Day One Pharmaceuticals

Clinical Study DAY101-001

FIREFLY-1: A Phase 2, Open-Label, Multicenter Study to Evaluate the Safety and Efficacy of the Oral Pan-RAF Inhibitor DAY101 in Pediatric Patients with RAF-Altered, Recurrent or Progressive Low-Grade Glioma and Advanced Solid Tumors

Statistical Analysis Plan

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	March 18, 2022	NA
1.1	May 9, 2022	Section 3.3.1 – [redacted] Section 4.2.2 – updated drug exposure summary based on the study CRF design and data entry guideline Other section – editorial changes and clarification
2.0	August 5, 2022	Section 4.2.4.1.2 – added AESI summary. Section 4.2.4.4 – [redacted]; clarified the portion of ECG analyses to be included in the cardiac safety modeling report; removed summary of morphological ECG changes. Other section – editorial changes.
3.0	October 25, 2022	Section 4.2.4.1.2 – revised the scope of Rhabdomyolysis and Intra-tumoral hemorrhage AESIs in accordance with clinical relevance. Other section – editorial changes.
4.0	February 3, 2023	Section 3.4.3.6 – added ORR, BOR, PFS, DOR, TTR and CBR based on RANO-LGG by IRC for Arm 1 as exploratory endpoints. Section 4.2.3.3.5 – added analyses methodology for ORR, BOR, PFS, DOR, TTR and CBR based on RANO-LGG by IRC. [redacted] Other sections – editorial changes.
5.0	June 5, 2023	Section 3.3.1 and 4.1.1– added analysis population set for efficacy endpoints based on RANO-LGG/ RAPNO-LGG Section 3.4.3.7, 3.4.3.8 and 4.2.3.3.6 – added exploratory analyses of PFS by BOR based on RANO-LGG/RAPNO-LGG Section 4.2.3.3.7 – added Analysis of Ongoing Treatment by IRC-assessed Best Overall Response (RANO-HGG) Other section – editorial changes.

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
aCRF	Annotated Case Report Form
ADaM	Analysis Data Model
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC_{0-t}	Area under the concentration-time curve from time zero to t
BCVA	Best corrected visual acuity
BLQ	Below the Limit of Quantitation
BOR	Best Overall Response
BP	Blood pressure
BRAF	v-raf murine sarcoma viral oncogene homolog B
BSA	Body surface area
C	Cycle
C_{ave}	Average plasma concentration
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma concentration
CBR	Clinical Benefit Rate
CI	Confidence interval
CL/F	Apparent oral clearance of drug
COVID-19	Corona Virus Disease 2019
CPK	Creatinine phosphokinase
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
DBP	Diastolic blood pressure
DOR	Duration of Response
DSMB	Drug Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form

Abbreviation / Acronym	Definition / Expansion
ECHO	Echocardiogram
EOT	End of Treatment
EOS	End of Study
FAS	Full Analysis Set
HGG	High-grade glioma
HLGT	High-level Group Term
HR	Heart Rate
IRC	Independent Radiology Review Committee
Kg	Kilogram
KM	Kaplan-Meier
LLOQ	Lower Limit of Qualification
LGG	Low-grade glioma
LOT	Line of Therapy
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase
MM	Medical Monitor
MR	Minor Response
MRI	Magnetic Resonance Imaging
MUGA	Multiple-Gated Acquisition
NCI	National Cancer Institute
NE	Not Evaluable
ORR	Overall Response Rate
OR	Overall Response
OS	Overall Survival
PD	Progressive Disease
PPL	Per Patient Listing
PedsQL-Core	Pediatrics Quality of Life™—Core
PFS	Progression-Free Survival
PK	Pharmacokinetic(s)
PLGGs	Pediatric Low-Grade Gliomas
PO	Per os, orally
PP	Per-Protocol

Abbreviation / Acronym	Definition / Expansion
PPSR	Proposed Pediatric Study Request
PR	Partial Response
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	Preferred Term
QOL	Quality of Life
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate by Fridericia's formula
ΔQTcF	Chang in QT interval corrected for heart rate by Fridericia's formula
QW	Once weekly
RANO	Response Assessment in Neuro-Oncology
RAPNO	Response Assessment in Pediatric Neuro-Oncology
RBC	Red Blood Cell
RP2D	Recommended Phase 2 dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SBP	Systolic Blood Pressure
SD	Stable Disease
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SPPD	Sum of Perpendicular Diameters
SRC	Safety Review Committee
StD	Standard Deviation
T3	Triiodothyronine
T4	Tetraiodothyronine
TEAE	Treatment Emergent Adverse Event
TSH	Thyroid Stimulating Hormone
TTR	Time to Response
VA	Visual Acuity
WBC	Red Blood Cell
WHO-DD	World Health Organization - Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) is to describe the statistical analysis methods and data processing principles for the analysis and reporting of data related to this study. This SAP is based upon the following study documents:

- Clinical Protocol DAY101-001/PNOC026, Version 3.0 (dated 21 Oct 2021)
- Transfer-annotated Case Report Form (aCRF), Version 12.0 (dated19 September 2022)

2. STUDY OBJECTIVES

2.1. Study Objectives for Arm 1

Primary Objective:	**Endpoint:**
To evaluate the efficacy of tovorafenib (DAY101) as measured by the overall response rate (ORR) as determined by an independent radiology review committee (IRC) following treatment with DAY101 in pediatric patients aged 6 months to 25 years, inclusive, with a relapsed or progressive low-grade glioma harboring a known activating v-raf murine sarcoma viral oncogene homolog B (BRAF) alteration	Overall response rate, defined as the proportion of patients with best overall confirmed response of complete response (CR) or partial response (PR) as determined by the Response Assessment in Neuro-Oncology - high-grade glioma (RANO-HGG) criteria
Secondary Objectives:	**Endpoints:**
To assess the safety and tolerability of DAY101	Type, frequency, and severity of adverse events (AEs) and laboratory abnormalities
To determine the relationship between pharmacokinetics (PK) and drug effects, including efficacy and safety	Pharmacokinetic profile of DAY101 (e.g., area under the concentration-time curve [AUC], C_{min}, etc.)
To evaluate the effect of DAY101 on the QT interval corrected for heart rate by Fridericia's formula (QTcF) prolongation and to explore the effects of DAY101 on electrocardiogram (ECG) parameters	Change from baseline QT interval corrected for HR by Fridericia's formula (ΔQTcF) Change from baseline PR interval (ΔPR) Change from baseline QRS interval (ΔQRS) Change from baseline heart rate (ΔHR) ECG waveform morphology
To determine the ORR based on the treating investigator's response assessment using RANO-HGG criteria	Measured by the proportion of patients with best overall confirmed response of CR or PR by RANO-HGG
To determine the ORR based on Response Assessment in Pediatric Neuro-Oncology –low-grade glioma (RAPNO-LGG) criteria as determined by an Independent Radiology review Committee (IRC)	Measured by the proportion of patients with best overall confirmed response of CR or PR or Minor Response (MR) by RAPNO-LGG criteria
To evaluate the duration of progression-free survival (PFS) based on RANO-HGG and RAPNO-LGG criteria following initiation of DAY101 as determined by 1) an IRC and 2) the treating investigator (RANO-HGG only)	Measured by the time following initiation of DAY101 to progression or death in patients treated with DAY101

To evaluate the duration of response (DOR) in patients with best overall response (BOR) of CR or PR or MR (RAPNO-LGG only) based on RANO-HGG and RAPNO-LGG criteria as determined by 1) an IRC and 2) the treating investigator (RANO-HGG only)	Measured by the length of response in patients with best overall confirmed response of CR or PR or MR (RAPNO-LGG only) by RANO-HGG and RAPNO-LGG criteria, as applicable
To evaluate time to response (TTR) (CR or PR or MR (RAPNO-LGG only) based on RANO-HGG and RAPNO-LGG criteria) following initiation of DAY101 as determined by 1) an IRC and 2) the treating investigator (RANO-HGG only)	Measured by the time to first response following initiation of DAY101 in patients with best overall confirmed response of CR or PR by RANO-HGG and confirmed response CR or PR or MR by RAPNO-LGG criteria
To evaluate the clinical benefit rate (CBR) based on the proportion of patients with BOR of CR, PR, MR (RAPNO-LGG only) or stable disease (SD), based on RANO-HGG and RAPNO-LGG criteria, lasting 12 months or more following initiation of DAY101, as determined by 1) an IRC and 2) the treating investigator (RANO-HGG only)	Measured by the proportion of patients with BOR of CR, PR, MR (RAPNO-LGG only) or SD lasting 12 months or more following initiation of DAY101
To evaluate the duration of overall survival following initiation of DAY101	Measured by the time following initiation of DAY101 to death of any cause in patients treated with DAY101
To evaluate changes in best corrected visual acuity (BCVA) outcomes	Measured by change from baseline in BCVA (converted as logMAR) for each eye
[redacted]	[redacted]
Exploratory objectives:	**Endpoints:**
To compare the response and time to response following initiation of DAY101 to that of the prior line of systemic therapy	Measured by the proportion of patients with best overall confirmed response of CR or PR and TTR by RANO-HGG criteria based on the prior line of therapy
To characterize changes in total tumor volume following treatment with DAY101 by magnetic resonance imaging (MRI) volumetric image analysis	Measured by determining tumor volume and volume changes based on MRI scan data
To characterize changes in apparent diffusion coefficients following treatment with DAY101 using diffusion-weighted imaging analysis	Measured by diffusion-weighted imaging based on MRI scan data
To evaluate changes in quality-of-life and health utilities measures using the Pediatrics Quality of Life™—Core Module (PedsQL-Core), Pediatrics Quality of Life™—Cancer (PedsQL-Cancer), and Patient-Reported Outcomes Measurement Information System (PROMIS®) assessment	Measured by changes from baseline in quality-of-life and health utilities measures using the PedsQL-Core, PedsQL-Cancer, and PROMIS® assessment
To describe the improvement in motor function	Measured by changes from baseline in the Vineland 3 Adaptive Behavior Scales

To determine the durability of response off treatment for drug holiday following discontinuation of DAY101 for patients with a radiographic response to DAY101 (CR or PR or MR (RAPNO-LGG only) as based on RANO-HGG and RAPNO-LGG criteria) as determined by 1) an IRC and 2) the treating investigator (RANO-HGG only)	Measured by the proportion of patients with best overall confirmed response of CR or PR or MR (RAPNO-LGG only) who enter a drug holiday period and time to progression as determined by RANO-HGG, RAPNO-LGG, or clinical criteria
To evaluate time to initiation of next treatment following discontinuation of DAY101	Measured by the proportion of patients who discontinue DAY101 therapy and time to next therapy initiation
To determine the ORR based on RANO-LGG as determined by an IRC	Measured by the proportion of patients with best overall confirmed response of CR or PR or MR by RANO-LGG
To evaluate the duration of progression-free survival (PFS) based on RANO-LGG criteria following initiation of DAY101 as determined by an IRC	Measured by the time following initiation of DAY101 to progression or death in patients treated with DAY101
To evaluate the duration of response (DOR) in patients with best overall response (BOR) of CR or PR or MR based on RANO-LGG criteria as determined by an IRC	Measured by the length of response in patients with best overall confirmed response of CR or PR or MR by RANO-LGG criteria
To evaluate time to response (TTR) (CR or PR or MR based on RANO-LGG criteria) following initiation of DAY101 as determined by an IRC	Measured by the time to first response following initiation of DAY101 in patients with best overall confirmed response of CR or PR or MR by RANO-LGG
To evaluate the clinical benefit rate (CBR) based on the proportion of patients with BOR of CR, PR, MR or SD lasting 12 months or more following initiation of DAY101 based on RANO-LGG criteria, as determined by an IRC	Measured by the proportion of patients with BOR of CR, PR, MR or SD lasting 12 months or more following initiation of DAY101

2.2. Study Objectives for Arm 2

Primary Objective:	**Endpoint:**
To assess the safety and tolerability of DAY101 in pediatric patients aged 6 months to 25 years, inclusive, with a relapsed or progressive low-grade glioma harboring a known or expected to be activating RAF alteration	Type, frequency, and severity of AEs and laboratory abnormalities
Secondary Objectives:	**Endpoints:**
To determine the ORR per RANO-HGG criteria as determined by 1) an IRC and 2) the treating investigator	Measured by the proportion of patients with best overall confirmed response of CR or PR as determined by the RANO-HGG criteria
To determine the ORR based on RAPNO-LGG– criteria as determined by an IRC	Measured by the proportion of patients with best overall confirmed response of CR or PR or MR by RAPNO–LGG criteria
To evaluate the duration of PFS based on RANO-HGG and RAPNO-LGG criteria following initiation of DAY101 as determined by 1) an IRC and 2) the treating investigator (RANO-HGG only)	Measured by the time following initiation of DAY101 to progression or death in patients treated with DAY101

To evaluate the DOR in patients with BOR of CR or PR or MR (RAPNO-LGG only) based on RANO-HGG and RAPNO-LGG criteria as determined by 1) an IRC and 2) the treating investigator (RANO-HGG only)	Measured by the length of response in patients with best overall confirmed response of CR or PR or MR (RAPNO-LGG only) by RANO-HGG and RAPNO-LGG criteria, as applicable
To evaluate TTR (CR or PR or MR (RAPNO-LGG only) based on RANO-HGG and RAPNO-LGG criteria) following initiation of DAY101 as determined by 1) an IRC and 2) the treating investigator (RANO-HGG only)	Measured by the time to first response following initiation of DAY101 in patients with best overall confirmed response of CR or PR or MR (RAPNO-LGG only) by RANO-HGG and RAPNO-LGG criteria, as applicable
To evaluate the clinical benefit rate based on the proportion of patients with BOR of CR, PR, MR (RAPNO-LGG only) or stable disease (SD), based on RANO-HGG and RAPNO-LGG criteria, lasting 12 months or more following initiation of DAY101, as determined by 1) an IRC and 2) the treating investigator (RANO-HGG only)	Measured on the proportion of patients with BOR of CR, PR, MR (RAPNO-LGG only) or SD lasting 12 months or more following initiation of DAY101
To evaluate the duration of overall survival following initiation of DAY101	Measured by the time following initiation of DAY101 to death of any cause in patients treated with DAY101
To determine the relationship between PK and drug effects, including efficacy and safety	Pharmacokinetic profile of DAY101 (e.g., AUC, C_{min}, etc.)
To evaluate the effect of DAY101 on QTcF prolongation and to explore the effects of DAY101 on ECG parameters	ΔQTcF ΔPR ΔQRS ΔHR ECG waveform morphology
Exploratory objectives:	**Endpoints:**
To characterize changes in total tumor volume following treatment with DAY101 by MRI volumetric image analysis	Measured by determining tumor volume and volume changes based on MRI scan data
To characterize changes in apparent diffusion coefficients following treatment with DAY101 using diffusion-weighted imaging analysis	Measured by diffusion-weighted imaging based on MRI scan data
To evaluate changes in BCVA outcomes	Measured by change from baseline BCVA (converted as logMAR) for each eye
To evaluate changes in quality-of-life and health utilities measures using the PedsQL-Core, PedsQL-Cancer, and PROMIS® assessment	Measured by changes from baseline in quality-of-life and health utilities measures using the PedsQL-Core, PedsQL-Cancer, and PROMIS® assessment
To describe the improvement in motor function	Measured by changes from baseline in the Vineland 3 Adaptive Behavior Scales
To determine the durability of response following discontinuation of DAY101 for patients with a radiographic response to DAY101 (CR or PR as based on RANO-HGG and RAPNO-LGG criteria) as determined by 1) an IRC and 2) the treating investigator (RANO-HGG only)	Measured by the proportion of patients with best overall confirmed response of CR or PR or MR (RAPNO-LGG only) who enter a drug holiday period and time to progression as determined by RANO-HGG, RAPNO-LGG, or clinical criteria

[redacted]	[redacted]

2.3. Study Objectives for Arm 3

Primary Objective:	**Endpoint:**
To evaluate the preliminary efficacy of DAY101 as measured by the ORR as determined by an IRC following treatment with DAY101 in pediatric patients aged 6 months to 25 years, inclusive, with a relapsed or progressive advanced solid tumor harboring a known or expected to be activating RAF fusion	Measured by the proportion of patients with best overall confirmed response of CR or PR by RECIST v1.1 criteria
Secondary Objectives:	**Endpoints:**
To assess the safety and tolerability of DAY101 in pediatric patients with advanced solid tumors	Type, frequency, and severity of AEs and laboratory abnormalities
To determine the relationship between PK and drug effects, including efficacy and safety	Pharmacokinetic profile of DAY101 (e.g., AUC, C_{min}, etc.)
To evaluate the effect of DAY101 on QTcF prolongation and to explore the effects of DAY101 on ECG parameters	ΔQTcF ΔPR ΔQRS ΔHR ECG waveform morphology
To determine the ORR based on the treating investigator's response assessment using RECIST v1.1 criteria	Measured by the proportion of patients with best overall confirmed response of CR or PR by RECIST v1.1 criteria
To evaluate the duration of PFS based on RECIST v1.1 criteria following initiation of DAY101 as determined by 1) an IRC and 2) the treating investigator	Measured by the time following initiation of DAY101 to progression or death in patients treated with DAY101
To evaluate the DOR in patients with BOR of CR or PR based on RECIST v1.1 criteria as determined by 1) an IRC and 2) the treating investigator	Measured by the length of response in patients with best overall confirmed response of CR or PR by RECIST v1.1 criteria
To evaluate TTR (CR or PR based on RECIST v1.1 criteria) following initiation of DAY101 as determined by 1) an IRC and 2) the treating investigator	Measured by the time to first response following initiation of DAY101 in patients with best overall confirmed response of CR or PR by RECIST v1.1
To evaluate the clinical benefit rate based on the proportion of patients with BOR of CR, PR, or SD, based on RECIST v1.1 criteria, lasting 6 months or more following initiation of DAY101 as determined by 1) an IRC and 2) the treating investigator	Measured on the proportion of patients with BOR of CR, PR, or SD lasting 6 months or more following initiation of DAY101
To evaluate the duration of overall survival following initiation of DAY101	Measured by the time following initiation of DAY101 to death of any cause in patients treated with DAY101

[redacted]	[redacted]
Exploratory objectives:	**Endpoints:**
To evaluate changes in quality-of-life and health utilities measures using the PedsQL-Core, PedsQL-Cancer, and PROMIS® assessment	Measured by changes from baseline in quality-of-life and health utilities measures using the PedsQL-Core, PedsQL-Cancer, and PROMIS® assessment
To determine the durability of response following discontinuation of DAY101 for patients with a radiographic response to DAY101 (CR or PR as based on RECIST v1.1 criteria) as determined by 1) an IRC and 2) the treating investigator	Measured by the proportion of patients with best overall confirmed response of CR or PR who enter a drug holiday period and time to progression as determined by RECIST v1.1 or clinical criteria

3. INVESTIGATIONAL PLAN

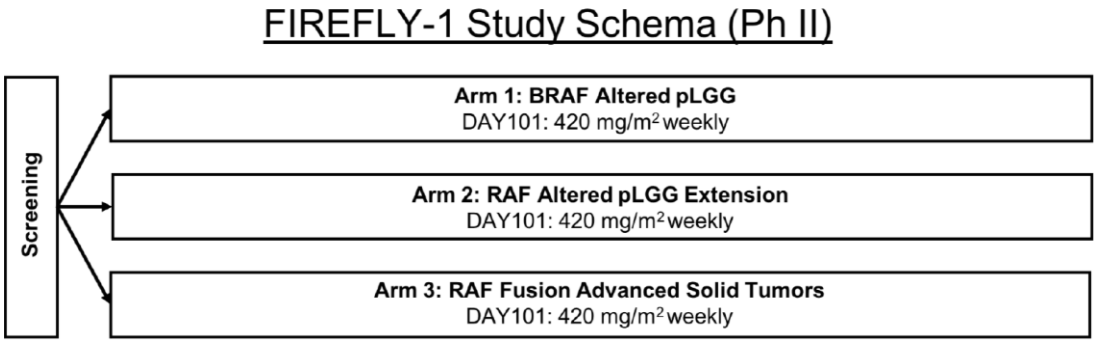
3.1. Overall Study Design and Plan

This is a Phase 2, open-label, multicenter study to evaluate the safety and efficacy of tovorafenib (DAY101) in patients aged 6 months to 25 years with three treatment arms:

- **Arm 1 (Low-Grade Glioma):** Patients aged 6 months to 25 years, inclusive, with recurrent or progressive low-grade glioma harboring a known activating BRAF alteration, including BRAF V600 mutations and KIAA1549: BRAF fusions.
- **Arm 2 (Low-Grade Glioma Extension):** Patients aged 6 months to 25 years, inclusive, with recurrent or progressive low-grade glioma harboring a known or expected to be activating RAF alteration. Opening of Arm 2 to enrollment will be based on the recommendation of the DSMB as described in Section 3.1.2 of the protocol.
- **Arm 3 (Advanced Solid Tumor):** Patients aged 6 months to 25 years, inclusive, with advanced solid tumors harboring a known or expected to be activating RAF fusion.

The study design schema is shown in Figure 1.

Figure 1: Study Design Schema



Abbreviations: pLGG, pediatric low-grade glioma.

The study consists of a screening period, a treatment period, an end-of-treatment (EOT) visit, a safety follow-up visit, and long-term follow-up assessments. Ongoing safety, disease stability/progression, survival, and subsequent anticancer therapies will be assessed in the long-term follow-up period.

3.1.1. Treatment Regimen

For all arms, treatment cycles will repeat every 28 days in the absence of disease progression or unacceptable toxicity. Patients will continue receiving DAY101 for a planned period of 26 cycles (approximately 24 months), until radiographic evidence of disease progression as determined by treating investigator, unacceptable toxicity, decision to enter a "drug holiday" period, patient withdrawal of consent, or death. Patients may be re-treated with DAY101 if there is radiographic evidence of disease progression after drug discontinuation.

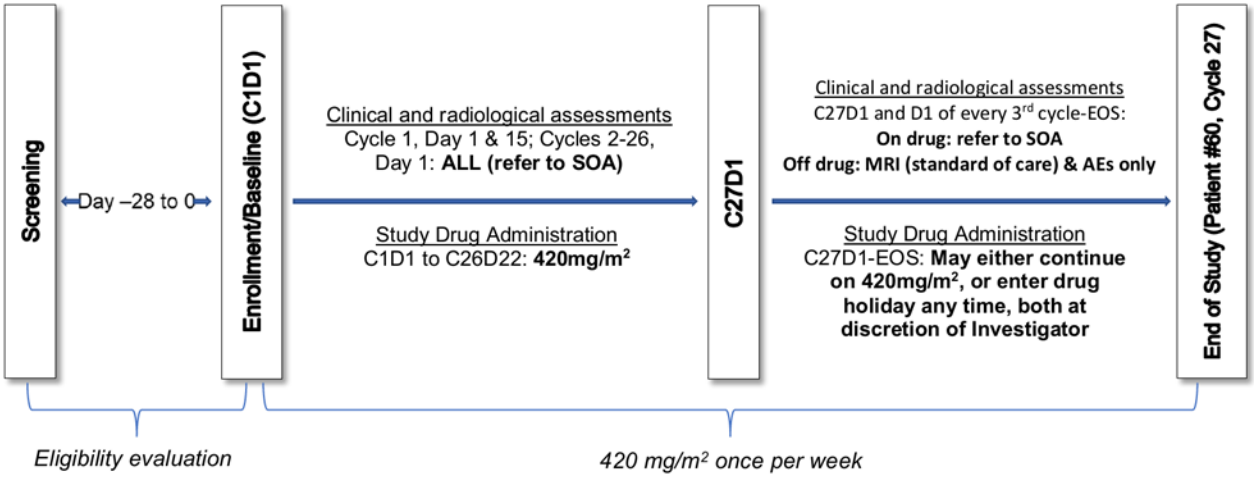
Patients who have radiographic evidence of disease progression may be allowed to continue DAY101 if, in the opinion of the investigator, and approved by the Sponsor, the patient is deriving clinical benefit from continuing study treatment. Patients being treated beyond progression with DAY101 will be reconsented prior to continuation of therapy. Disease assessments for patients being treated beyond progression should continue as per regular schedule.

DAY101 will be administered at the recommended Phase 2 dose (RP2D) dose of 420 mg/m^2(not to exceed 600 mg), PO once weekly (QW) (Days 1, 8, 15, and 22 of a 28-day cycle). Body surface area (BSA(m^2)) will be determined by the Mösteller Formula $\sqrt{height \times weight/3600}$.

DAY101 is administered as an oral tablet or reconstituted liquid suspension formulation.

The study treatment schema is shown in Figure 2.

Figure 2: Treatment Schema



Abbreviations: C, cycle; D, day; EOS, end of study; CT, computerized tomography; MRI, magnetic resonance imaging; SOA, schedule of assessments.

3.2. Determination of Sample Size

Approximately 140 patients in total will be enrolled across all treatment arms of this study. The arms will be enrolled as follows:

- **Arm 1:** A sample size of 60 evaluable patients based on FAS criteria provides 88% power to reject the null ORR of 21%, assuming that the true underlying ORR of DAY101 is 40% based on a test at the 2-sided 0.05 level. A result of at least 20 out of 60 (0.33) will be statistically significant.
- **Arm 2:** Up to 60 patients based on practical consideration to allow patients with pediatric low-grade glioma to receive treatment with DAY101 after Arm 1 has fully accrued and the Drug Safety Monitoring Board (DSMB) has recommended opening to enrollment.
- **Arm 3:** A modified Simon 2-stage design will be used to enroll up to 20 evaluable patients based on evaluation of ORR (confirmed PR or CR per Response Evaluation Criteria in Solid Tumors [RECIST] v1.1)

  The statistical assumptions will require approximately 12 evaluable patients in the first stage and 20 evaluable patients in total. In the first stage, if ≤ 1 objective response (PR or CR per RECIST v1.1) is seen in the first 12 patients, Arm 3 will stop any further recruitment and the treatment will be considered as not effective in this setting; however, if ≥ 2 objective responses occur, an additional eight patients will be recruited.

  A null hypothesis (H_0) of 5% is assumed. A sample size of 20 patients provides 90% power to reject the null ORR of 5%, assuming that the true underlying ORR of DAY101 is 25% based on a test at alpha 1-sided at 0.1. A result of at least three out of 20 will be statistically significant.

3.3. Analysis Data Sets

3.3.1. Efficacy Analysis Sets

The efficacy analysis sets include full analysis set, RANO-LGG analysis set and RAPNO-LGG analysis set.

The full analysis set (FAS) includes all patients enrolled in the study who received at least 1 dose of study treatment and have measurable disease per RANO-HGG as determined by the IRC at baseline.

The RANO-LGG analysis set includes all patients enrolled in the study who received at least 1 dose of study treatment and have measurable disease per RANO-LGG as determined by the IRC at baseline.

The RAPNO-LGG analysis set includes all patients enrolled in the study who received at least 1 dose of study treatment and have measurable disease per RAPNO-LGG as determined by the IRC at baseline.

3.3.2. Safety Analysis Set (SAS)

Safety analysis set (SAS) is defined as all patients enrolled in the study who received at least 1 dose of study treatment.

3.3.3. Per-Protocol Analysis Set (PP)

The per protocol analysis set (PP) will include all patients in FAS without any major protocol deviations as defined by the process below.

Protocol deviations will be reviewed, assessed, and classified within a data review meeting before database lock. The PP will be used to conduct sensitivity analyses for primary efficacy endpoints ORR and for Arm 1 progression-free survival.

Upon database release, protocol deviations will be sent to Day One for review. Decisions regarding the exclusion of patients and/or patient data from PP set will be made prior to database lock.

The PP will be used to conduct sensitivity analyses for primary efficacy endpoints ORR and for Arm 1 progression-free survival.

3.3.4. Pharmacokinetic Analysis Set (PK)

Pharmacokinetic analysis set is defined as patients in the FAS who have at least 1 measurable PK concentration.

3.4. Endpoints

Tumor response will be assessed using RANO-HGG, RAPNO-LGG, RANO-LGG and RECIST v1.1 criteria by 1) an IRC and/or 2) the treating investigator, respectively.

3.4.1. Primary Efficacy Variable – Overall Response Rate (ORR)

Arm 1 primary efficacy endpoint ORR will be calculated by the number of patients with best overall confirmed response of CR or PR as determined by an IRC, using the RANO-HGG criteria for Arm 1 FAS.

A response will be considered as confirmed response when a response assessment of CR or PR is confirmed by a second scan ≥ 28 days after the initial response. If a CR with confirmation scan shows PR or if a PR with confirmation scan shows CR, PR will be assigned.

Patients with initial CR or PR after the start of subsequent anti-cancer therapy will not be included as responders in the ORR calculation.

3.4.2. Secondary Efficacy Variable*s*

Secondary efficacy endpoints include ORR, BOR, PFS, DOR, TTR, and CBR for each arm based on different criteria, as well as OS.

3.4.2.1. Overall Response Rate (ORR)

Following the same definition as Arm 1 primary endpoint, ORR will also be derived as secondary endpoints using RANO-HGG criteria by Investigator for Arms 1 and 2, RAPNO-LGG criteria by IRC for Arms 1 and 2; and using RECIST v1.1 criteria for Arm 3 by IRC and Investigator respectively.

Subjects with confirmed MR by RAPNO-LGG will also be considered as responder. If a CR/PR with confirmation scan shows MR or if a MR with confirmation scan shows CR/PR, MR will be assigned.

Same as primary ORR, patients with initial CR, PR, or MR (RAPNO-LGG only) after the start of subsequent anti-cancer therapy will not be included as responders in the ORR calculation.

3.4.2.2. Best Overall Response (BOR)

BOR is defined as the best overall response (CR, PR, SD, minor response [MR, RAPNO-LGG only], progressive disease [PD], and not evaluable [NE]) recorded from the start of the treatment but prior to the date of any subsequent anti-cancer therapy, among patients in efficacy analysis populations for the three arms. A subject died without any post-baseline imaging assessment will be classified as NE.

3.4.2.3. Progression-Free Survival (PFS)

PFS is defined from the first dose administration of DAY101 to disease progression or death of any cause, whichever occurs first.

Details of PFS censoring are presented in Table 1.

Table 1: Censoring rules of PFS

	Situation	Event / Censored Date	Event/ Censored
1	No evaluable post-baseline results, no death within two scheduled visits after the first dose	First Dose Date	Censored
2	No evaluable post-baseline visits, death within two scheduled visits after the first dose	Death Date	Event
3	Subsequent anti-cancer therapy started prior to the documented progression or death	Date of the last adequate imaging examination prior to subsequent anti-cancer therapy start date	Censored
4	Progression or death (by any cause) immediately after missing two or more consecutive visits	Date of the last adequate imaging examination before progression or death	Censored
5	Progression or death (by any cause) not immediately after missing two or more consecutive visits	Disease progression date, or death date if no PD	Event
6	No progression or death at the time of analysis	Date of the last adequate imaging examination	Censored

The earliest date of measurable tumor, non-measurable tumor and new lesion will be used as PFS event date if it is declared as disease progression at a visit.

For Arm 1 and Arm 2, tumor assessments were done every 3 cycles post treatment. Window for two consecutive visits (measured as the days from the last scan (or from first dose)) is 6 cycles.

For Arm 3, tumor assessments were performed every two cycles through 12 months of treatment, and every three cycles thereafter. Windows for two consecutive visits at different scenarios are calculated as following:

- Window for two consecutive visits after the first dose is 4 cycles
- If the last assessment prior to PD/Death is before or at the end of Cycle 8, window for two consecutive visits is 4 cycles
- If the last assessment prior to PD/Death is at the end of Cycle 10, window for two consecutive visits is 5 cycles
- If the last assessment prior to PD/Death is after or at the end of Cycle 12, window for two consecutive visits is 6 cycles

3.4.2.4. Duration of response (DOR)

Duration of response is defined as the time from the date of initial confirmed response to the date of disease progression or death of any cause. The end date for duration of response should be the same date as the PFS. If a patient has no disease progression and no death after the confirmed response, DOR will use the PFS censoring time.

3.4.2.5. Time to response (TTR)

TTR is measured by the time from first study dose date to the first confirmed response following initiation of DAY101 in FAS and RAPNO evaluable patients with confirmed response of CR or PR or MR (RAPNO-LGG). The date of the first scan of the confirmed response will be considered as the start date of the response.

3.4.2.6. Clinical benefit rate (CBR)

The clinical benefit rate will be evaluated based on the proportion of patients with best overall response of CR, PR, or SD lasting 12 months (6 months for Arm 3) or more following the initiation of DAY101 in FAS patients and RAPNO evaluablefor three arms.

3.4.2.7. Overall Survival (OS)

Overall survival is defined as from the date of first dose to the date of death. A subject not known to have died at the time of analysis will be censored at the date of last known to be alive.

3.4.3. Exploratory Variables

3.4.3.1. Primary ORR and time to response by prior lines of therapies

The Line of Therapy (LOT) will be defined based on the prior systemic anti-cancer therapy in a single agent or a regimen consisting of a combination of therapies. The defined LOT will be entered into eCRF by site as 1, 2, 3, >3, or NA.

The Arm 1 ORR and TTR based on RANO-HGG criteria by IRC will be calculated/summarized by the number of prior lines of therapies.

3.4.3.2. The sum of perpendicular diameters (SPPD)

The sum of perpendicular diameters (SPPD) of measurable lesions along with its change from baseline will be calculated at each assessment, and the best change from baseline SPPD (the minimum) prior to the disease progression, or prior to the start of next subsequent anti-cancer therapy will be derived.

3.4.3.3. Tumor volume change

Changes in total tumor volume following treatment with DAY101 will be characterized by the IRC utilizing volumetric measurement tools. Changes from baseline will be calculated at each assessment, and the best change from baseline prior to disease progression, or prior to the start of subsequent anti-cancer therapy will be derived.

3.4.3.4. Durability of response off treatment for drug holiday

Durability of response will be assessed for patients who have a drug holiday. A patient has a drug holiday if completed 26 cycles treatment with no radiological PD, and was re-treated after the radiographic evidence of PD.

The durability of response following discontinuation of DAY101 will be evaluated for Arm 1/Arm 2 based on RANO-HGG criteria, for Arm 3 based on RECIST 1.1 criteria by Investigator.

The durability of response will be measured by the proportion of patients with confirmed response of CR, PR who entered into a “drug holiday” period after completed 26 cycles of DAY101 treatment and re-treated after radiology evidence of disease progression, and the corresponding DOR of those subjects.

3.4.3.5. Time to first subsequent anti-cancer therapy (TFST)

TFST was defined as the time from the date of first dose to the start date of the first subsequent anti-cancer therapy (not including the re-treatment of DAY101) following the discontinuation of DAY101, or date of death, whichever is earlier.

Any patient not known to have received a first subsequent anti-cancer therapy, or to have not died at the time of the analysis, will be censored at the last date the patient was known not to have received a first subsequent anti-cancer therapy (i.e., the last contact date where this was confirmed).

3.4.3.6. ORR, BOR, PFS, DOR, TTR and CBR based on RANO-LGG

ORR, BOR, PFS, DOR, TTR and CBR will be assessed based on RANO-LGG by IRC for Arm 1.

Subjects with confirmed MR by RANO-LGG will also be considered as responder. If a CR/PR with confirmation scan shows MR or if a MR with confirmation scan shows CR/PR, MR will be assigned. Patients with initial CR, PR or MR after the start of subsequent anti-cancer therapy will not be included as responders in the ORR calculation.

3.4.3.7. PFS by BOR based on RANO-LGG

PFS distribution by best overall response based on RANO-LGG criteria by IRC will be presented for RANO-LGG analysis set in Arm 1.

3.4.3.8. PFS by BOR based on RAPNO-LGG

PFS distribution by best overall response based on RAPNO-LGG criteria by IRC will be presented for RAPNO-LGG analysis set in Arm 1.

3.4.3.9. Analysis of Ongoing Treatment by IRC-assessed Best Overall Response (RANO-HGG Criteria)

The duration of ongoing treatment will be analyzed by BOR based on RANO-HGG criteria by IRC in the Full Analysis Set in Arm 1.

3.4.4. Safety Variables

All treated patients will undergo a safety follow-up visit at 30 days after the last dose.

Safety endpoints include study drug exposure, adverse events, laboratory parameters, vital signs, ECG, LVEF or fractional shortening, visual acuity outcomes, Lansky or Karnofsky score, and physical examination.

All safety variables will be assessed in the safety analysis sets for Arm 1, Arm 2, and Arm 3.

3.4.4.1. Adverse Event

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical study patient, temporally associated with the use of study intervention, whether or not considered related to the study intervention. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Information regarding the occurrence of AEs will be collected throughout participation in this study, starting from the time of treatment with DAY101 until 30 days after the last dose of DAY101.

TEAE will be defined as an AE that starts on or after the first administration of study drug until 30 days after the last dose of DAY101.

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- In patient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Deaths due to disease progression are not reportable serious adverse events (SAEs).

3.4.4.2. Clinical laboratory values

Local laboratories will be used for laboratory safety evaluations in this study. For a list of the parameters to be evaluated, see Table 2 .

Table 2: List of Laboratory Parameters

Clinical Serum Chemistry	Alkaline phosphatase albumin Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Creatinine phosphokinase (CPK) blood urea nitrogen/urea cholesterol creatinine glucose lactate dehydrogenase total bilirubin total protein sodium potassium chloride phosphorus bicarbonate
Hematology	CBC with differential White blood cell (WBC) count Neutrophil count & percentage Lymphocyte count & percentage Monocyte count & percentage Eosinophil count & percentage Basophil count & percentage Red blood cell (RBC) count Hemoglobin Hematocrit Platelet count
Pregnancy Test	Urine/Serum pregnancy test
Thyroid Function Tests	Thyroid stimulating hormone (TSH) Triiodothyronine (T3) and

	Tetraiodothyronine (T4) [either free or total T3/T4 may be assessed based on the local practice]

Laboratory normal ranges will be provided by the local laboratory. For parameters where a National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v.5.0 scale exists, laboratory results will be graded according to the NCI CTCAE v.5.0 severity grade. For parameters for where an NCI CTCAE v.5.0 scale does not exist, an indicator of whether the value is below, within, or above the normal range will represent severity instead.

Routine laboratory tests will be performed locally. Laboratory values will be assigned toxicity grades when available using the NCI CTCAE, version 5.0 or later.

3.4.4.3. Vital signs (VS)

Vital signs include the following:

- Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP).
- Heart rate, respiratory rate, body temperature.
- Height in cm, weight in kg, and BSA(m^2) determined by the Mösteller Formula: $\sqrt{height \times weight/3600}$.

Normal ranges for blood pressure are based on age, sex, and height in age 1-17 years old (refer to Appendix 1).

Normal Range for pulse, temperature, and weight is listed as below:

- Pulse Rate (beats/min)
  - Low: ≤50 bpm and ≥15 bpm decreases from baseline;
  - High: ≥120 bpm and ≥15 bpm increases from baseline.
- Temperature (°C)
  - High = ≥38.3 °C and ≥1 °C increase from baseline.
- Weight (kg)
  - Low = ≥ 7% relative decrease from baseline;
  - High = ≥ 7% relative increase from baseline.

3.4.4.4. Electrocardiogram

For each electrocardiogram (ECG) parameter, the average of triple ECG results at each timepoint will be derived for summaries and analysis.

The following change from baseline will be evaluated:

- Change from baseline QT interval corrected for HR by Fridericia's formula (ΔQTcF).
- Change from baseline PR interval (ΔPR).
- Change from baseline QRS interval (ΔQRS).

- Change from baseline heart rate (ΔHR).

3.4.4.5. Left ventricular ejection fraction (LVEF)

Echocardiogram or Multiple-Gated Acquisition (MUGA) to assess LVEF or fractional shortening (FS) will be performed following the protocol schedule. Any clinically significant changes in echocardiogram (ECHO)/MUGA that occur during the study will be reported as AEs in the eCRF.

3.4.4.6. Karnofsky or Lansky Performance Status Scales

The Karnofsky score (0: Dead to100: Normal) [1] will be assessed for those aged 16 years or older (Table 3), and the Lansky score (0: Unresponsive to100: Full active) [2]will be assessed for those younger than 16 years (Table 4). Karnofsky or Lansky Performance Status Scales will be classified into classes of 0, 10-40, 50-70, and 80-100. When patients turn 16 years old, they will use Karnofsky Performance assessment.

Table 3: Karnofsky Performance Score (≥ 16 years old)

Score	Karnofsky Description
100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares of self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

Table 4: Lansky Performance Score (< 16 years old)

Score	Lansky Description
100	Fully active, normal
90	Minor restrictions in strenuous physical activity
80	Active, but tired more quickly
70	Greater restriction of plan *and* less time spent in play activity
60	Up and around, but active play minimal; keep busy by being involved in quieter activities
50	Lying around much of the day, but gets dressed; no active playing, participants in all quiet play and activities
40	Mainly in bed; participates in quiet activities
30	Bed bound; needing assistance even for quiet play
20	Sleeping often; play entirely limited to very passive activities
10	Doesn't play; doesn't get out of bed
0	Unresponsive

3.4.4.7. Physical Examination

Physical examinations include review of systems (chest, extremities, genitourinary, head, ears, eyes, nose, throat, lymph nodes, musculoskeletal, pulmonary, and skin) during screening. Symptom-directed physical examination, including measurement of weight and height may be performed at other time points after screening.

3.4.4.8. Visual Acuity (VA) Outcomes

Patients who have an underlying visual function deficit related to the primary malignancy or optic pathway glioma (OPG) will have a visual acuity examination every time they have a radiographic disease assessment and at the EOT visit. Investigator assessment of visual acuity changes will be provided at each timepoint and may have incorporated practical and clinical factors such as patient age, methodology, and compliance into overall interpretation.

The best corrected visual acuity for each eye will be compared to baseline in Arm 1 and Arm 2 safety analysis sets. The change from baseline of BCVA at each time point will be calculated.

VA progression measured by age-appropriate methodologies such as Teller Acuity Cards® II, HOTV and EDTRS and is defined as an increase of ≥ 0.2 logMAR (corrected for age) from baseline. VA response is an improvement (decrease) of ≥ 0.2 logMAR (corrected for age) from baseline.

A 0.2 logMAR worsening (or up to a two-card drop in Teller acuity) will not be considered visual progressive disease at the first on-therapy staging evaluation (at the end of cycle 3) if the tumor response assessed at the same timepoint is SD or better. In these cases, a repeat VA assessment will be required six weeks later to confirm that further visual progression is not occurring. If the repeat VA is stable or improved from pretreatment baseline, the patient will remain on protocol therapy.

3.4.5. Health-Related Quality of Life

The PedsQL 4.0 Generic Core Scales and the PedsQL 3.0 Cancer Module domains and global scale will be used to assess treatment and disease impact on quality of life.

The PROMIS Pediatric/Parent Proxy Profile 49 (or 57 for patients greater than 17 years of age) will be used to assess treatment and disease impact on overall health.

These health-related quality of life data will be analysed and reported separately.

3.4.6. Pharmacokinetic Variables

Plasma concentrations of DAY101 will be determined with a validated bioanalytical assay.

Where possible, the following PK parameters will be calculated where appropriate:

- Maximum plasma concentration (C_{max})
- Time to C_{max} (T_{max})
- Minimum plasma concentration (C_{min})
- Average plasma concentration (C_{ave})
- Area under the plasma concentration-time curve from time zero to t (AUC_{0-t})

- Apparent plasma clearance (CL/F)

4. STATISTICAL METHODS

4.1. General Presentation Considerations

4.1.1. Populations for analyses

Efficacy analysis will be performed based on full analysis set (FAS), RANO-LGG analysis set, RAPNO-LGG analysis set, and per-protocol analysis set (PP).

Table 5 contains the analysis population for the study primary and secondary/exploratory endpoints based on RANO-HGG, RANO-LGG, RAPNO-LGG, RECISIT v1.1 criteria by IRC and/or by Investigator.

Table 5: Efficacy Analysis Population of Primary, Secondary and Exploratory Endpoints

Endpoints	Reviewer	RANO-HGG evaluable (FAS)	RANO-LGG evaluable	RAPNO-LGG evaluable	RECIST evaluable
ORR (BOR)	IRC	ARM 1 (Primary), ARM 2	ARM 1, ARM 2	ARM 1, ARM 2	ARM 3
	Investigator	ARM 1, ARM 2	N/A	N/A	ARM 3
DOR	IRC	ARM 1, ARM 2	ARM 1, ARM 2	ARM 1, ARM 2	ARM 3
	Investigator	ARM 1, ARM 2	N/A	N/A	ARM 3
PFS	IRC	ARM 1, ARM 2	ARM 1, ARM 2	ARM 1, ARM 2	ARM 3
	Investigator	ARM 1, ARM 2	N/A	N/A	ARM 3
TTR	IRC	ARM 1, ARM 2	ARM 1, ARM 2	ARM 1, ARM 2	ARM 3
	Investigator	ARM 1, ARM 2	N/A	N/A	ARM 3
CBR	IRC	ARM 1, ARM 2	ARM 1, ARM 2	ARM 1, ARM 2	ARM 3
	Investigator	ARM 1, ARM 2	N/A	N/A	ARM 3

Abbreviations: BOR = Best overall response; CBR = Clinical benefit rate; DOR = Duration of response; N/A = Not Available; ORR = Overall response rate; PFS = Progression free survival; TTR = Time to response.

Disposition, demographics and baseline characteristics, medical history, prior and concomitant medications summaries, and prior anti-cancer therapy will be summarized/analyzed based on safety analysis set (SAS).

Safety analysis will be performed on SAS.

4.1.2. General Statistical Considerations

Continuous data will be summarized in terms of the mean, standard deviation (StD), median, minimum, maximum, and number of observations, unless otherwise stated. Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. In general, the minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The StD will be reported to two more decimal places than the raw data recorded in the database. The maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number and percentages of patients. Percentages will be presented to one decimal place. Percentages will not be presented for zero counts.

A month is operationally defined to be 30.4375 days. Six months is operationally defined to be 182.625 days. One year is defined to be 365.25 days.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001".

Confidence intervals (CI) for ORR/CBR will be presented to 3 decimal places.

All report outputs will be produced using SAS® version [9.4] or a later version in a secure and validated environment.

4.1.3. Baseline

In general, baseline is the last available assessments prior to the start of DAY101 on Cycle 1 Day 1, except the baseline of ECG which is the average of triple ECGs at the last timepoint prior to the first dose of Day 101.

Assessments on the day of the first dose where neither time nor a nominal pre-dose indicator are recorded will be considered prior to the first dose if such assessments are required by the protocol to be conducted before the first dose of study treatment.

The average will be taken as a baseline value if there is more than one value equally eligible (same date/datetime prior to the first dose of study drug). For categorical results (i.e. some of the urinalysis measurements) where taking an average is not possible then the best value would be taken as baseline as this is the most conservative.

4.1.4. Study day

Study day will be calculated relative to the date of first dose DAY101 (i.e. Study Day = Assessment Date - Date of first dose + 1). For visits that occur prior to the date of the first dose of study drug, study day is calculated as date of assessment - date of the first dose. There is no study day 0.

4.1.5. Analysis Visit Window

No analysis visit windows will be identified for the safety summaries. Visit-based data summaries will be based on the protocol scheduled visits.

If more than one assessment is available for a given post baseline visit, the worst observation (e.g. highest CTCAE grade or further away from the normal range for laboratory results, the highest value for vital signs) will be selected for visit-based summaries as this is the most conservative.

Unscheduled assessments will be included in listings, but not in visit-based summaries. All unscheduled assessments will be considered in summaries for the extreme post-baseline value (e.g. the minimum/maximum, the best/worst post-baseline).

4.1.6. Handling Missing Data

In general, other than for partial dates, missing data will not be imputed and will be treated as missing.

All analyses and descriptive summaries will be based on the observed data. Unless otherwise specified, missing data will not be imputed. The number and percentage of patients with missing data may be summarized by major reasons (e.g. assessment not performed due to COVID-19 epidemic).

Safety assessment values of the form of "< or ≤ x" (i.e. below or equal to the lower limit of quantification) or "> or ≥ x" (i.e. above or equal to the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but will displayed as is in listings.

4.1.6.1. Missing and Partial Dates

Imputing partial AE and prior/concomitant medication start dates:

1. If the year is unknown, the date will not be imputed and will be assigned a missing value.
2. If the month is unknown, then:
   - If the year matches the first dose date, then impute to the month and day of the first dose date.
   - Otherwise, impute to 'January 1st' of the year.
3. If the day is unknown, then:
   - If the month and year match the first dose date, then impute to the day of the first dose date.
   - Otherwise, impute to the 1st of month.

Imputing partial prior/concomitant medication stop dates:

1. If the year is unknown, the date will not be imputed and will be assigned a missing value.
2. If the month is unknown, then assign 'December 31st'.
3. If the day is unknown, then impute to the last day of the month.
4. If the resulting imputed end date is after the end of study date, then impute as the end of study date.

Imputing partial Adverse events end date:

No imputation will be applied for the adverse event end date.

Imputing missing/partial death dates:

1. Impute as the last known alive date + 1 day if the year/month from partial death date is the same as the last known alive date or if completely missing.
2. If the death year/month is later than the last known alive date:
    - If missing day only, impute as the 1st of the month.
    - If missing day and month, impute as the 1st of January

Imputing partial first subsequent anti-cancer therapy start date:

1. If only day is missing or day and month are missing, then impute as max(earliest possible date of the partial date information, last dosing date + 1)
2. If the start date is totally missing, then impute as the last dosing date + 1.

4.2. Statistical Analyses

4.2.1. Patient Information

4.2.1.1. Patient Disposition

Patient disposition will be summarized as follows:

- Number of patients treated (i.e., received at least one dose of study drug treatment)
- Number of patients in each analysis populations
- Number and percentage of patients who early discontinued from the study (including reasons EOS)
- Number and percentage of patients who early discontinued from the treatment (including reasons for EOT)
- The number and percentage of patients who died during the study, during 30 days post end of treatment safety follow-up period, and during long term follow-up period

A by-patient listing of analysis set details will be provided. This listing will include information such as: included in each analysis set, the first/last dose date, end of treatment status, end of study status, and EOT/EOS reasons.

Screening failures and patients not included in the per-protocol set will be presented in listings, respectively.

4.2.1.2. Protocol Deviations

A summary of the number and percentage of patients with a major protocol deviation as well as by type of deviation will be provided. A by-patient listing of all protocol deviations classified as minor or major will be provided.

4.2.1.3. Demographic and Other Baseline Characteristics

The following demographic and baseline variables at screening period will be summarized based on the SAS:

- Race
- Ethnicity
- Gender
- Age
- Age group: 6 months to < 2 years, 2 years to < 6 years, 6 years to < 12 years, 12 years to < 16 years, 16 years to ≤ 25 years
- Baseline height and weight
- Baseline height and weight Proposed Pediatric Study Request (PPSR)
- Baseline body surface area

Disease factors:

- Cancer history (primary tumor location, histology, pre-operative staging, post-operative staging)
- Prior BRAF inhibitor therapy (yes, no)
- Prior Mitogen activated protein kinase (MEK) inhibitor therapy (yes, no).
- BRAF Alteration (BRAF V600E/K mutation, BRAF fusion, and Other)
- Karnofsky/Lansky performance score (0-100)
- Baseline tumor volume by IRC
- Baseline SPPD by IRC and Investigator
- The number of prior lines of therapies

Baseline height and weight per PPSR is to assess patients' height/weight against standard growth chart (compare to the height and weight curves on Central for Disease Control and Prevention website).

A listing of patents' demographic and baseline information will be provided.

4.2.1.4. Medical History

Medical History will be coded by Medical Dictionary for Regulatory Activities (MedDRA) 23.0 or higher version.

The number and percentage (%) of patients reporting a medical history, as recorded on the eCRF, will be summarized by system organ class (SOC) and preferred term (PT).

A by-patient listing of medical history will be provided.

4.2.1.5. Prior and Concomitant Medication

Prior medication is defined as medications with an end date prior to the first dose of study treatment. Concomitant medication is defined as medications that (1) started before the first dose of study drug and are continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug.

Prior and concomitant medications will be coded to the generic term using the current version of the World Health Organization Drug (WHO Drug) Dictionary.

The number (%) of patients who took prior and concomitant medications will be summarized by ATC level 3 classification code and WHO Drug preferred term. If a patient has taken concomitant medications more than once, the patient will be counted only once in the total.

By-patient listings of prior and concomitant medication including dose, route, unit, frequency of administration, indication for administration, and dates of medication will be provided.

4.2.1.6. Prior Anti-cancer therapy

The number (%) of patients received any prior systemic anti-cancer therapy and received any prior radiotherapy will be summarized, the best prior systemic therapy response will be included in the table.

Prior systemic anti-cancer therapy, prior and concurrent radiotherapy data will be provided in listings.

4.2.1.7. Prior and Concurrent Surgery or Procedures

Listing for prior and concurrent surgery and procedures will be provided.

4.2.2. Treatment Exposure and Compliance

Exposure will be summarized on the safety analysis set. The following summaries will be produced:

- Number of cycles treated (Including DAY 101 re-treatment cycles after drug holiday). A cycle will be counted if received at least one dose of DAY101 in a cycle
- Duration of maximum exposure (days) = date of last dose of study drug including DAY101 re-treatment after drug holiday– date of first dose of study drug + 1
- Length of drug holiday = one day prior to the date of DAY101 re-treatment – date of last dose of study drug prior to the drug holiday
- Duration of exposure (days) excluding drug holiday = Duration of maximum exposure – the length of drug holiday.
- Total actual dose received (mg) overall (Including DAY 101 re-treatment after drug holiday)
- Total expected dose (mg) overall (Including DAY 101 re-treatment cycles after drug holiday) = total planned dose excluding intended interruption due to AE, COVID-19, disease progression, etc.

- Treatment compliance (%) overall (Including DAY 101 re-treatment cycles after drug holiday) = total actual dose overall (mg) / total expected dose overall (mg) ×100%.
- Number of patients who completed 26 cycles treatment period

A by-patient listing of study drug administration will be provided.

4.2.3. Efficacy Analyses

All efficacy analysis of endpoints by RANO-HGG criteria will be based on FAS. All efficacy analysis of endpoints by RANO-LGG criteria will be based on RANO-LGG analysis set. All efficacy analysis of endpoints by RAPNO-LGG criteria will be based on RAPNO-LGG analysis set. Selected analysis may be repeated for PP as needed.

By-patient listings of all primary and secondary efficacy endpoints will be provided.

4.2.3.1. Primary Efficacy Analyses

4.2.3.1.1. Overall Response Rate (ORR)

The number and percentage of patients with best overall confirmed response (CR/PR) by IRC using RANO-HGG criteria will be calculated on Arm 1 FAS population. An exact binomial test will be used to compare the observed response rate to the hypothesized null ORR of 21%, and a 95% CI will be calculated using the Clopper-Pearson method.

Sensitivity analyses for Arm 1 ORR based on PP population will be performed.

4.2.3.1.2. Subgroup analysis for ORR

The uniformity of the treatment effects for the primary efficacy will be performed in the following subgroups (defined Section 4.2.1.3) for Arm 1 FAS population:

- BRAF-alteration (BRAF fusion versus BRAF mutation)
- Number of prior lines of therapies
- Prior MEK inhibitor therapy
- Prior BRAF inhibitor therapy
- Sex
- Age group as defined in Section 4.2.1.3
- Race

The same methodology as the ORR primary analysis will be performed in each subgroup. Subgroup categories may be collapsed for small subgroups (i.e. less than 5).

4.2.3.2. Secondary Efficacy Analyses

If data are sparse for any of the secondary efficacy endpoints, statistical analysis may not be performed. Only descriptive summary statistics of available data or listings will be produced as appropriate.

4.2.3.2.1. Overall Response Rate (ORR)

The number and percentage of patients with best overall confirmed response by Investigator using RANO-HGG criteria in Arm 1 will be calculated. The ORR along with 95% exact Clopper-Pearson confidence interval will be calculated.

Same analysis and summaries will also be produced for ORR using RAPNO-LGG criteria in Arm 1, and RANO-HGG criteria (and RAPNO-LGG criteria, if applicable) in Arm 2; and using RECIST v1.1 criteria by IRC and Investigator in Arm 3.

4.2.3.2.2. Best Overall Response (BOR)

The number and percentage of patients in each response category (CR, PR, MR [RAPNO-LGG only], SD, PD and NE) will be summarized in efficacy analysis populations of Arm 1, 2, and 3.

The associated swimmer plots for each arm will be provided. Confirmed CR/PR, MR (RAPNO-LGG only), SD, PD, and NE will be marked in the swimmer lane based on different criteria by IRC and(or) by Investigator (as detailed in Table 5). The end of the lane is the last contact date or death date if subject died. The treatment end date will also be marked in the lane.

The swimmer plot by the same subgroup as primary ORR will be provided for Arm 1 FAS.

4.2.3.2.3. Progression-Free Survival (PFS)

PFS will be summarized in efficacy analysis populations of Arm 1, 2, and 3 and graphically displayed by the Kaplan-Meier method. The number (%) of patients with PFS events due to disease progression or due to death, and categories of PFS censoring reason will be summarized.

Kaplan-Meier (K-M) curves, K-M estimates 25th, 50th (median), and 75th percentiles along with their corresponding 2-sided 95% CIs for PFS will be presented. The percentage of progression free survival with 95% CI at timepoints 3, 6, 12, 18, and 24 months will be provided.

Arm 1 PFS by IRC/Investigator will be repeated for PP population.

4.2.3.2.4. Duration of response (DOR)

DOR will be analyzed using the same methodology as for the analysis of PFS. The analysis will be performed in efficacy analysis populations who have a best overall confirmed response of CR or PR or MR (RAPNO-LGG only) in Arm 1, 2, and 3.

4.2.3.2.5. Time to Response (TTR)

Statistical summaries for TTR will provided based on efficacy analysis populations of Arm 1, 2, and 3.

4.2.3.2.6. Clinical benefit rate (CBR)

The clinical benefit rate will be analyzed as the same method as ORR.

4.2.3.2.7. Overall Survival (OS)

Descriptive summaries will be provided for OS data in each arm.

4.2.3.3. Exploratory Analyses

The following exploratory analysis will be performed based on appropriate efficacy analysis sets.

4.2.3.3.1. Primary ORR and Time to Response by Prior Lines of Therapies

The Arm 1 ORR and TTR based on RANO-HGG, RANO-LGG and RAPNO-LGG criteria by IRC will be summarized (or analyzed if data allow) by the number of prior lines of therapies.

The ORR by the number of prior lines of therapies will be calculated, with the corresponding 95% CI using the Clopper-Pearson method for each subgroup of the number of prior lines of therapies if having sufficient data in each subgroup.

TTR by the number of prior lines of therapies will be summarized.

4.2.3.3.2. SPPD and Tumor volume change

SPPD and tumor volume original values, change from baseline at each scheduled visit, and the best change from baseline will be summarized. Waterfall plots with each patient's best percentage change in SPPD/tumour volume ordered from the largest increase to the largest decrease will be provided. Spider plots for the SPPD/tumor volume change from baseline over time will also be provided.

4.2.3.3.3. Durability of Response off treatment for drug holiday

The proportion of patients with confirmed response of CR or PR or MR (RAPNO-LGG only) who entered into a "drug holiday" period will be calculated (the corresponding 95% CI will be calculated using the Clopper-Pearson method if data allow).

The number (%) of subjects with best objective response SD and entered into a "drug holiday" will be summarized as well.

The DOR among Arms 1, 2, and 3 efficacy analysis populations of patients with best overall confirmed response who enter a drug holiday period will be analyzed using the same methodology as DOR, and graphically displayed using the Kaplan-Meier method if needed.

The duration of "drug holiday" and the time from the start of drug holiday to disease progression will be summarized for all subjects who entered into "drug holiday", and by subjects' BOR categories.

4.2.3.3.4. Time to First Subsequent Anti-cancer Therapy (TFST)

Time to first subsequent anti-cancer therapy among Arm 1 FAS patients who discontinue DAY 101 therapy will be analyzed using the same methodology as PFS.

4.2.3.3.5. ORR, BOR, PFS, DOR, TTR and CBR based on RANO-LGG

The number and percentage of patients with best overall confirmed response by IRC using RANO-LGG criteria for Arm 1 will be calculated. The ORR along with 95% exact Clopper-Pearson confidence interval will be calculated.

The number and percentage of patients in each response category (CR, PR, MR, SD, PD and NE) will be summarized for Arm 1.

PFS will be analyzed using the same methodology as specified in section 4.2.3.2.3 by IRC for Arm 1.

DOR will be analyzed using the same methodology as for the analysis of PFS. The analysis will be performed in patients who have a best overall confirmed response of CR or PR or MR for Arm 1.

TTR and CBR will also be analyzed for Arm 1.

4.2.3.3.6. Analysis of PFS by BOR based on RANO-LGG/RAPNO-LGG

The Kaplan-Meier (KM) method will be used to estimate PFS distribution by best overall response based on RANO-LGG/RAPNO-LGG criteria by IRC in Arm 1 patients. The KM-estimated PFS curves in each BOR category (CR, PR, MR, SD, or PD/NE) will be presented for a visual description of the differences of PFS across BOR categories. The 6-month, 9-month and 12-month rates will be used to describe PFS in each BOR category. Log-rank tests will be conducted comparing the PFS of patients with a BOR of MR against the PFS of patients in other BOR categories, and corresponding two-sided nominal p-values will be presented without adjusting for multiple comparisons.

4.2.3.3.7. Analysis of Ongoing Treatment by IRC-assessed Best Overall Response (RANO-HGG Criteria)

The number of patients who are still on treatment will be summarized based on RANO-HGG criteria by IRC in the Full Analysis Set. The median and range of the duration of the ongoing treatment will also be analyzed by BOR.

4.2.4. Safety Analyses

Unless specified otherwise, all safety summaries and analyses will be based upon the Safety Analysis Set.

For safety by-visit summaries, number and percentage of patients missing assessment results due to COVID-19 epidemic will be presented.

4.2.4.1. Adverse Events

The AE terms will be coded by system organ class (SOC) and preferred term (PT) using the MedDRA (Version 23.0 or later). AEs will also be graded according to the latest version of NCI CTCAE grade.

In general, only TEAEs will be included in summary tables. AEs occurring prior to first dose of study treatment and AEs occurring after 30 days of last dose of study treatment will be listed separately as needed.

4.2.4.1.1. Summary of Adverse Events

Summary information (the number and percent of patients by treatment) by SOC and PT will be tabulated for:

- All TEAEs
- All TEAEs causally related to study medication
- TEAEs with CTCAE grade 3 or higher
- TEAEs with CTCAE grade 3 or higher, causally related to treatment
- TEAEs with outcome of death
- TEAEs with outcome of death causally related to treatment
- TEAEs leading to dose reduction
- TEAEs leading to dose interruption
- TEAEs leading to dose modification (dose reduction or dose interruption)
- All Serious TEAEs
- All Serious TEAEs causally related to study medication
- TEAEs leading to discontinuation of treatment
- TEAEs leading to discontinuation of treatment, causally related to treatment
- TEAEs by age group (Defined in Section 4.2.1.3)
- All Serious TEAEs causally related to study medication by age group (Defined in Section 4.2.1.3)

An overall summary of the number and percentage of patients in each category will be presented.

AEs will be assigned CTCAE grades and summaries of the number and percentage of patients will be provided by maximum reported CTCAE grade, SOC and PT.

Patients having the same TEAE more than once over the course of the study will be counted only once in the calculation of incidence for that TEAE. Similarly, if a patient had more than one TEAE in a single SOC, this patient will be counted only once in the total number of patients with TEAE for that SOC; if a patient had more than one TEAE for a PT, this patient will be counted only once in the total number of patients with TEAE for that PT. If a patient had a TEAE more than once within a SOC or PT, the occurrence with the highest CTCAE grade/maximum severity will be used in the calculation of the incidence of individual TEAE by CTCAE grade/severity. If relationship to treatment is missing for an AE it is assumed to be related.

Where AE onset date is missing or partially missing, it will be imputed as the imputation rule specified in Section 4.1.6.1. AE with missing onset date will be considered as TEAE.

By subject listings for all AEs (including TEAE and non-TEAE), serious AE, treatment related AE, AEs leading to study drug discontinuation, and AEs with an outcome of death will be provided. TEAEs will be flagged in those listings. All reported AEs will be listed along with the date of last dose, date of onset, date of resolution (if AE is resolved), duration of AE (if AE end

date is not partial or missing), CTCAE grade, seriousness (except SAE listing), action taken, outcome and relationship to study drug.

A separate listing for AEs onset within 30 days after the last dose will be provided.

4.2.4.1.2. Adverse Events of Special Interest

Adverse events of special interest (AESI) of DAY101 will be summarized as below based on TEAEs:

- Rhabdomyolysis/myopathy (Narrow scope), based on the selected terms from SMQ "Rhabdomyolysis/myopathy", will include the following:
  - Muscle infarction
  - Muscle necrosis
  - Myoglobin blood increased
  - Myoglobin blood present
  - Myoglobin urine present
  - Myoglobinaemia
  - Myoglobinuria
  - Myopathy
  - Myopathy toxic
  - Necrotising myositis
  - Rhabdomyolysis
  - Thyrotoxic myopathy
- Ventricular arrhythmias, based on SMQ "Ventricular tachyarrhythmias"
- Intra-tumoral hemorrhage, based on SMQ "Haemorrhagic central nervous system vascular conditions" and MedDRA PT "Tumour haemorrhage"
- Secondary primary malignancies, based on SMQ "Non-haematological malignant tumours"
- Ophthalmologic events, based on MedDRA SOC "Eye disorders", excluding HLGTs "Congenital eye disorders (excl glaucoma)", "Ocular neuromuscular disorders", and "Ocular neoplasms"

The AESIs will be summarized by group term, PT and CTCAE grade. A separate listing for AESIs will be provided.

4.2.4.2. Clinical Laboratory Values

Summary tables for laboratory parameters will include the following:

- For quantitative results, the assessment results along with the change from baseline will be descriptively summarized by protocol scheduled visits, including the maximum/minimum post-baseline value.
- For qualitative results, the number (%) of patients of each recorded results will be summarized by protocol scheduled visits.
- Shift table comparing baseline and post-baseline values in terms of normal range (low, normal, high, missing) and by CTCAE grade (Grade 0 to Grade 4) will be produced, presenting numbers and percentages in each intersection of baseline/post-baseline categories.
- Incidence (number and percent) of patients with outside normal range laboratory values by scheduled visits and overall will be presented.

Optional laboratory parameters will be listed, but not summarized.

By-patient listings of all laboratory data, with abnormal values flagged, will be provided. Pregnancy testing results will be presented in a listing.

4.2.4.3. Vital Signs

Summary statistics (mean, median, standard deviation, minimum and maximum) of the original values and change from baseline to post-baseline assessments will be provided by assessment for all vital sign parameters and body weight at each time point.

A shift table comparing baseline versus post-baseline values in terms of normal range (low, normal, high, or missing) will be produced, presenting numbers and percentage in each intersection of baseline/post-baseline categories.

The number and percentage of patients with abnormal change values will be summarized for each vital sign parameter by visit.

All vital signs data will be listed.

4.2.4.4. ECG

The average of triple ECG results at the same timepoint will be used for the summaries. In case of missing one or two assessment(s) of triple ECGs, the average of available results will be used.

QT intervals were corrected for heart rate (QTc) using Fridericia's correction factors (QTcF). The adequacy of the correction method will be assessed graphically (plots of QT and QTcF versus RR) and will be provided in the separate cardiac safety modeling report if applicable. Supplementary transformations may be considered, as appropriate.

The absolute values along with the changes from baseline will be summarized for QT, HR, RR, PR, QRS, and QTcF by protocol scheduled visit. For each patient, the maximum change from baseline will be calculated as well as the maximum post-baseline value.

Outlier analysis of the QTcF data will be conducted and summarized as follows:

- The number of patients with maximum post baseline corrected QT values ≥ 480 msec.
- The number of patients with maximum post baseline corrected QT values ≥ 500 msec.
- The number of patients with an increase from baseline corrected QT values ≥ 60 msec.
- The number of patients with corrected QT values ≥ 500 msec, and an increase from baseline corrected QT values ≥ 60 msec

Shift tables will be provided for baseline versus worst on study QTcF using Maximum CTCAE Grade.

The effect of drug concentrations on QTcF change from baseline will be explored graphically. Additional concentration-QTcF analyses may be performed. Data may be pooled with other study results and/or explored further with C-QTc or PK/PD models. Concentration-QTc analyses will be provided in the separate cardiac safety modeling report.

All ECG data will be presented in listings.

4.2.4.5. Left Ventricular Ejection Fraction (LVEF) / Shortening Fraction (FS)

Visit-based summaries of the assessment results, along with the change from baseline will be provided.

The number and percentage of patients with abnormal post-baseline LVEF or FS value meet below criteria will be summarized by visit, and meet the criteria at least one post-baseline assessment:

For LVEF,

- ≥10 percentage points decrease from baseline, and absolute value < 50%, or
- ≥15 percentage points decrease from baseline, and absolute value ≥ 50%

For FS,

- ≥10 percentage points decrease from baseline, and absolute value < 29%, or
- ≥15 percentage points decrease from baseline, and absolute value ≥ 29%

All LVEF/ FS data will be presented in data listings.

4.2.4.6. Karnofsky or Lansky Performance Status Scales

The number and percentage of patients in each category on the Karnofsky or Lansky Performance Status scale (0, 10-40, 50-70, and 80-100) will be summarized at each protocol scheduled visit.

By-patient listings of scores for Karnofsky or Lansky Performance Status scales will be provided.

4.2.4.7. Physical Examination

Physical examination data will be presented in a listing and results with clinical significance abnormalities will be flagged.

4.2.4.8. Visual Acuity Outcomes

The BVCA absolute values, as assessed by standard, age-specific visual acuity assessments (e.g., Teller Acuity Cards® II, HOTV, etc.) reported in logMAR, along with the changes from baseline will be summarized at each protocol scheduled visit.

The number and percentage of patients with VA progression change values (decline or increase ≥ 0.2 logMAR) will be summarized by visit, and all post treatment assessments during the study.

By-patient listings of visual acuity outcomes will be provided.

4.2.5. Health-related Quality of Life

Quality of life data summaries and analysis methodologies will be detailed in a separate analysis plan.

4.2.6. Pharmacokinetic Analyses

Plasma concentrations will be summarized by nominal sample time using standard summary statistics for PK concentrations (geometric mean, geometric coefficient of variation, geometric mean ± standard deviation, arithmetic mean, standard deviation, minimum, maximum and n).

All plasma concentrations will be listed.

PK parameters may be summarized and listed separately.

Handling of values below the limit of quantification (BLQ) in listings and for the calculation of descriptive statistics at each time point**:**

- All concentrations below the limit of quantification (BLQ) or missing data will be labeled as such in the concentration data listings.
- Values that are BLQ will be substituted with zero for the calculation of descriptive statistics of concentration by time point and will be displayed as “not calculable” or NC for the calculation of statistical summaries.

For graphs of arithmetic means all BLQ concentrations will be substituted by zeros.

[redacted]

[redacted]

5. DSMB AND INTERIM ANALYSES

5.1. Safety Monitoring (Data and Safety Monitoring Board [DSMB])

An SRC and independent DSMB will review cumulative study data over the course of the study to evaluate safety, protocol conduct, and scientific validity and integrity of the trial. The DSMB will be responsible for closely reviewing the safety data from the interim data review analyses and for providing their recommendations on continuation of the study.

5.2. An Interim Data Review

[redacted]

6. DEVIATIONS FROM PROTOCOL

- Definition of efficacy analysis sets, Section 3.3.1
- Definition of ORR for RAPNO-LGG criteria (including MR as response), Section 2 study objective tables for Arm 1 and Arm 2, and Section 3.4.2.1.
- Definition of TEAE is modified, Section 3.4.4.1
- Exploratory endpoints (ORR, BOR, PFS, DOR, TTR and CBR based on RANO-LGG by IRC for Arm 1), Section 3.4.3.6
- Exploratory analysis of PFS by BOR based on RANO-LGG (Section 3.4.3.7) and RAPNO-LGG (Section 3.4.3.8)

7. REFERENCE

[1] Karnofsky D and Burchenal J., "The clinical evaluation of chemotherapeutic agents in cancer," *Evaluation of Chemotherapeutic Agents ,* 1949. e. MacLeod C. New York, NY, Columbia University Press: 191–205.

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[3] S. R., "Optimal two-stage designs for phase II clinical trials.," *Control Clin Trials. 1989;10:1-10..*

[4] Wen PY, Macdonald DR, Reardon DA, et al, "Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group", J *Clin Oncol,* 2010 Apr 10;28(11):1963-72.

[5] Wen PY, Chang SM, Van den Bent MJ, et al, "Response Assessment in Neuro-Oncology Clinical Trials", *J Clin Oncol*. 2017 Jul 20;35(21):2439-2449.

[6] Fangusaro J, Witt O, Hernáiz Driever P, et al, "Response assessment in paediatric low-grade glioma: recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group", *Lancet Oncol,* 2020 Jun;21(6):e305-e316.

8. APPENDIX I

Blood Pressure Normal Range

Table 6 and Table 7 present the normal ranges for blood pressure in the 50th, 90th, 95th, and 99th percentiles for Systolic Blood Pressure (SBP) and Diastolic blood pressure (DBP) for boys and girls, respectively. The information is further categorized into the appropriate age and percentile of height category.

- **Normal:** Blood pressure (BP) less than the 90th percentile
- **Prehypertension:** BP between the 90th and 95th percentile

  BP equal to or exceeding 120/80 mmHg is prehypertension, even if this figure is less than the 90th percentile.
- **Hypertension:** BP greater than the 95th percentile
  - Stage I hypertension: 95th percentile to the 99th percentile plus 5 mmHg
  - Stage II hypertension: >99th percentile plus 5 mmHg

Table 6: Blood Pressure Levels for Boys by Age and Height Percentile

AGE (Years)		SBP (mmHg) Percentiles of Height (%)							DBP (mmHg) Percentiles of Height (%)						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78

	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

Table 7: Blood Pressure Levels for Girls by Age and Height Percentile

AGE (Years)		SBP (mmHg) Percentiles of Height (%)							DBP (mmHg) Percentiles of Height (%)						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87

10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

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