CT Application(s) Summary Report

- **Protocol Title:** A Phase 3, Randomized, International Multicenter Trial of DAY101 Monotherapy Versus Standard of Care Chemotherapy in Patients with Pediatric Low-Grade Glioma Harboring an Activating RAF Alteration Requiring First-Line Systemic Therapy (LOGGIC/FIREFLY-2)
- **Protocol Code Number:** DAY101-002
- **Public Registry Number:** 2025-510742-13-00
- **Version:** 3.0
- **Date:** 31 July 2024

- **Investigational Medicinal Product being Tested:**

Biological ☐ **Pharmaceutical** ■ **Innovative** ☐

Herbal Medicine ☐ **Medical Device** ☐

- **Sponsor:** Day One Biopharmaceuticals, Inc. (Day One)

- **Indication:** Pediatric Low-Grade Glioma Harboring an Activating RAF Alteration Requiring First-Line Systemic Therapy

- **Investigator's Brochure (IB)**
  Version: Edition 13
  Date: 20 December 2024

- **Name of all Sites:**
  Children Cancer Hospital Egypt (CCHE/57357)
- **Name of PI(s):**
  Prof. Dr. Alaa El Haddad

- **EDA Approval Date:**
  - Amendment Approval dated 28 Jan 2026 for Protocol Amendment 3.0 dated 31 Jul 2024, Investigator's Brochure Edition 13 dated 20 Dec 2024, and ICFs version 2.0 dated 23 Jul 2025.
  - Initial Approval on 19 Feb 2025.

- **Summary of Pre-Clinical Studies**

1. Description of Investigational Medicinal Product

Tovorafenib (DAY101) is an oral, selective, CNS-penetrant, small molecule Type II rapidly accelerated fibrosarcoma (RAF) kinase inhibitor. The tovorafenib drug product is formulated as an immediate-release tablet or as PfOS for oral administration.

Assessment of Nonclinical Studies

Primary Pharmacodynamics

The primary pharmacology program is considered adequate and consistent with regulatory expectations. The mechanism of action of tovorafenib as a Type II RAF kinase inhibitor has been sufficiently characterized through in vitro biochemical assays, cellular systems, and in vivo tumor models. The demonstrated inhibition of BRAF mutations and fusions, including KIAA1549:BRAF, and the absence of paradoxical MAPK activation are of particular relevance to the proposed indication.

Overall, the primary pharmacology data are considered sufficient and supportive of the proposed therapeutic indication.

Secondary Pharmacodynamics

The secondary pharmacology program is considered adequate and aligned with ICH S7A recommendations. Off-target activity was evaluated across a broad panel of receptors, transporters, and enzymes. The observed interactions were limited and occurred at concentrations substantially higher than clinically relevant exposures.

These data indicate a favorable selectivity profile, and no clinically relevant off-target pharmacology has been identified. The assessment is considered complete and acceptable.

Safety Pharmacology

The safety pharmacology program is considered adequate and compliant with ICH S7A/S7B. Core battery studies addressing cardiovascular, central nervous system, and respiratory functions were conducted, including GLP-compliant studies.

In vitro hERG inhibition was observed at concentrations with an adequate safety margin relative to clinical exposure. In vivo findings (e.g. increases in heart rate and blood pressure) were characterized and considered non-adverse at tested doses. No significant CNS or respiratory liabilities were identified.

Overall, the safety pharmacology profile is considered acceptable, with no findings that would preclude clinical development, although the observed cardiovascular effects warrant continued clinical monitoring.

Pharmacokinetics and Metabolism (ADME)

The ADME package is considered comprehensive and in line with ICH M3(R2) requirements. Pharmacokinetics were evaluated across multiple species, including those used in toxicity studies, and using validated analytical methods.

Absorption, distribution, metabolism, and excretion have been adequately characterized. The demonstration of brain penetration is relevant to the intended CNS indication. Metabolic pathways have been identified, and interspecies comparisons indicate that rats and monkeys are appropriate toxicological species.
The evaluation of CYP and transporter interactions is adequate. While induction potential was identified for certain CYP enzymes, and inhibition of BCRP was observed in vitro, these findings are appropriately characterized and should be considered in the clinical context.
Overall, the ADME program is considered complete and acceptable, with no major deficiencies identified.

Toxicology

The repeat-dose toxicity program is considered adequate and in line with ICH M3(R2). Studies were conducted in two relevant species (rat and monkey) with appropriate durations (up to 3 months) to support clinical development, and pivotal studies were performed in compliance with GLP.
Toxicological evaluations, including reproductive toxicity, genotoxicity, and carcinogenicity, are considered generally in line with ICH S9 expectations for anticancer pharmaceuticals.
Overall, the toxicology data are considered sufficient to characterize the toxicity profile of tovorafenib and support its clinical use under the proposed conditions.

Overall Nonclinical Conclusion

The nonclinical package for tovorafenib is generally adequate and largely consistent with applicable ICH guidelines, including ICH M3(R2) and S7A/S7B, with appropriate characterization of pharmacology, safety pharmacology, and ADME. The data support the proposed mechanism of action and provide evidence of target engagement and antitumor activity. Overall, the nonclinical data are considered sufficient to support clinical development in the proposed indication.

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- **Phase:** 3

- **Objective(s):**

Primary Outcome Measures:

Outcome Measure	Measure Description	Time Frame
Objective response rate (ORR) of tovorafenib monotherapy versus SoC chemotherapy	ORR assessed per Response Assessment in Pediatric Neuro Oncology (RAPNO) criteria by Independent Review Committee (IRC), and defined as the proportion of participants with overall confirmed response of complete response (CR), partial response (PR), or minor response (MR).	Up to 60 months

- **Rationale:**

Pediatric low-grade glioma is a serious, life-altering, and potentially fatal disease with significant disease and treatment-associated morbidity. Low-grade glioma patients suffer from significant damage to important functional structures of the brain, particularly when located in central midline structures. Loss of visual, neurologic, cognitive, emotional, and endocrinological functions are clinically significant acute and long-term morbidities that need to be considered. This is crucial for the treatment of any child with low-grade glioma, as the disease does not only compromise OS, but rather causes long-term functional damage to key functions of the brain (Packer 2017). While current SoC chemotherapy treatments have been described, limited efficacy, treatment-related morbidities, and long-term cognitive impairments suggest the urgent unmet need to develop additional effective treatment options. To date, prospective data evaluating the impact of antitumor treatment on motor, neurological, and visual functions are essentially lacking.
Although the majority of patients with pediatric low-grade gliomas included in series for chemotherapy or radiotherapy suffer from severe clinical symptoms or radiological progression, little information has been collected prospectively concerning the clinical benefit of treatment, such as vision or neurological/motor functions. While small series indicate that both modalities are capable to stabilize or improve vision in a fraction of chiasmatic-hypothalamic glioma (CHG) (Janss 1995, Packer 1997, Cappelli 1998, Grabenbauer 2000, Laithier 2003), vision seems to deteriorate in the majority of patients over time (Dalla Via 2007, Campagna 2010, Shofty 2011, Avery 2012, Fisher 2012). Results suggest that visual outcome relates to the extent of visual pathway involvement, age, and radiological tumor response (Laithier 2003, Fisher 2012), but there have neither been sufficiently large prospective studies nor uniform modes to assess visual

function to confirm. Recent consensus has been obtained for the measurement of visual parameters across larger patient populations (Avery 2012). In addition, it is now widely recognized that functional outcome of patients with low-grade glioma should be assessed in any contemporary study aiming to evaluate treatment strategies (Guerreiro Stucklin 2016). Finally, an international consensus report on low-grade glioma clinical study design emphasizes the need for functional outcome determination in addition to classical radiological assessments (Packer 2017).

a significant body of data clearly shows that a majority of patients with pediatric low-grade glioma harbor a BRAF alteration that drives tumor growth (most commonly KIAA1549: BRAF fusion or BRAF V600 mutation). The use of Type I BRAF inhibitors is limited to patients with BRAF V600 mutation due to the risk of paradoxical activation of the MAPK pathway and tumor growth if used for patients with a BRAF fusion. Because the majority of BRAF alterations in patients with pediatric low-grade glioma are BRAF fusions, use of Type I BRAF inhibitors is contraindicated. Currently approved MEK inhibitors can block MAPK signaling resulting from either BRAF V600 mutations or the KIAA1549:BRAF fusion, but do not directly inhibit BRAF. In addition, MEK inhibitors are associated with significant cardiac, dermatologic, and ophthalmologic toxicities.

The Type II RAF inhibitor tovorafenib has been shown preclinically to be able to inhibit both BRAF V600 mutations and BRAF fusions and has been shown to have significantly greater CNS penetration than available Type I BRAF inhibitors or MEK inhibitors. To date, tovorafenib has been administered to 44 pediatric patients with pediatric low-grade glioma in the ongoing Phase 1 Study PNOC014. In addition, 137 pediatric low-grade glioma patients have been dosed with tovorafenib in Arm 1 and Arm 2 of the FIREFLY-1 study. In viewing the totality of data available, tovorafenib has been generally well-tolerated thus far in pediatric patients.

While these tumors and the associated treatments are significant sources of morbidity in the developing child, if these children can survive into young adults, most of these tumors undergo senescence (Jacob 2011). Historically, chemotherapy has been administered to patients with incompletely resected low-grade gliomas in part to delay the need for additional treatments with high morbidity, such as radiotherapy (Gnekow 2017). However, it is unclear if chemotherapy improves long-term cognitive outcomes, as comparable patterns of deficits have been reported with chemotherapy alone (Traunwieser 2020). Therefore, patients with pediatric low-grade glioma may benefit from treatment with a RAF inhibitor, such as tovorafenib, for not only inhibition of tumor growth, but also by preventing or at least delaying the need for more toxic alternative therapies such as systemic chemotherapy or radiation.

The purpose of this study is to evaluate the efficacy, safety, and tolerability of tovorafenib monotherapy versus SoC chemotherapy in patients with pediatric low-grade glioma harboring an activating RAF

alteration requiring first-line systemic therapy. The primary efficacy endpoint will be evaluated by ORR of tovorafenib versus SoC chemotherapy as determined by an IRC using RAPNO criteria. Furthermore, this study includes outcomes to evaluate improvements in neurological outcomes, patient-reported outcomes (PROs), and visual functions in OPG patients to better describe the overall impact on patients' lives and activities of daily living.

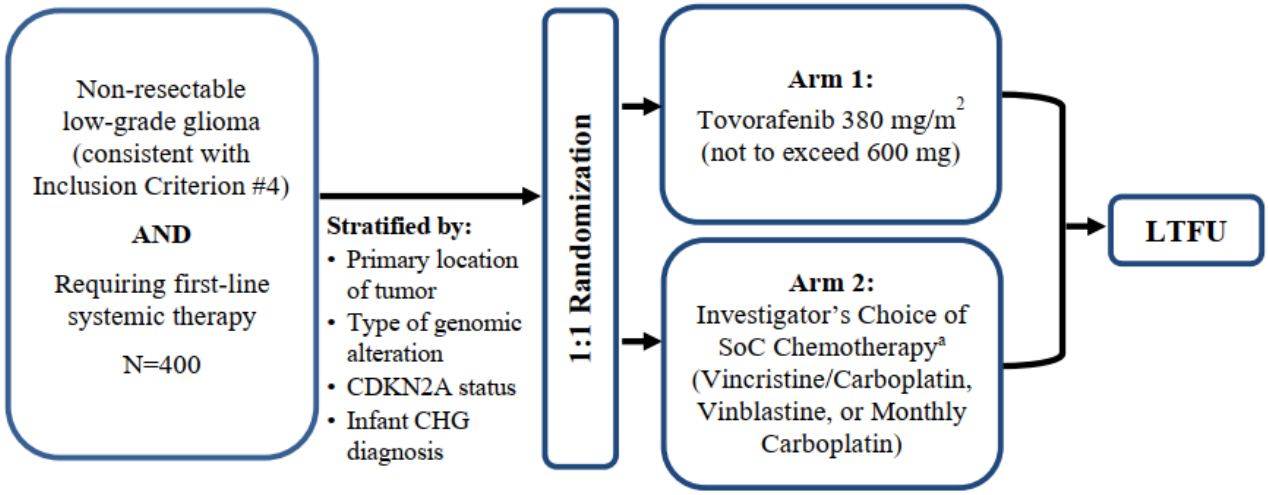
- **Design:**

Study Design

This is a 2-arm, randomized, open-label, multicenter, global, Phase 3 study to evaluate the efficacy, safety, and tolerability of tovorafenib monotherapy versus SoC chemotherapy in patients with pediatric low-grade glioma harboring an activating RAF alteration requiring first-line systemic therapy. Patients with RAF alterations will be identified through molecular assays as routinely performed at Clinical Laboratory Improvement Amendments (CLIA) of 1988 or other similarly certified laboratories. Approximately 400 treatment naïve low-grade glioma patients will be randomized 1:1 to either tovorafenib (Arm 1) or an Investigator's choice of SoC chemotherapy (Arm 2). Randomization will be stratified by primary location of the tumor (supratentorial midline vs. other), type of genomic alteration (fusion vs. mutation), CDKN2A status (deletion vs. wild-type/unknown), and infant CHG diagnosis (yes vs. no).

This study consists of a Screening phase, a Treatment phase that includes an End of Treatment (EOT) Visit, and a long-term follow-up (LTFU) period that includes a 30-Day Safety Follow-Up (SFU) Visit. Upon completion of the Treatment phase (including EOT Visit), ongoing safety, disease stability/progression, survival status, and subsequent anticancer therapies will be assessed in the LTFU period. For each patient, study participation is up to 5 years, inclusive of the Treatment phase and a LTFU period.

Study Design Schema



Abbreviations: CDKN2A, cyclin-dependent kinase inhibitor 2A; CHG, chiasmatic-hypothalamic glioma; COG-V/C, Children's Oncology Group – Vincristine/Carboplatin; LTFU, long-term follow-up; SIOPe-LGG-V/C, International Society for Paediatric Oncology – Low-Grade Glioma Vincristine/Carboplatin; SoC, Standard of Care. a Arm 2: COG–V/C, SIOPe-LGG–V/C, vinblastine, or monthly carboplatin

- **Recommendation &/ or Questions & Answers:**

Requirements	Applicant's Reply
Clarification is required regarding the duration of treatment (number of cycles) of Arm 1 receiving Tovorafenib for participants who will not experience disease progression based on RANO-LGG criteria, unacceptable toxicity, or withdraw their consent to treatment.	Participants on Arm 1 receiving tovorafenib (DAY101) may continue treatment cycles every 28 days unless they meet one of the criteria outlined in Study FIREFLY-2 Protocol Amendment dated 25 October 2023, Section 7.1 Discontinuation of Study Treatment. Patients who do not meet any of the criteria, including disease progression, unacceptable toxicity, or withdrawal of consent to treatment, may continue tovorafenib until the end of the study. Study duration per the protocol is limited to up to 5 years for a given participant, inclusive of the Treatment Phase and Long-term Follow-up (LTFU) Phase; thus, a patient could receive up to ~65 cycles of tovorafenib on study
It is required to specify which of the laboratories submitted in the package will be responsible for conducting molecular assays for the identification of RAF alterations.	As noted in the Protocol Amendment 2 Section 3.1 Study Design and Section 4.1 Inclusion Criterion #1, patients with RAF alterations will be identified through molecular assays as routinely performed at Clinical Laboratory Improvement Amendments (CLIA) or other similarly certified laboratories. The Sponsor confirms that Children Cancer Hospital Egypt (CCHE) 57357 Laboratory at the investigational site will be responsible for conducting molecular assays for identification of RAF alterations. The College of American Pathologist Certificate of Accreditation and the Joint Commission International Accreditation for Radiology and Diagnostic Imaging for CCHE 57357 were submitted to EDA with the initial submission
As mentioned in section 3.1, "*Patients in Arm 2 who have evidence of disease progression will be given the option to switch therapy to tovorafenib*", a rationale is required for not offering Arm 1	The Sponsor hereby provides justification for one-way crossover in the current Study FIREFLY-2 Protocol Amendment 2, dated 25 October 2023. The purpose of the cross-over

participants the choice to switch to the standard of care arm in case of disease progression.	design is to allow patients who are randomized to chemotherapy and whose disease has progressed to receive tovorafenib therapy, as tovorafenib is not commercially available in Egypt, and to allow for collection of additional exposure and safety data for tovorafenib. Arm 1 patients who experience disease progression while on tovorafenib may be initiated on another therapy per standard of care, as indicated in Section 6.15 Long-Term Follow-Up, and the subsequent anticancer therapy is not limited to the agents or regimens prescribed in the protocol; thus, crossover from Arm 1 to Arm 2 is not described. However, if the patient remains on study for continuous data collection, the specific agents will be recorded in the appropriate electronic clinical report form (eCRF).
As mentioned in Table 19 and Table 20 "*participants who have ototoxicity Grade ≥ 2 CTCAE v5.0 (ie, threshold shift > 20 dB at 1-4 kHz in at least one ear*" and "*participants who have non-hematological toxicity 2 Grade ≥ 4 CTCAE v5.0*" will be withdrawn from the study, a justification is required for withdrawing participants totally from the study not only from study treatment in order to allow for their follow up according to the study protocol.	The Sponsor appreciates EDA's concern and hereby submits a Protocol Clarification Letter (PCL) to correct the error and clarify in Table 19 and Table 20 that "*participants who have ototoxicity Grade ≥ 2 CTCAE v5.0 (ie, threshold shift > 20 dB at 1-4 kHz in at least one ear*" and "*participants who have non-hematological toxicity 2 Grade ≥ 4 CTCAE v5.0*" should stop further treatment. Contact Sponsor's Medical Monitor or designee if this occurs. The patient may remain on study and continue into LTFU.
As mentioned in protocol section 5.4.4, "*If tumor-directed surgery is clinically indicated while on study for Arm 1 patients receiving tovorafenib, the Sponsor will request a tumor specimen. Collection is optional and a separate tissue collection ICF will be provided*". Clarification is required whether this practice is applicable to Egypt since the separate tissue collection ICF is not provided in the submitted package.	The Sponsor confirms that optional tumor and a separate tissue collection for patients in Arm 1 (tovorafenib) is not applicable to participants and investigational sites in Egypt. As noted in the Cover Letter submitted with the initial submission, the Participant and Parental Optional Tumor informed consent forms (ICFs) were not provided to EDA. The Participant and Parental Optional Tumor ICFs have been cancelled as the two optional tumor ICFs will not be used nor

	submitted. The site-specific Main Participant and Parental ICFs have been adapted accordingly and the country ICFs will be adapted with the next amendment as these will not be used by the site. The archival tumor samples collected at Screening and the pharmacokinetic (PK) blood samples from all patients at investigational sites in Egypt will be normally collected as per the Schedule of Assessments, with the only condition of leftover biological samples also described in the Cover Letter submitted with the initial submission.
With respect to inclusion criterion number 10, the normal limits for serum creatinine are defined for individuals under the age of 19, but since the study permits patients under the age of 25, it is required to clarify what will be the reference for normal serum creatinine for participants over the age of 19.	The serum creatinine levels for participants over 19 years of age will be interpreted according to the local laboratory reference ranges. The protocol describes normal limits for participants 19 years of age and under as some laboratories do not have local pediatric-specific reference ranges for creatinine.
IMP FILE DEFICIENCY	
2.1.P.8 Stability. Kindly update the stability data till a 24-month time interval for both formulations: Tablets and powder for oral suspension, to support the proposed shelf-life for the investigational batches (36 months).	The Sponsor agrees with EDA and commits to updating the stability data for both tovorafenib tablet and powder for oral suspension (PfOS) formulations to support a 36-month shelf-life in the next available tovorafenib Investigational Medicinal Product Dossier (IMPD). The data to support the proposed shelf-life of 36 months is provided in Appendix 1. The appendix contains data for 24 months of tovorafenib tablets (foil/foil) and PfOS formulations.

- **Abbreviation:**

ADME	Absorption, Distribution, Metabolism, and Excretion
BCRP	Breast Cancer Resistance Protein
CCHE	Children Cancer Hospital Egypt
CLIA	Clinical Laboratory Improvement Amendments

CNS	Central Nervous System
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient Of Variation
CYP	Cytochrome P450 Enzyme
DAY101	Tovorafenib
eCRF	Electronic Case Report Fom
EDA	Egyptian Drug Authority
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
IB	Investigator's Brochure
ICH	International Council for Harmonisation
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
Khz	Kilohertz
LGG	Low-Grade Glioma
LPLV	Last Patient Last Visit
LTFU	Long-Term Follow-Up
MAPK	MAP Kinase
PCL	Protocol Clarification Letter
PfOS	Powder For Oral Suspension (Also Referred to as Powder for Reconstitution)
PI	Principal Investigator
PK	Pharmacokinetic(S)
RAF	Rapidly Accelerated Fibrosarcoma
RANO	Response Assessment in Neuro-Oncology
RAPNO	Response Assessment in Pediatric Neuro-Oncology
RAPNO-LGG	Response Assessment in Pediatric Neuro-Oncology- Low-Grade Glioma (RAPNO-LGG)
SoC	Standard of Care