEAEs leading to discontinuation
- Disease progression
- Interruption of vorasidenib treatment >28 days (refer [Section 6.3.1](#))
- Confirmed pregnancy - for female participants only (study therapy should be immediately interrupted based upon a positive urinary hCG test, and permanently discontinued if confirmed by a serum β -hCG test)
- Lost to follow-up: the participant stopped coming for visits and study personnel were unable to contact the participant
- Note: In cases in which the participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (telephone calls, letter to the participant's last known mailing address, or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Protocol violation: non-adherence to study treatment regimen or protocol requirements
- Sponsor termination of the study (refer [Section 6.3.2](#))

If participants are terminated from the study because of sponsor decision, sponsor will continue to provide drug to participants who are benefiting from treatment.

For participants enrolled and who received at least one treatment and voluntarily withdraw or are withdrawn from the study early at the discretion of the investigator, an attempt should be made to perform the EOT visit. Participants evaluable for the primary safety endpoint who are withdrawn from the study will not be replaced.

For participants who withdraw from treatment because of an AE, every effort must be made to perform protocol-specified EOT procedures at the withdrawal visit (refer [Section 3.2.3](#)).

For participants enrolled (screened and meeting all eligibility criteria) but withdrawn from the study before receiving treatment on C1D1, no further examinations will be required. These participants will be considered dropouts.

5.2.2 Early Study Termination

Additionally, the sponsor may stop the study at any time for safety, regulatory, legal, or other reasons aligned with Good Clinical Practice (GCP). This study may be terminated at the discretion of the sponsor or any regulatory agency.

An investigator may elect to discontinue or stop the study at their study site for any reason, including safety or low enrolment.

6 STUDY TREATMENTS

Vorasidenib will be provided as 10-mg and 40-mg strength tablets to be administered orally. All study drugs are for investigational use only and are to be used only within the context of this study. All study drug products will be supplied by the Sponsor.

6.1 Study Drug Administration

All participants will receive an oral daily dose of vorasidenib as mentioned below:

- a. For adult participants: 40 mg orally once daily
- b. For paediatric participants (12 years of age and older): Dosage will be based on body weight:
 - ≥ 40 kg: 40 mg orally once daily
 - < 40 kg: 20 mg orally once daily

Participants will undergo treatment for six consecutive cycles, each consisting of 28 days. Dosing will be continuous, with no planned intercycle rest periods.

Subjects should be instructed to take their daily dose at approximately the same time each day. Each dose should be taken with a glass of water and consumed over as short a time as possible. Subjects should be instructed to swallow tablets whole and to not chew the tablets. Each daily dose should be taken after at least 2 hours of fasting (water is allowed). Food intake should be avoided for at least 1 hour after study drug administration. If the subject forgets to take the daily dose, then they should take their dose within 6 hours after the missed dose. If more than 6 hours have elapsed, then that dose should be omitted, and the subject should resume treatment with the next scheduled dose.

For further details and final guidance and information of study intervention administration, dispensing, handling, and storage, Investigators or study personnel are instructed to refer to the recent approved version of vorasidenib label.

6.2 Dose Modifications

For any AE, including AEs not specifically mentioned in [Table 2](#), the Investigator may decide to interrupt or modify the dose of vorasidenib based on clinical judgement. These decisions should be discussed with the Medical Monitor before implementation if feasible. The first dose reduction level will be from 40 mg QD to 20 mg QD, and if necessary, a second dose reduction from 20 mg QD to 10 mg QD will be permitted on study for management of AEs ([Table 2](#)). Reescalation may be allowed with approval from the Medical Monitor.

Table 1 Recommended Vorasidenib Dosage Reductions for Adverse Reactions

Dosage Reduction	Recommended Dose and Schedule
<i>Adults and Pediatric patients 12 years and older weighing at least 40 kg</i>	
First	20 mg once daily
Second	10 mg once daily
<i>Adults and Pediatric patients 12 years and older weighing less than 40 kg</i>	
First	10 mg once daily
Permanently discontinue vorasidenib in patients unable to tolerate 10 mg once daily.	

Dose interruptions up to 28 days will be permitted at the discretion of the Investigator in consultation with the Medical Monitor for reasons including management of AEs and for mitigating circumstances (e.g., planned procedures).

If the subject cannot resume study treatment within 28 days, the subject should be discontinued from study medication; exceptions may be made in consultation with the Medical Monitor. If study treatment is discontinued, the subject will complete the EOT and Follow-up visits.

An interruption in study treatment is recommended for subjects who require a minor surgical procedure (e.g., tooth extraction) during the study period. Study drug should be interrupted 24 to 48 hours before the surgery and resumed 24 to 48 hours after the surgery is completed.

6.2.1 Dose Modifications due to AEs

Table 2 includes dose hold and modification guidelines for vorasidenib to manage AEs during study treatment

Table 2 Vorasidenib Dose Modification Guidelines for Adverse Reaction

Adverse reaction	Severity ^a	Management and Dosage Modifications
Hepatotoxicity (Elevation of ALT or AST)	Grade 1 ALT or AST increase > ULN to 3 x ULN <i>without</i> concurrent total bilirubin >2 x ULN	Continue vorasidenib at current dose. Monitor liver laboratory tests weekly until recovery to <Grade 1.
	Grade 2 ALT or AST >3 to 5 X ULN <i>without</i> concurrent total bilirubin >2 X ULN	<u>First occurrence:</u> Withhold vorasidenib until recovery to ≤grade 1 or baseline. - Recovery in ≤28 days, resume at the same dose. - Recovery in >28 days, resume vorasidenib at reduced dose (<i>see Table 1</i>). <u>Recurrence:</u> Withhold vorasidenib until recovery to ≤grade 1 or baseline, and resume vorasidenib at reduced dose (<i>see Table 1</i>).
	Grade 3 ALT or AST >5 to 20 X ULN <i>without</i> concurrent total bilirubin >2 X ULN	<u>First occurrence:</u> Withhold vorasidenib until recovery to ≤grade 1 or baseline. - Recovery in ≤28 days, resume vorasidenib at reduced dose (<i>see Table 1</i>). - If not recovered in ≤28 days, permanently discontinue vorasidenib <u>Recurrence:</u> Permanently discontinue vorasidenib.
	Grade 2 or 3 Any ALT or AST >3 to 20 X ULN <i>with</i> concurrent total bilirubin >2 X ULN	<u>First occurrence:</u> Withhold vorasidenib until recovery to ≤grade 1 or baseline. Resume vorasidenib at reduced dose (<i>see Table 1</i>). <u>Recurrence:</u> Permanently discontinue vorasidenib.
	Grade 4 Any ALT or AST >20 X ULN	Permanently discontinue vorasidenib.

Adverse reaction	Severity ^a	Management and Dosage Modifications
Other Adverse Reactions	Grade 3	<u>First occurrence:</u> Withhold vorasidenib until recovery to ≤Grade 1 or baseline. • Resume vorasidenib at reduced dose (see Table I). <u>Recurrence:</u> Permanently discontinue vorasidenib.
	Grade 4	Permanently discontinue vorasidenib.
<u>Abbreviations:</u> ALT= Alanine Aminotransferase; AST= Aspartate Aminotransferase; ULN = Upper Limit of Normal ^a Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 6.0.		

6.3 Study Drug Accountability

Accountability for the study treatment at the study site is the responsibility of the Investigator. The Investigator will ensure that the study treatment is used only in accordance with this protocol. Where allowed, the Investigator may choose to assign drug accountability responsibilities to a pharmacist or other appropriate individual.

The Investigator or delegate will maintain accurate drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each participant, and return to Servier India Private Limited/ designee (or disposal of the drug, if approved by Servier India Private Limited). These records will adequately document that the participants were provided the doses as specified in the protocol and should reconcile all study treatment received from Servier India Private Limited. Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and participant numbers. The Sponsor/designee will review drug accountability at the site on an ongoing basis during monitoring visits.

Study treatment must not be used for any purpose other than the present study. Study treatment that has been dispensed to a participant and returned unused must not be re-dispensed to a different participant.

Participants will receive instructions for home administration of study treatment along with a diary to record the date and time of each dose, as well as the number of tablets taken.

All unused and used study treatment should be retained at the site until they are inventoried and verified by study site personnel and/or the study monitor. All used, unused, or expired study treatment will be returned to Sponsor/designee or if authorized, disposed of at the study site per the site's Standard Operating Procedures (SOPs), and documented. All material containing vorasidenib will be treated and disposed of as hazardous waste in accordance with governing regulations.

6.4 Study Drug Compliance Monitoring

On Day 1 of each treatment cycle, participants will receive the appropriate number of sponsor-packaged, labelled bottles of vorasidenib to cover 4 weeks of dosing. Alternatively, they may be provided with enough medication to last until their next study visit. Participants will be instructed to return all bottles—

used, unused, or empty—at the start of the next cycle or at their next visit to assess compliance. The number of bottles dispensed will also account for the applicable visit window at that point in the study.

Participants will receive instructions for home administration of vorasidenib along with a diary to record the date and time of each dose, as well as the number of tablets taken.

6.5 Prohibited and Concomitant Therapy

Certain concomitant medications may significantly alter the pharmacokinetics of vorasidenib or impact the effectiveness of co-administered drugs. Concomitant medication use during the study should therefore be managed in accordance with the approved label for vorasidenib.

6.5.1 Prohibited Concomitant Medications

The following medications are prohibited:

- Anticancer therapy other than the treatment outlined in the protocol is not permitted while subject is receiving study drug. If alternative therapy is required for treatment of the subject's disease, the subject should be discontinued from the study treatment.
- Co-administration of vorasidenib with **strong CYP1A2 inhibitors** is prohibited because these agents can substantially increase vorasidenib plasma concentrations.
- Likewise, vorasidenib may reduce the plasma concentrations and therapeutic effect of **CYP2C19 and CYP3A4 substrates with a narrow therapeutic index**; therefore, concomitant use of such agents is not permitted.

6.5.2 Concomitant Therapy to be Avoided or Used with Caution

The following medications are to be avoided or used with caution:

- **Moderate CYP1A2 inducers** may lower vorasidenib plasma concentrations and potentially reduce its therapeutic efficacy; alternative therapies should be considered whenever possible.
- Vorasidenib may also decrease exposure to sensitive **CYP3A4 substrates** lacking a narrow therapeutic index, and these medications should be used cautiously with consideration of alternatives.

6.5.3 Allowed Concomitant Therapy

Medications and treatments other than those specified above are permitted during the study. All intercurrent medical conditions and complications of the underlying malignancy will be treated at the discretion of the Investigator according to acceptable local standards of medical care.

Participants should receive analgesics, antiemetics, anti-infectives, antipyretics, blood products, and any other best supportive care measures (excluding anticancer therapy) as necessary, assuming no drug interaction potential.

Therapeutic drug monitoring (TDM) and seizure-medication–related assessments should be performed at the discretion of the Investigator, based on the patient's clinical condition, concomitant antiepileptic medications, and standard medical practice.

6.5.3.1 Neutropenia Therapeutics

Growth factors (granulocyte colony-stimulating factor, granulocyte-macrophage colony stimulating factor) can be used to support participants who have developed dose-limiting Grade 4 neutropenia or Grade 3 neutropenia with fever and/or infection. The use of erythropoiesis stimulating agents is permitted according to the American Society of Clinical Oncology Guidelines.

6.5.3.2 Steroids

A physiologic dose of steroids (e.g., 10 mg/day prednisone or equivalent) is permitted for medical conditions not related to glioma. The use of chronic steroids to treat an underlying medical condition that is not malignancy should be reviewed by the Medical Monitor. The dose and type of all corticosteroids administered for the 5 days before each MRI are to be reported in the subject dosing diary for all subjects.

6.5.4 Contraception

Women of childbearing potential (WOCBP) are defined as those who have experienced menarche, have not undergone sterilization (bilateral tubal ligation, bilateral salpingectomy, or total hysterectomy), and are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea with no identified cause other than menopause).

A sterile male is defined as one for whom azoospermia has been previously demonstrated in a semen sample examination as definitive evidence of infertility. Males with known low sperm counts (consistent with sub-fertility) are not to be considered sterile for purposes of this study.

Women of childbearing potential (WOCBP) and male participants who are sexually active with partners of childbearing potential must use effective contraception, as deemed appropriate by the Investigator and in accordance with the approved product label, from the start of the screening period until at least 3 months after the last dose of study drug.

Participants should discuss with the Investigator regarding the discontinuation of contraception after the above time point. Periodic abstinence, safe period contraception, and withdrawal are not acceptable methods of contraception.

6.5.5 Use in Nursing Women

It is unknown whether vorasidenib and its metabolites are excreted in human milk. No studies in animals have been conducted to evaluate the excretion of vorasidenib and its metabolites in milk. A risk to the newborns/infants cannot be excluded.

7 STATISTICAL PLAN

A Statistical Analysis Plan (SAP) will be prepared as a separate document and finalized before the database lock. Any deviation from the original statistical plan will be described and justified in the final report, as appropriate. The procedure for accounting for missing, unused, and spurious data will be included in the Statistical Analysis Plan. All statistical analysis will be conducted using SAS®, Version 9.4 or higher.

Electronic Case Report Forms (eCRFs) will be used to collect information required for statistical analysis. The eCRF will be designed as per protocol and protocol amendment(s). CDM team will set up the study database/application as specified in Data Management Plan. Data will be cleaned through query generation and resolution. Medical coding, handling of external data etc. will be done as per the Data Management Plan. Medical coding will be done by using standard medical dictionaries like Med-DRA and WHODD.

The following analysis sets will be evaluated and used for the presentation of the data. Only subjects who sign informed consent will be included in the analyses:

Full Analysis Set (FAS): The Full Analysis Set will include all subjects who are enrolled into the study. The FAS will be the default analysis set for all effectiveness analyses.

Per-Protocol Set (PPS): The Per-Protocol Set will include all enrolled subjects from the Full Analysis Set who completed the study without major protocol violations and adhered sufficiently to key protocol requirements. The PPS will be used as a supportive analysis population to evaluate the consistency and robustness of effectiveness.

Safety Analysis Set: The Safety Analysis Set will include all subjects who receive at least one dose of the study treatment, regardless of their protocol compliance. The safety analysis set will be the primary analysis set for all safety analyses.

7.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics such as age, sex, weight, and height will be summarized descriptively. Variables that are measured on a continuous scale, such as age of the participant at time of enrolment, number of non-missing observations (n), mean, median, SD, minimum, and maximum will be tabulated. Variables that are measured on a categorical scale will be summarized using frequencies and percentages.

7.2 Analysis of Primary and Co-primary Endpoints

Key Primary Endpoint:

- *Incidence of Treatment Emergent Adverse events (TEAEs)*

Co-Primary Endpoints:

- *Incidence of Treatment Emergent Serious Adverse Events (TESAEs)*
- *Incidence of AE of Special Interest (AESI) i.e. LFT derangement*
- *Incidence of TEAEs leading to dose interruption, reduction or discontinuation*
- *Incidence of TEAEs leading to death*

- *Incidence of Treatment Related Adverse Events (TRAEs)*

The primary endpoint and co-primary endpoints will be analysed by using safety analysis set.

The incidence of TEAEs will be reported as the number and percentage of subjects experiencing at least one TEAE overall and will be further tabulated by System Organ Class (SOC) and Preferred Term (PT) using MedDRA coding v28.1, 01SEP2025 or higher. For each SOC and PT, a subject will be counted only once, regardless of the number of occurrences, and the highest severity grade recorded will be used in the summary. Additional descriptive summaries will include TEAEs by severity level and by relationship to study treatment (related vs unrelated), as assessed by the investigator.

Electrocardiograms (ECGs), vital signs, physical examination findings, and clinical laboratory test results will be analyzed descriptively. For ECGs, vital signs, and laboratory parameters, observed values and changes from baseline will be summarized by study visit using descriptive statistics. Values will also be classified relative to normal reference ranges, and the incidence of clinically significant abnormalities and worst post-baseline values will be summarized. Physical examination findings will be summarized descriptively, with abnormal findings tabulated by visit and by body system.

Serious TEAEs, AESI, treatment-related TEAEs, and TEAEs leading to study drug discontinuation, dose modification, or interruption, death will also be tabulated separately.

Adverse events will be coded according to the NCI CTCAE version 6.0 grading system.

7.3 Analysis Secondary Endpoints

- *Response Rates as per RANO 2.0 Criteria*

The Response Assessment in Neuro Oncology for Low Grade Glioma (RANO 2.0) criteria will be analyzed using the Full Analysis Set (FAS).

The Response Assessment in Neuro-Oncology for Low-Grade Glioma (RANO 2.0) criteria will be used to evaluate radiographic tumor response and progression based on changes in MRI measurements [T1-weighted sequences (pre- and post-contrast) and T2/FLAIR sequences], with progression defined as a ≥ 25 % increase in lesion size or appearance of new lesions according to RANO 2.0 standards. Response outcomes (e.g., complete response, partial response, minor response, stable disease, progressive disease) will be summarized descriptively as the number and percentage of subjects in each category at prespecified timepoints. Response rates will be reported with exact confidence intervals. No formal hypothesis testing will be performed for RANO-based categories; results will support interpretation of treatment effect on imaging-based outcomes.

7.4 Sample Size Determination

A total of 15 participants will be enrolled in the study. A formal power-based sample size calculation was not performed due to the rarity of Grade 2 astrocytoma and oligodendroglioma harbouring susceptible IDH1 or IDH2 mutations, particularly within the Indian population.

Vorasidenib has demonstrated safety and effectiveness in global clinical studies, and this study is being conducted as a post-marketing, real-world evaluation to further characterize the safety profile of vorasidenib in Indian adult and paediatric participants (≥ 12 years) following surgical intervention.

From a statistical perspective, a sample size of 15 participants allows for the detection of common adverse events (AEs) occurring at a rate of approximately 20% with a high probability (approximately 96%). Specifically, the probability of observing at least one AE when the true AE rate is 20% is given by:

$$P(\geq 1 \text{ AE}) = 1 - (1 - p)^n = 1 - (0.8)^{15} \approx 0.96$$

In addition, if no AEs are observed in 15 participants, the upper bound of the confidence interval for the true AE rate depends on the method used. Using the exact binomial approach:

- The one-sided 95% upper confidence bound is approximately 18.1%
- The two-sided exact 95% confidence interval upper bound is approximately 21.8%

This distinction is important for interpretation. The two-sided confidence interval is typically preferred for regulatory reporting; therefore, in the context of 0 observed events among 15 participants, the true AE rate cannot be ruled out to be as high as approximately 21.8%.

Overall, this sample size is considered appropriate for a feasibility-driven, descriptive Phase IV safety study in a rare, molecularly defined population, and provides clinically meaningful bounds for post-marketing safety surveillance.

This provides a clinically meaningful statistical boundary for post-marketing safety surveillance in this rare molecularly defined population.

Therefore, the selected sample size of 15 participants is considered adequate to meet the primary objective of estimating the incidence of adverse events associated with vorasidenib in the real-world Indian clinical setting, while remaining feasible given the rarity of the target population.

In pivotal trials of vorasidenib in adult and pediatric patients with Grade 2 IDH-mutant glioma, common adverse events (e.g., fatigue, headache, diarrhoea, elevated liver enzymes) occurred at rates of approximately 15–40%, and Grade 3 or higher adverse events were reported in approximately 22–23% of patients, demonstrating that a 20% threshold aligns with observed clinical safety data.

7.5 Interim Analysis

No interim analysis is planned for the present study.

8 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Monitoring of AEs will be conducted throughout the study from the time of signing ICF until SFU. All AEs should be monitored and followed up until they are resolved or are clearly determined to be due to a participant's stable or chronic condition or intercurrent illness(es) or until the participant is lost to follow-up or participant has withdrawn consent or resulted in the death of the participant.

Adverse Event Reporting Period: Investigators will seek information on AEs at each study visit as outlined below. All AEs, whether reported by the participant or noted by study personnel, will be recorded in the participant's medical record and on the AE page of the eCRF.

8.1 Definition

8.1.1 Adverse Events (AEs)

An AE (also referred to as an adverse experience) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any of the following:

- Any unfavourable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not considered related to the drug
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., Screening invasive procedures such as biopsies)
- An AE can arise from the use of any drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose

Disease progression will not be considered an AE (or an SAE) in this study but will be collected as an outcome or reason for discontinuation, as appropriate. However, 'Death due to disease progression' may be included as an SAE. Adverse events (or SAEs) considered as complications of disease progression should be reported.

8.1.2 Related Adverse Events

A related AE is any AE for which there is a reasonable possibility that the drug caused the AE.

Assessment of Causality of Adverse Events

Investigators should use their knowledge of the participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be

related to the study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study treatment
- Course of the event, considering especially the effects of dose reduction, discontinuation of study treatment, or reintroduction of study treatment (where applicable)
- Known association of the event with the study treatment or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the participant or use of concomitant medications known to increase the occurrence of the event.
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

Table 3 WHO-UMC Causality Assessment

Causality term	Assessment criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction. • Cannot be judged because information is insufficient or contradictory. • Data cannot be supplemented or verified

8.1.3 Serious Adverse Event

An AE or suspected adverse reaction is considered serious (an SAE) if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Fatal (i.e., the AE actually causes or leads to death).
- Life-threatening, meaning that the participant was at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that hypothetically might have caused death had it occurred in a more severe form).
- Inpatient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period but planned prior to study entry are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected manner during the study (e.g., surgery performed earlier than planned).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect in a neonate/infant born to a mother or father exposed to study treatment.
- Important medical event as assessed by the Investigator or Sponsor. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent 1 of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an AE (rated as mild, moderate, or severe/life-threatening/fatal, or according to NCI CTCAE criteria); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

8.2 Procedures for Reporting of AEs and SAEs

Investigator Responsibility:

All AE/SAEs will be recorded after signing the ICF till the end of the study shall be recorded and reported by the Investigator.

The procedures for recording and reporting AEs/SAEs will differ by study phase, as outlined below:

- **Study Phase (Interventional Phase)**
All AEs and SAEs occurring from the date of ICF signing until completion of the safety follow-up period (i.e., 7 weeks after the last study dose) will be recorded and reported in accordance with Good

Clinical Practice (GCP), NDCT Rules-2019, and all applicable regulatory requirements for interventional clinical trials.

- **Extension Phase (Observational Phase)**

As the extension phase is observational in nature, all AEs and SAEs will be collated and reported to the relevant health authorities as an addendum to the Clinical Study Report (CSR).

- **Post-Treatment Assessment (PTA) / Post-Extension Phase**

As no active data collection is planned after completion of the extension phase, Investigators will be required to report any AEs and SAEs to the Sponsor and/or the Sponsor's representative in accordance with routine pharmacovigilance practices.

Study Phase:

Recording and reporting of all SAEs occurring during study phase i.e from Signing the ICF till the safety follow up (7 weeks post last study dose) will follow NDCT 2019 and applicable rules. All SAEs regardless of causal relationship will be reported by the site to the Sponsor/ designee, Central Licensing Authority i.e., the Drugs Controller General of India (DCGI), and IEC of the site within 24 hours of knowledge of the occurrence of the event. Follow-up information on an existing SAE will be reported by the Investigator after the initial report. Where appropriate, hospitalization or autopsy reports will be made available. All SAEs will be followed up until resolution (i.e., asymptomatic, stabilization, or death). The Investigator will prepare and submit a detailed analysed report of all the SAEs to the Head of the Institution where the trial is being conducted, to the Chairman of the IEC that accorded approval for the conduct of the trial, and the Central Licensing Authority within 14 days of knowledge of the occurrence of SAE. This notification will be as per the "New Drugs and Clinical Trials Rules 2019".

If the SAE resolves after the submission of the 14-day analysed report, the Investigator will prepare and submit a follow-up due analysis report upon resolution of the SAE.

To report SAEs, an SAE report form and/or (as per site practice), the Table 5 of the New Drugs and Clinical Trials Rules (March 2019) must be completed and signed by the Investigator or designee and should be submitted to the following stakeholders:

- To DCGI via SUGAM Portal
- To IEC: IEC notification will be done by hard copy submission or e-mail as per the site IEC SOP
- To Sponsor and CRO

Sponsor-Servier India Responsibility:

Sponsor will review the seriousness of all the reported Adverse Events (related or not related) and will submit the ICSRs and complete the SAE reporting to the CLA, Head of institution (HoI) and to IEC and or to other sites as per regulatory compliance within timelines.

Detailed Safety Management Plan (SMP) to be referred for safety reporting.

All AEs (serious and non-serious) spontaneously reported by the participant and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic

procedures will be recorded on the appropriate page of the eCRF. Any clinically relevant deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded on the appropriate pages of the eCRF.

All AEs, whether serious or not, will be described in the source documents and on the AE page of the eCRF. All new events, as well as those that worsen in severity or frequency relative to baseline, which occur after participants have received at least 1 dose of study treatment through 7 days following the last dose of study treatment, must be recorded. Adverse events that are ongoing at the time of treatment discontinuation, should be followed through the 7 weeks post-treatment assessment.

Information to be reported in the description of each AE includes:

- A medical diagnosis of the event (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event should be recorded)
- The date of onset of the event
- The date of resolution of the event
- Whether the event is serious or not
- Severity of the event (see below for definitions)
- Relationship of the event to study treatment
- Action taken for AE/SAE management: none (no action taken); drug treatment required; non-drug treatment required (e.g., surgery, etc.); hospitalization or prolongation of hospitalization required (complete SAE page); diagnostic procedure performed

The action taken with study treatment administration will be one of the following:

Table 4 Action Taken with the study treatment

Action Taken with the study treatment (Vorasicidenib)	Description
Treatment interrupted	The treatment was temporarily discontinued
Treatment withdrawn	The treatment was permanently discontinued
Unknown /Not known	Not known, not observed, not recorded
Dose Modification	The AE resulted in a modification of dose or frequency of dosing
No action taken	The AE did not result in any modification of dose or frequency of dosing
Not applicable	The AE occurred prior to the first dose or following last scheduled dose

If treatment with vorasidenib is withdrawn due to an SAE, participants will be transitioned to appropriate alternative therapy based on the investigator's clinical judgement and as per standard treatment guidelines. The choice of alternative treatment will not be dictated by the sponsor and will remain entirely at the discretion of the treating physician. Such participants who are withdrawn from study treatment must complete their EOT visit.

- Outcome: participant recovered without sequelae; participant recovered with sequelae; not recovered/not resolved (event ongoing); recovering, fatal (notify within 24 hours), unknown (if none of the other situations apply or are known).

Severity of all AEs, including clinically significant treatment-emergent laboratory abnormalities, will be graded according to the NCI CTCAE version 6.0. Adverse events not listed by the CTCAE will be graded as follows:

- Mild: The event is noticeable to the participant but does not interfere with routine activity.
- Moderate: The event interferes with routine activity but responds to symptomatic therapy or rest.
- Severe: The event significantly limits the participant's ability to perform routine activities despite symptomatic therapy.
- Life-threatening: An event in which the participant was at risk of death at the time of the event.
- Fatal: An event that results in the death of the participant.

8.2.1 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- a. If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- b. If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- c. If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- d. If dizziness leads to a fall and subsequent fracture, all 3 events should be reported separately on the eCRF.
- e. If neutropenia is accompanied by a severe or serious infection, both events should be reported separately on the eCRF.

All AEs should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

8.2.2 Adverse Events of Special Interest (AESIs)

An AESI can be serious or non-serious and is an event of special interest to the Sponsor. In the present study, LFT derangement is the designated AESI

Any Grade 2 or higher ALT or AST elevation with an elevated total bilirubin $\geq 2 \times$ ULN should be reported as an SAE as per NCI CTCAE version 6.0. Ongoing monitoring and rapid communication by the Investigator to the Sponsor and CRO is required to allow for further characterization and reporting to regulatory authorities.

8.2.3 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between participant evaluation time points. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens in intensity or grade.

When an AE becomes serious (regardless of changes in grade or severity), the eCRF should be updated to reflect this. As such, a new SAE (with onset date for when AE became serious) should be added to the eCRF.

However, the same does not hold true for AEs that change from serious to non-serious events. When an AE does not resolve but is downgraded from a serious to a non-serious event, a new AE is not required to be captured on the eCRF.

A recurrent AE is one that resolves between participant evaluation time points and subsequently recurs. Each recurrence of an AE should be recorded separately on the Adverse Event eCRF.

8.2.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an AE. A laboratory test result should be reported as an AE if it meets any of the following criteria:

- a. Accompanied by clinical symptoms
- b. Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- c. Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- d. Clinically significant in the Investigator's judgment

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin $5 \times \text{ULN}$ associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range. Where possible, please enter a condition (e.g., neutropenia) rather than the lab finding (e.g., decreased neutrophils).

8.2.5 Progression of Underlying Disease

Progression of underlying disease should not be reported as an AE if it is clearly consistent with its suspected progression. Clinical symptoms of progression may be reported as AEs if the symptoms cannot be determined as exclusively due to the progression of the participant's underlying disease or do not fit the expected pattern of progression for the disease.

If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.

8.2.6 Pre-existing medical conditions

A pre-existing medical condition is defined as any condition present at the time of the Screening Visit or any clinically significant abnormality identified in the screening laboratory results. Such conditions should be recorded on the Medical History eCRF. A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

8.2.7 Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE, except as outlined below.

The following hospitalization scenarios are not considered to be SAEs:

- Hospitalization for respite care.
- Standard procedure for protocol therapy administration; however, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- Administration of blood or platelet transfusion as routine treatment of studied indication; however, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling); however, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- An elective treatment of or an elective procedure for a pre-existing condition (planned prior to signing of ICF), unrelated to the studied indication, which has not worsened from baseline.

8.2.8 Overdose or Incorrect Administration

Study treatment overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not an AE unless it results in untoward medical effects.

Any study treatment overdose or incorrect administration of study treatment should be noted on the Study Drug Administration eCRF. All AEs associated with an overdose or incorrect administration of study

treatment should be recorded on the Adverse Event eCRF. If the associated AE fulfils seriousness criteria, the event should be reported to the Sponsor within 24 hours after learning of the event.

8.3 Pregnancy Reporting

Pregnancy is neither an AE nor an SAE, unless a complication relating to the pregnancy occurs (e.g., spontaneous abortion, which may qualify as an SAE).

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female participant or partner of a male participant occurring while the participant is on study treatment, are considered immediately reportable events. If a female partner of a male participant taking investigational product becomes pregnant, the male participant taking study treatment should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately. In pregnant female participants, study treatment is to be discontinued immediately, and the participant instructed to return any unused study drug to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported immediately to Servier India Private Limited/CRO and Ethics committee overseeing the site using the Pregnancy Report Form. The Investigator must follow up and document the course and outcome of all pregnancies even if the participant was discontinued from the study or if the study has finished. The female participant or partner of a male participant should receive any necessary counselling regarding the risks of continuing the pregnancy and the possible effects on the foetus. Monitoring should continue until conclusion of the pregnancy.

All outcomes of pregnancy (from a female participant or the sexual partner of a male participant) must be reported by the Investigator to the Sponsor or Medical Monitor on a Pregnancy Outcome Report form within 4 weeks after he/she has gained knowledge of the delivery or elective abortion.

Any SAE that occurs during pregnancy must be recorded on the SAE report form (e.g., maternal serious complications, spontaneous or therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs.

Females of reproductive potential must have a negative serum pregnancy test prior to the start of therapy, or a confirmation from an obstetrician in case of equivocal serum pregnancy results.

Females of reproductive potential must undergo a urine pregnancy test to be conducted on C1D1 and confirmed negative prior to dosing, and on Day 1 of all subsequent cycles. The test should be conducted pre-dose, and these participants should undergo a urine pregnancy test at EOT.

8.3.1 Reporting of SAEs as per the “New Drugs and Clinical Trials Rules 2019”

All SAEs will be recorded after signing the ICF till the end of the study phase.

All SAEs from signing of ICF till completion of safety follow up, regardless of causal relationship will be reported by the site to the sponsor/contract research organization (CRO), Central Licensing Authority, and IEC of the site within 24 hours of occurrence of the event.

To report SAEs, a serious adverse event (SAE) report form/ Table 5 must be completed and signed by the investigator or designee and should be submitted to the Central Licensing Authority, site EC, sponsor at Servier.india.PV@servier.com: and CRO at safety@jssresearch.com. Follow-up information on an existing SAE will be reported by the investigator after the initial report, where appropriate, hospitalization or autopsy reports will be made available. All SAEs will be followed up until resolution (i.e., asymptomatic, stabilization, or death).

The investigator will prepare and submit a detailed analysed report of all the SAEs to the Head of the Institution where the trial is being conducted, to the chairman of the IEC that accorded approval for the conduct of the trial and Central Licensing authority with 14 days of knowledge of occurrence of SAE. Sponsor will independently submit the detailed analysis report to the Central Licensing Authority, Ethics committee and head of institution as well within 14 days of knowledge of the occurrence of SAE. This notification will be as per the “New Drugs and Clinical Trials Rules 2019”.

If the SAE resolves after the submission of the 14-day analysed report, the investigator/sponsor/CRO will prepare and submit a follow-up due analysis report upon resolution of the SAE.

8.4 Follow up of Participants after Adverse Events

8.4.1 Investigator Follow Up

The Investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, or until the participant is lost to follow-up, or the participant withdraws consent or participant's death. Every effort should be made to follow all SAEs considered related to study treatment or trial-related procedures until a final outcome can be reported.

All pregnancies reported during the study should be followed until pregnancy outcome.

8.4.2 Sponsor Follow Up

For SAEs, AESIs, and pregnancies, the Sponsor or a designee may follow-up by email, EDC query, telephone, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

8.4.3 Post Study Adverse Events – In Extension Phase

In the extension phase, all AEs and SAE will be reported by investigators to sponsor and sponsor's representative till completion of the extension phase. All AEs & SAEs reported in this phase will be collated and notified to HA in addendum to CSR.

AE/SAEs in PTA (post completion of extension phase) will be recorded and reported as per routine pharmacovigilance practice.

9 STUDY DRUG MANAGEMENT

9.1 Packaging

Packaging and labelling will be prepared to meet all regulatory requirements.

Vorasidenib tablets are supplied in two strengths:

1. 10 mg tablets: White to off-white, round film-coated tablet imprinted with “10” in black ink on one side and plain on the other side. Each carton contains one 30-count bottle of 10 mg tablets with desiccant canister(s) and child-resistant cap.
2. 40 mg tablets: White to off-white, oblong film-coated tablet imprinted with “40” in black ink on one side and plain on the other side. Each carton contains one 30-count bottle of 40 mg tablets with desiccant canister(s) and child-resistant cap.

It will be labelled as “investigational product for this study” as required by local regulations.

9.2 Blinding of Study Product

Since this is an open label study, there will be no blinding related procedures.

9.2.1 Receipt of Drug Supplies

Upon receipt of the study treatment supplies, an inventory must be performed, and a study product receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study product in each shipment (IMP) will be documented in the study files. The investigator must notify study sponsor of any damaged or unusable IMP that was supplied to the investigator’s site.

9.2.2 Storage

Vorasidenib tablets must be stored according to the approved label (package insert).

All drug supplies for study will be provided by the sponsor. All study drugs must be stored in a secure, limited-access location and may be dispensed only by the investigator or by a member of the staff specifically authorized by the investigator. A separate investigational product management manual will capture all the details related to order, supply, storage, dispensing, administration, and associated logs.

All the study drugs provided by the Sponsor should only be used for this clinical study and should not be used for any purposes other than those specified in this protocol. The investigator must commit to not provide the study drug to any person unrelated to this study. Study drug that is discontinued for special reasons should be stored under the same storage conditions until the inspector has checked it and arranged it to be recycled.

9.2.3 Return or Destruction of Study Drug

An improperly used or expired IMP must not be disposed of and should be retained at the study center. These IMPs must remain available for inspection during monitoring visits.

The amount of used and unused IMP shall be counted during in-person monitoring visits to ensure accountability. The researcher shall maintain an IMP record book at the study centre. Designated study staff will keep study products record books, where study products delivery to the study centre, study products usage, unused study products return, as well as storage conditions shall be recorded. At the completion of the study, there will be a final reconciliation of study products shipped, study products consumed, and study products remaining. This reconciliation will be logged on the product reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return. All unused study drugs should be returned to the Sponsor for destruction after the study is completed/terminated or beyond the shelf life. The return of study drug will be arranged by the CRA designated by the Sponsor.

10 STUDY ADMINISTRATION

Sponsor's designee JSS-Asia Pacific will be responsible for study administration as described in this section.

10.1 Regulatory and Ethical Considerations, Including the Good Clinical Practices

The study will be conducted in conformity with International Council on Harmonization-Good Clinical Practice (ICH-GCP E6(R2)) guidelines, the Helsinki Declaration, and the local regulatory requirements (Indian GCP, ICMR) and New Drugs and Clinical Trials Rules-2019.

The Investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and relevant IBs. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations.

10.1.1 Institutional Ethics Committee

The study protocol, amendments to the protocol (if applicable), study treatment information, participant information sheet, ICF, and consent form updates (if applicable) and other study specific documents will be submitted to the IEC, which is constituted according to local law to obtain approval before initiation of the study. This study will be initiated after the protocol is reviewed and approved by the concerned IEC. The approval should be kept in the site master file with a copy in the trial master file. The investigator will report promptly to the IEC any new information that may adversely affect the safety of the participants or the conduct of the trial.

10.1.2 Informed Consent of the participant

The investigator (or designee) will obtain freely given written, signed, and dated ICF from each participant/parent/LAR (whichever applicable) in this clinical trial, after adequate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspects of the study, and prior to conduct of any study-related screening procedure on the participant. The ICF must be signed before performance of any study-related activity. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive. The participant/LAR will be given sufficient time and the opportunity to ask questions to consider the study's implications before deciding to participate in the study. The ICF and participant information sheet that is used must be approved by the sponsor or its designee; by the reviewing IEC/IRB and appropriate regulatory authority and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements.

If the participant or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the participant or legally acceptable representative is obtained.

A copy of signed and dated ICF along with the participant information sheet will be provided to all participants enrolled in the study. The confidentiality of the participant's identity and records will be maintained. Should there be any amendments to the protocol, such that they would directly affect the participant's study participation (e.g., change in study procedure), the participant information sheet along with the ICF, will also be amended appropriately. The investigator (or designee) must obtain participant's signature on this amended ICF, indicating that they consent to continue their study participation.

10.2 Medical Monitoring

It is the responsibility of the investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see [Section 12](#)). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

11 DATA HANDLING AND RECORD KEEPING

11.1 Confidentiality

Information about participants will be kept confidential and managed according to the requirements of the ICH-GCP Guidelines. The anonymity of participants must be maintained. Participants will be specified on study documents by their participant number, initial or birth date, not by name. Documents that identify the participant (e.g., the signed informed consent document) must be maintained in confidence by the investigator.

All clinical study findings and documents will be kept as confidential. Study documents (protocols and other material) will be stored appropriately to ensure their confidentiality. The investigator and members of his/her research team (including the IEC) must not disclose such information without prior written approval from the sponsor, except to the extent necessary to obtain informed consent from participants who wish to participate in the study or to comply with regulatory requirements.

If a participant revokes authorization to collect or use protected health information (PHI), the investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the participant is alive) at the end of their scheduled study period.

11.2 Source Document/ electronic Case Report Form (eCRF) Completion

Source documents/eCRFs will be completed for each study participant. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the participant's source document/eCRF. The source document/eCRF should indicate the participant's participation in the study and should document the dates and details of study procedures, AEs, and participant status.

The Investigator, or designated representative, should complete the source document/eCRF as soon as possible after information is collected, preferably on the same day that a study participant is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

The Investigator must sign and date the Investigator's Statement at the end of the source document/eCRF to endorse the recorded data.

The Investigator will retain all completed source documents.

11.3 Data Management

All data for participants recruited for the trial will be entered onto the eCRFs via an EDC system provided by the Sponsor or designee. Only authorized staff may enter data onto the eCRFs. If an entry error is made, the corrections to the eCRFs will be made according to eCRF guidelines by an authorized member of the site staff.

Electronic case report forms will be checked for correctness against source document data by the Sponsor's monitor. If any entries into the eCRF are incorrect or incomplete, the monitor will ask the

Investigator or the study site staff to make appropriate corrections, and the corrected eCRF will again be reviewed for completeness and consistency. Any discrepancies will be noted in the eCRF system by means of electronic data queries. Authorized site staff will be asked to respond to all electronic queries according to the eCRF guidelines.

11.4 Case Report Forms

Data reflecting the participant's participation with the study product under investigation will be reported to the sponsor (or an authorized representative). The data will be recorded on the designated eCRFs provided or approved by the sponsor.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the investigator or hospital that relate to the participant's medical history, that verify the existence of the participant, the inclusion and exclusion criteria and all records covering the participant's participation in the study. They include laboratory notes, memoranda, pharmacy dispensing records, participant files, etc.

The investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. The investigator must submit a completed electronic CRF (eCRF) for every participant who does not fail screening. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified. All data must be entered in English. The eCRFs should always reflect the latest observations on the participants. Therefore, the eCRFs are to be completed as soon as possible after the participant's eligibility has been confirmed and thereafter during or after the participant's visit. To avoid inter observer variability, every effort should be made to ensure that the same individual who makes the initial baseline determinations completes subsequent evaluations. The investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, the investigator should indicate this in the eCRF. The investigator will be required to sign off on the clinical data.

The monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections and alterations are to be made by the responsible investigator or his/her designee. The monitor is not allowed to enter data in the eCRFs.

If additional corrections are needed, the responsible monitor or data manager will raise a query. The appropriate investigational staff will answer queries sent to the investigator.

For each participant that has signed the informed consent but does not qualify for allocation to treatment, i.e., screen failure, no data is to be collected in the eCRF but captured on a screening log. This includes at a minimum the participant identification number, the informed consent date, and the reason for screen failure. The screening log is monitored, provided to the sponsor, and must be included in the Trial Master File.

Electronic data capture (EDC) will be used for this trial, meaning that all CRF data will be entered in electronic forms at the investigational site. Data collection will be completed by authorized study site

personnel designated by the investigator. Appropriate training and security measures will be completed with the investigator and all authorized study site personnel prior to the study being initiated and any data being entered into the system for any participants. Roles and rights of the site personnel responsible for entering the clinical data into the eCRF will be determined in advance.

Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Also, the queries and resolutions will be audit trailed by the EDC application meaning that the name of investigational staff, data manager and Monitor, time and date stamp are captured. eCRF records will be automatically appended with the identification of the creator, by means of their unique user identification (ID). Specified records will be electronically signed by the investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the investigator's unique user identification (ID) and password; date and time stamps will be added automatically at time of electronic signature. If an entry on an eCRF requires change, the correction should be made in accordance with the relevant software procedures. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

11.5 Records Retention

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

12 STUDY MONITORING, AUDITING, AND INSPECTING

12.1 Study Monitoring Plan

This study will be monitored according to the SOPs and study's monitoring plan. The investigator will allocate adequate time for such monitoring activities. The investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above-noted study-related documents and study related facilities (e.g., pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

12.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IEC, the sponsor, government regulatory bodies, and university compliance and quality assurance groups of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.). Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable university compliance and quality assurance offices.

12.3 Protocol Compliance

The Investigator will conduct the study in compliance with the protocol. Modifications to the protocol should not be made without agreement of both the Investigator and the Sponsor. Changes to the protocol will require written IRB/IEC approval/favourable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to participants. The IRB/IEC may provide, if applicable, where regulatory authority(ies) permit, expedited review and approval/favourable opinion for minor change(s) in ongoing studies that have the approval/favourable opinion of the IRB/IEC. The Sponsor or designee will submit all protocol modifications to the regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to participants, the Investigator will contact the Sponsor or Medical Monitor, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the source documents/eCRF.

12.4 Study and Site Closure

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the PI or site staff, as appropriate, in accordance with applicable regulations, ICH-GCP guidelines, sponsor or its designee's procedures. In addition, sponsor reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multi-centre studies, this can occur at one or more or at all sites. If sponsor determines such action is needed, sponsor or its designee will discuss this with the PI including the reasons for taking such action, at that time.

When feasible, sponsor or its designee will provide advance notification to the PI of the impending action prior to it taking effect. The PI also has the right to temporarily suspend or prematurely discontinue this

study for mutually agreed reason(s) with the sponsor. Sponsor or its designee will also promptly inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. The PI must inform the IEC/IRB promptly and provide the reason for the suspension or termination, if required by applicable regulations.

13 STUDY FINANCES

13.1 Funding Source

The clinical trial will be funded by Servier India Private Limited.

13.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted conflict of interest committee with a committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study.

13.3 Liability and Insurance

The Sponsor has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

14 REPORTS ON STUDY RESULTS

Final report will be in ICH E3 form.

The final report is to be signed by the PIs, and the representatives of the sponsor and the CRO.

15 PUBLICATION PLAN

The organizer of this study is Servier India Private Limited.

All information regarding vorasidenib supplied by the Sponsor or designee to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of vorasidenib and may be disclosed to regulatory authority(ies), other Investigators, corporate partners, or consultants as required.

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17 APPENDICES

APPENDIX 1 Schedule of Assessments

Visit	Screening ¹	Treatment Visits 4-Week (28-Day) Cycles												EOT	SFU ²
Cycle	Day -28 to Day 0	Cycle 1				Cycle 2		Cycle 3		Cycle 4		Cycle 5	Cycle 6	Within +3 days from last dose (W25)	Within 7 weeks from last dose (W32)
Study Day ± window period (in days) (Weeks)		D1 (W1)	D8±3 (W2)	D15±3 (W3)	D22±3 (W4)	D1±3 (W5)	D15±3 (W7)	D1±3 (W9)	D15±3 (W11)	D1±3 (W13)	D15±3 (W15)	D1±3 (W17)	D1±3 (W21)		
Procedures															
Informed consent/ Assent ³	X														
Eligibility Criteria	X														
Medical/ Surgical History and Concomitant Illness	X														
Demographics	X														
IDH1/ IDH2 Mutation analysis ⁴	X														
Enrolment	X														
Prior Medications	X														
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height and weight ⁵	X	X				X		X		X		X	X	X	
Vital Signs ⁶	X	X				X		X		X		X	X	X	
Physical Examination including neurological exam ⁷	X	X				X		X		X		X	X	X	
12-lead ECG ⁸	X	X				X		X		X		X	X	X	
Pregnancy tests ⁹ (for WOCBP only)	X	X				X		X		X		X	X	X	
Hematology, Serum Chemistry ¹⁰	X	X				X		X		X		X	X	X	
Evaluate Disease/ Response ¹¹	X							X					X ¹¹	X	
LFT Monitoring ¹⁰	X	X		X		X	X	X		X		X	X	X	
Coagulation Studies ¹²	X	X		X		X	X	X		X		X	X	X	
Vorasidenib Administration ¹³		X (Continuous)													
Study diary and Study medication accountability ¹⁴		X	X	X	X	X	X	X	X	X	X	X	X	X	

Notes:

1. Screening assessments conducted prior to informed consent but within 28 days of C1D1 need not be repeated and results may be entered into the eCRF.
2. If a participant discontinues study treatment at a regularly scheduled visit, safety follow-up (SFU) assessments may be performed at that visit.
3. Written informed consent must be obtained before commencing any study related procedures.
4. Participants must have documented IDH1/ IDH2 mutated disease (from fresh or banked tumor tissue) to be eligible for the study.
5. Height at Screening only. Weight will be noted on Day 1 of each cycle, prior to dosing.
6. Vital signs (temperature, BP [sitting for 5 minutes], pulse rate, respiratory rate) are to be taken at Screening and at any point when abnormal vital signs are suspected. All clinically relevant abnormal vital sign results will be reported as AEs.
7. Clinically directed examinations, including neurological examination will be conducted. A comprehensive physical exam will be conducted at screening, while limited physical exam will be performed at all other applicable visits (refer [Section 4.1.2](#)).
8. All ECGs should always be obtained after the participant has been resting in a sitting/supine position for at least 5 minutes. When the timing of a blood sample coincides with the timing of an ECG measurement, the ECG will be completed before the collection of the blood sample (within 10 minutes).
9. For Women of Childbearing Potential (WOCBP) only: A serum β -hCG pregnancy test is required at Screening and must be verified as negative within 72 hours prior to study treatment administration. A urine pregnancy test will be conducted on C1D1 and confirmed negative prior to dosing, and on Day 1 of all subsequent cycles. A urine pregnancy test should also be conducted at SFU.
10. Haematology: Haemoglobin, haematocrit, red blood cell (RBC) count, white blood cell (WBC) count and differential (% neutrophils, % bands) and platelet count. No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. After C1, samples may be collected up to 48 hours prior to CxD1 or at SFU. Chemistry: Sodium, potassium, calcium, magnesium, phosphorus, albumin, glucose, blood urea nitrogen (BUN)/urea, creatinine, uric acid and lactate dehydrogenase. (LDH). No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. After C1, samples may be collected up to 48 hours prior to CxD1 or at EOT. LFT Monitoring: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, and serum albumin.
11. A screening tumor assessment (MRI Brain) must be done before the first administration of study treatment. Tumor evaluations performed within 21 days prior to the screening visit need not be repeated. Response assessment per RANO 2.0 criteria will be conducted at screening, C3 and at either C6/ EOT visit.
12. Coagulation includes activated partial thromboplastin time, prothrombin time and international normalized ratio.
13. If vorasidenib is usually taken in the morning, the tablets on C1D1 and on Day 1 of all subsequent cycles should be taken at the clinic following completion of all required assessments.
14. The study diary will be issued on C1D1 and retrieved from the participants at EOT. Participants are required to bring the study diary with them at every visit to the study site, so that it can be reviewed by the study staff. Study diary will be used to record dosing details for vorasidenib, as well as AE and concomitant medications used (if any) when participant is an outpatient.
While participant is inpatient, details of vorasidenib administration may be captured on study diary or standard hospital inpatient dosing record. All missed or vomited doses should be noted in the diary. Treatment compliance of vorasidenib administration is to be assessed based on return of unused study drug as well as study diaries. All doses of study drugs (vorasidenib) will be documented in the eCRF, including documentation of any missed doses and dose administer