

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

217700Orig1s000

218033Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 108340

MEETING MINUTES

Day One Biopharmaceuticals, Inc.
Attention: Linda Fletcher, PharmD
Senior Manager, Regulatory Science
2000 Sierra Point Parkway, Suite 501
Brisbane, CA 94005

Dear Dr. Fletcher:¹

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tovorafenib.

We also refer to the video conference between representatives of your firm and the FDA on April 19, 2023. The purpose of the meeting was to discuss the content and presentation of data to support the upcoming NDAs (NDA 217700 for tablets and NDA 218033 for powder for reconstitution (PfR)).

A copy of the official minutes of the video conference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact me at Jacqueline.Glen@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Jacqueline Glen, MS
Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic
Diseases for DO2
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes
- Meeting Slides

¹ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.



MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: April 19, 2023 at 12:00 PM – 1:00 PM, Eastern Time (ET)
Meeting Location: Video teleconference

Application Number: 108340
Product Name: tovorafenib

Indication: The treatment of patients 6 months of age and older with relapsed or refractory pediatric low-grade glioma harboring a BRAF fusion or rearrangement or BRAF V600 mutation

Sponsor Name: Day One Biopharmaceuticals, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Diana Bradford
Meeting Recorder: Jacqueline Glen

FDA ATTENDEES

Nicole Drezner, Acting Deputy Director, Division of Oncology 2 (DO2)
Diana Bradford, Cross Disciplinary Team Leader, DO2
Sonia Singh, Clinical Reviewer, DO2
Erin Larkins, Acting Supervisory Associate Director, DO2
Amy Barone, Cross Disciplinary Team Leader, DO2
Elizabeth Duke, Clinical Reviewer, DO2
Justin Malinou, Clinical Reviewer, DO2
Jeanette Nashed, Clinical Analyst, DO2
Michael Barbato, Clinical Reviewer, DO2
Kristin Wessel, Clinical Reviewer, DO2
Marjilla Seddiq, Clinical Reviewer, DO2
Claudia Miller, Acting Nonclinical Team Leader, Division of Hematology/Oncology
Toxicology (DHOT) Products
Stephanie Aungst, Nonclinical Reviewer, DHOT
Hong Zhao, Clinical Pharmacology Team Leader, Division of Cancer Pharmacology II (DCP II)
Suryatheja Ananthula, Clinical Pharmacology Reviewer, DCP II
Xing Wang, Quality Assessment Lead, Office of New Drug Products (ONDP), Office of Pharmaceutical Quality (OPQ)
Nan Yang, Product Quality Reviewer, ONDP, OPQ
Pallavi Mishra-Kalyani, Biometrics Team Leader, Division of Biometrics V (DBV)

Anitha Govada, Senior Pharmacology Quality Assessor, Biopharmaceutics Branch 1 (BB1), ONDP, OPQ

Payal Agarwal, Biopharmaceutics Reviewer, BB1, ONDP, OPQ

Jingyu Yu, Pharmacologist, Office of Clinical Pharmacology (OCP)

Huali Wu, Pharmacologist, OCP

Martha Donoghue, Acting Associate Director for Pediatric Oncology, Oncology Center of Excellence

Jacqueline Glen, Regulatory Health Product Manager, Division of Regulatory Operations (DRO)

SPONSOR ATTENDEES

Sam Blackman, MD, PhD, Founder and Chief Medical Officer

Cydrienne Chatto, BS, Associate Director, Regulatory Science

Davy Chiodin, PharmD, Chief Development Officer

Daniel Da Costa, PharmD, Director, Clinical Development

Linda Fletcher, PharmD, Senior Manager, Regulatory Science

Jerald Grace, PharmD, Senior Director, Regulatory Science

Mark Kieran, MD, PhD, Vice President, Clinical Development

Kimberly Lindstrom, PhD, Vice President, Regulatory Science

Peter Manley, MD, Senior Director, Clinical Development

Lisa McLeod, MD, MSCE, Senior Medical Director, Pharmacovigilance & Patient Safety

Xin Zhao, MD, PhD, Vice President, Biometrics

(b) (4), MD, Subject Matter Expert - (b) (4)

(b) (4), MD, Subject Matter Expert - (b) (4)

(b) (4), MD, Subject Matter Expert - (b) (4)

(b) (4), MD, Subject Matter Expert - (b) (4)

(b) (4), MD, Subject Matter Expert - (b) (4)

BACKGROUND

On January 23, 2020, sponsorship of IND 108340 was transferred from Takeda Pharmaceuticals, Inc. to DOT Therapeutics-1 Inc. (Day One).

On April 27, 2020, FDA issued written comments for an End-of-Phase (EOP) 1 meeting to discuss the design of FIREFLY-1, a single-arm trial evaluating the safety and efficacy of DAY101 in up to 60 pediatric and adult patients (6 months to 25 years of age) with recurrent or progressive low-grade glioma (LGG) harboring a known activating BRAF alteration. The teleconference scheduled for April 30, 2020, was canceled upon Day One's request after receiving FDA's preliminary comments.

U.S. Food and Drug Administration

Silver Spring, MD 20993

www.fda.gov

On August 31, 2020, DAY101 received Breakthrough Therapy Designation for the treatment of pediatric patients with low-grade glioma (LGG) harboring an activating RAF alteration that has progressed after one or more prior systemic therapies.

On September 24, 2020, DAY101 was granted Orphan Drug Designation (DRU-2020-7683) for the treatment of malignant glioma.

On February 22, 2021, FDA issued written comments for a meeting to discuss the development programs for drug metabolism and pharmacokinetics (DMPK), clinical pharmacology, and companion diagnostic for DAY101 in patients with relapsed or progressive RAF-altered LGG and to confirm acceptability of the plans in support of a new drug application (NDA). The teleconference scheduled for February 25, 2021, was canceled upon Day One's request after receiving FDA's preliminary comments.

An EOP 2 meeting was held on October 4, 2021, to discuss the trial design and statistical assumptions of DAY101-002 (LOGGIC/FIREFLY-2), a proposed Phase 3 study of first-line treatment of DAY101 intended to support a marketing application for pediatric and adolescent patients with LGG harboring an activating RAF alteration requiring systemic therapy.

On July 26, 2021, DAY101 was granted Rare Pediatric Disease Designation for treatment of LGG harboring an activating RAF alteration.

On September 29, 2021, Day One requested a meeting to obtain FDA feedback on their Chemistry, Manufacturing and Controls (CMC) and Clinical Pharmacology development program for DAY101 in anticipation of an NDA filing in pediatric patients with relapsed/refractory LGG. The teleconference scheduled for December 10, 2021, was canceled upon Day One's request after receiving FDA's preliminary comments.

On February 14, 2022, Day One requested a meeting to obtain FDA feedback on the proposed content and format of their planned NDA for DAY101. A Type B, comprehensive post-breakthrough designation meeting was granted. In the meeting minutes issued on April 25, 2022, FDA provided advice regarding various components of the planned NDA and expressed concern that the sample size from FIREFLY-1 proposed for inclusion in the NDA may be insufficient to characterize the consistency of the treatment effect across subgroups based on type of BRAF alteration. The teleconference scheduled for April 27, 2022, was canceled upon Day One's request after receiving FDA's preliminary comments.

On March 4, 2022, FDA received the protocol for FIREFLY-2. This randomized, open-label, multicenter first-line study evaluates the efficacy, safety and tolerability of tovorafenib monotherapy versus standard of care chemotherapy in pediatric patients with LGG harboring an activating RAF alteration requiring systemic therapy. The first patient enrolled in this study received first dose on March 3, 2023.

On May 20, 2022, FDA issued written responses only for a Type B, CMC content and format meeting for the planned NDA.

On November 1, 2022, FDA and Day One convened an informal teleconference to discuss an FDA Advice/Information Request dated September 22, 2022 and the results of an interim analysis of 22 patients enrolled in FIREFLY-1 as per blinded independent central review (BICR) according to Response Assessment in Pediatric Neuro-oncology-Low Grade Glioma (RAPNO-LGG) criteria. FDA noted that a lower ORR was observed by RAPNO-LGG criteria in the interim analysis and recommended that Day One consider a later data cutoff that would permit a higher percentage of responders to be followed at least 6 months at the time of NDA submission (compared to the proposed 50% of responders followed for at least 6 months).

On February 16, 2023, Day One submitted a meeting request to review the topline safety and efficacy data from Study DAY101-001/PNOC026 (FIREFLY-1) and to discuss the content and presentation of data to support two planned applications for tovorafenib, NDA 217700 for immediate-release tablets and NDA 218033 for powder for reconstitution (PfR). FDA granted a Type B, pre-NDA meeting scheduled for April 19, 2023. The briefing package was received on March 16, 2023. Supplemental information, including top-line data according to Response Assessment in Neuro-Oncology (RANO)-LGG criteria were provided in a PDF document formally received on March 31, 2023.

Disease Background

Low-grade gliomas, classified as Grade I and Grade II tumors by the World Health Organization (WHO), are the most common brain tumors in children accounting for 30% of all childhood brain tumors. The majority of pediatric LGGs (pLGGs) are driven by up-regulation of the RAS/MAPK pathway with the most common genetic alteration being KIAA1549:BRAF wildtype fusions (30 – 40% of pLGG). BRAF V600E point mutations are less common and have been demonstrated in approximately 15% of pLGGs. Other RAF alterations, including other BRAF fusions and CRAF fusions, have been reported in LGG.

Patients who require systemic treatment for progressive LGG are typically treated with chemotherapy (most often carboplatin and vincristine; thioguanine, procarbazine, lomustine and vincristine; or single agent vinblastine). Dabrafenib in combination with trametinib is approved for pediatric patients 1 year of age and older with LGG with a BRAF V600E mutation who require systemic therapy, and for the treatment of adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options.

Planned Application

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

Day One plans to submit two NDAs for tovorafenib (tablets and PfR) for the treatment of patients 6 months of age and older with relapsed or refractory pLGG harboring a BRAF fusion or rearrangement or a BRAF V600 mutation in June 2023. These applications will be supported by data from FIREFLY-1 with a data cutoff (DCO) date of December 22, 2022. Day One intends to submit updated safety data with a DCO in May 2023, as part of a 90-day safety update, for ongoing commercial sponsored clinical studies. Updated efficacy data (including ORR and DOR as assessed by IRC using RANO-High Grade Glioma [HGG] and RANO-LGG criteria) from FIREFLY-1 will also be provided in the 90-day update. Day One plans to submit an Assessment Aid and request rolling review for these NDAs.

FIREFLY-1

FIREFLY-1 is an ongoing open-label, multicenter, single arm, multi-cohort study evaluating the safety and efficacy of tovorafenib in patients 6 months to 25 years of age with relapsed or progressive pLGG and advanced solid tumors harboring a RAF alteration, including BRAF mutations and fusions. The primary endpoint is confirmed ORR according to RANO-HGG as assessed by IRC. Responses are also to be assessed by RAPNO-LGG and RANO-LGG.

Patients are enrolled into one of three cohorts as listed below:

- *“Arm 1”*: Recurrent or progressive LGG harboring a known activating BRAF alteration, including BRAF V600 mutations and KIAA1549:BRAF fusions (intent-to-treat population). A total of 77 patients were enrolled and received at least one dose of tovorafenib. Data from patients in this cohort is intended to provide evidence of effectiveness and support the proposed indication.
- *“Arm 2”*: Expansion of recurrent or progressive LGG harboring a known or expected to be activating RAF alteration (e.g., BRAF or CRAF/RAF1 fusion or BRAF V600 mutation). A total of 59 patients were enrolled and received at least one dose of tovorafenib. Patients without measurable disease by RANO were permitted to enroll for expanded access. Efficacy data from this cohort are not intended to support the planned NDA.
- *“Arm 3”*: Up to 20 patients with advanced solid tumors harboring a known or expected to be activating RAF fusion (e.g., BRAF or CRAF/RAF1 fusion). At the time of data cutoff, only 2 patients with non-LGG malignancies were enrolled.

Patients in all arms received tovorafenib at the proposed recommended Phase 2 dose (RP2D) of 420 mg/m² (not to exceed 600 mg) administered as tablets or powder for reconstitution orally once weekly in 28-day cycles. Per protocol, patients were to be treated for a planned period of 26 cycles (approximately 24 months) until radiographic evidence of disease progression, unacceptable toxicity, decision to enter a “drug holiday” period, patient withdrawal of consent, or death. The median duration of tovorafenib exposure in Arm 1 was 330 days (12 cycles).

Efficacy analysis of Arm 1 as reported by Day One in the briefing package includes all patients enrolled who received at least one dose of tovorafenib and had measurable disease per RANO-HGG as determined by the IRC at baseline for a total of 69 patients. See Table 1 below for a summary of the top-line data by RANO-HGG and RAPNO-LGG criteria.

**Table 1: Summary of FIREFLY-1 Efficacy Results
(DCO 12/22/22)**

	RANO-HGG N=69	RAPNO-LGG N=69	RANO-LGG N=69
Pts. with response, N ORR (CR + PR)	43 62% (95% CI: 50, 74)	13 19% ¹ (95% CI: 10, 30)	12 17% ¹ (95% CI: 9, 28)
CR, N (%)	4 (9%)	0	0
Responders with ≥ 6 mos. follow-up after response, N	36	Not provided	Not provided
Responders with DOR ≥ 6 mos., N (%)	35 (97%)		
Median DOR (months) ²	Not yet reached (95% CI: 9, NE*)	Not provided	Not provided
Median time to response (months)	2.8 months (range: 2.6-8.3)	Not provided	Not provided

*Not estimable.

¹As noted in the efficacy summary slides provided by Day One, the response rates as per RAPNO-LGG and RANO-LGG were calculated in 69 patients who received at least 1 dose of study treatment and have measurable disease per RANO-HGG as determined by the IRC at baseline.

²Based on estimates using the Kaplan-Meier method.

For the analysis of the primary endpoint, ORR by RANO-HGG for Arm 1 was assessed by an IRC and adjudicated if the two readers were not in agreement with respect to responder (CR or PR) vs. non-responder based on best overall response. The ORR by RAPNO-LGG criteria was similarly calculated for Arm 1 by an IRC; however, these data were not independently adjudicated. If an adjudication event for RANO-HGG was triggered, the accepted reader's results were used for the RAPNO analyses. Day One has requested the IRC to include independent adjudication of RAPNO data and will share results of the revised analyses once revisions have been completed. Additionally, Day One states that fully adjudicated RANO-LGG data analysis is ongoing and will be included in the NDA submission.

Additional subgroup analyses based on prior therapy and BRAF fusion or mutation are presented in Table 2.

Table 2: FIREFLY-1 Subgroup Analyses by Prior Therapy and Genomic Alteration

ORR in patients with:	RANO-HGG
Prior MEK therapy (n=39)	67% (95% CI: 50, 81) - 26 responders: 2 CR, 24 PR
Prior BRAF therapy (n=5)	80% (95% CI: 28, 100) - 4 responders: 2 CR, 2 PR
BRAF fusions ¹ (n=59)	66% (95% CI: 53, 78) - 39 responders: 2 CR, 37 PR
BRAF V600 mutations ¹ (n=10)	40% (95% CI: 12, 74) - 4 responders: 2 CR, 2 PR

¹As per Table 8 (on page 33) in the briefing package, "BRAF fusions" includes KIAA1549-BRAF fusions, BRAF tandem duplication, BRAF rearrangements, and other non-KIAA 1549-BRAF fusions. All patients with "BRAF V600 mutations" appear to have the BRAF V600E mutation.

Day One proposes that the pooled safety database supporting the application consist of 280 patients who have received tovorafenib as a single agent and a total safety population of over 400 patients who have been exposed to at least one dose of tovorafenib. In addition to the pooled safety analyses, Day One will provide PK data and summary safety information (but not datasets) from the investigator-sponsored study, PNOC014. Day One proposes to submit PK data from PNOC014 within 30 days of NDA submission.

In the briefing package, Day One provided safety analyses for patients in Arms 1 and 2 who received at least one dose of study treatment (total n = 136). See Table 3 below (copied from page 43 of the briefing package) for a summary of adverse events in this patient subset.

Table 3: Summary of Adverse Events (Safety Analysis Set: Arm 1 and Arm 2)

	Arm 1 (LGG) N=77 n (%)	Arm 2 (LGG) N=59 n (%)	Arms 1 and 2 N=136 n (%)
All TEAEs	77 (100)	59 (100)	136 (100)
Grade 3 or higher TEAEs	45 (58.4)	23 (39.0)	68 (50.0)
Serious TEAEs	26 (33.8)	19 (32.2)	45 (33.1)
Treatment-related serious TEAEs	10 (13.0)	4 (6.8)	14 (10.3)
Fatal (Grade 5) TEAEs ^a	1 (1.3)	0	1 (0.7)
TEAEs leading to dose reduction	18 (23.4)	7 (11.9)	25 (18.4)
TEAEs leading to study drug interruption	33 (42.9)	18 (30.5)	51 (37.5)
TEAEs leading to study drug discontinuation	4 (5.2)	1 (1.7)	5 (3.7)
Treatment-related TEAEs leading to study drug discontinuation	3 (3.9)	1 (1.7)	4 (2.9)

Abbreviations: LGG = low-grade glioma; TEAE = treatment-emergent adverse event.

^a One patient died from neurological decompensation considered attributable to the patient's underlying disease, not related to tovorafenib.

TEAE is defined as an adverse event that starts on or after the first administration of tovorafenib until 30 days after the last dose of tovorafenib.

Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. Patients with multiple severities for AE are counted only once under the AE with the maximum severity.

Medical Dictionary for Regulatory Activities (MedDRA) version 23.1; Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Data cutoff date: 22 December 2022.

Source: Modified from Table 14.3.2.1.1.

All patients experienced at least one TEAE. The most frequently ($\geq 50\%$) reported TEAEs were hair color changes, increased blood creatinine phosphokinase (CPK), fatigue and anemia. The most commonly ($> 5\%$) reported Grade 3 or higher TEAEs were anemia, increased blood CPK, and maculopapular rash. Serious adverse events (SAEs) occurred in 45 (33%) of patients; pyrexia, seizure, headache, hydrocephalus, vomiting, dehydration and hyponatremia occurred in more than 2 patients each. One patient in Arm 1 had a fatal TEAE of "brain death" from neurological decompensation that was reported as due to progressive disease. Additionally, one patient death in Arm 3 was reported as due to progressive disease.

Dose interruptions occurred in 38% of patients, and dose reductions occurred in 18% of patients. Five patients discontinued treatment due to TEAEs, including hemolysis, autoimmune hemolytic anemia, ventricular extrasystoles, growth retardation, tumor hemorrhage, and shunt malformation.

Companion Diagnostic Development

Day One has partnered with Foundation Medicine, Inc. to develop an FDA-approved companion diagnostic (CDx) to support patient selection for treatment with tovorafenib.

(b) (4)

FIREFLY-2

FIREFLY-2 is an ongoing, randomized, open-label, global Phase 3 trial assessing first-line tovorafenib as a single agent versus standard of care (SOC) chemotherapy in

U.S. Food and Drug Administration

Silver Spring, MD 20993

www.fda.gov

patients less than 25 years of age with pLGG harboring an activating RAF alteration requiring systemic therapy.

Approximately 400 patients with treatment-naïve LGG will be randomized 1:1 to receive either tovorafenib in Arm 1 (at a dose of 420 mg/m² [not to exceed 600 mg] once weekly in 28-day cycles) or an investigator's choice of SOC in Arm 2 (consisting of two comparable vincristine/carboplatin regimens or single agent vinblastine). 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 chiasmatic-hypothalamic glioma diagnosis (yes/no).

Day One anticipates a recruitment period of [REDACTED] (b) (4)

FDA sent Preliminary Comments to Day One Day One Biopharmaceuticals on April 13, 2023.

DISCUSSION

Preamble

We agree that there is an unmet medical need for additional therapies for pediatric patients with relapsed or refractory LGG with BRAF alterations and appreciate your efforts to investigate tovorafenib in this patient population.

As stated previously, evaluation of efficacy in FIREFLY-1 with response criteria specifically devised for LGG (i.e., RAPNO-LGG and RANO-LGG) is preferred over RANO-HGG as LGG is a radiographically distinct tumor from HGG. Since contrast enhancement is inconsistent in LGG, with some tumors showing minimal if any enhancement, LGG tumor response is more accurately captured by T2-weighted and T2-weighted FLAIR imaging. Therefore, we consider response criteria that rely upon percent change in the T2/FLAIR signal rather than contrast enhancement to be more suitable for regulatory decision making in this patient population.

Although the reported tumor response rate as per RANO-LGG is 17% (95% CI: 9, 28), this response rate does not appear to be calculated in patients with IRC-assessed measurable disease by LGG criteria at baseline, which limits interpretability. Further, the duration of response has not been provided for responders (patients who demonstrated a complete or partial response) as per LGG criteria. A response rate of 17%, regardless of durability of response, is unlikely to be sufficient to demonstrate substantial evidence of effectiveness for this indication. In the absence of comprehensive topline data with adequate duration of follow-up, we consider the data provided in the briefing package for this meeting to be incomplete.

To better characterize the potential clinical benefit of tovorafenib, we strongly advise that you provide efficacy analyses, including relevant subgroup analyses, as per response criteria designed to evaluate LGG, and consider using a later data cutoff for a more complete assessment of the durability of response observed with tovorafenib. As the information provided in the meeting package indicates that time to response with DAY101 treatment may take up to 11 months according to LGG criteria, we recommend an additional 6 months of follow-up beyond the December 2022 cutoff. However, we welcome further discussion regarding the appropriate length of time for additional follow-up that will also permit submission of your planned NDAs in a timely manner.

1. Does the Agency agree that the provided safety and efficacy results from the registrational study FIREFLY-1 are sufficient to support submission of an initial NDA for the proposed indication?

FDA Response: No, we do not agree. Please refer to the preamble. We are concerned that responses as assessed by RANO-HGG may not accurately reflect a clinically meaningful response in the setting of primarily non-contrast-enhancing tumors. As previously communicated in the informal TCON held on November 1, 2022, we note that the ORR (18.8%) calculated by RAPNO-LGG, assuming the same 69 patients have measurable disease according to LGG criteria by IRC, is substantially lower than the ORR (62.3%) calculated by RANO-HGG. Similarly, the reported ORR as per RANO-LGG is 17.4%, which is consistent with RAPNO-LGG.

Due to variable contrast enhancement in LGG, we strongly recommend you provide additional analyses of ORR and DOR as per RAPNO-LGG or RANO-LGG as assessed by IRC, ensuring that measurable disease at baseline is evaluated using the appropriate corresponding LGG criteria and using a data cutoff that will enable sufficient follow-up from onset of response. Ideally, all responders should be followed for a minimum of 6 months post onset of response. In addition, provide analyses of ORR and DOR in clinically relevant subgroups (i.e., BRAF alteration type, etc.).

Regarding safety results, characterization of the safety profile of tovorafenib and an analysis of the risk:benefit of treatment with tovorafenib in the proposed indication will be determined during the review of the application. As previously noted during the November 2022 TCON, your planned pooling strategy to compose a safety database of 280 patients who received tovorafenib as a single agent and a total safety population of over 400 patients who have been exposed to at least one dose of tovorafenib appears acceptable; however, if a later data cutoff (DCO) is used based on efficacy considerations, patients from study Day 101-102 may also need to be included in the safety pool if a substantial number of additional patients have been enrolled and have available safety data (beyond the four patients that were preliminarily projected) at the time of the later DCO.

Additionally, please confirm that the safety population will include at least 136 pediatric patients treated at the RP2D.

Sponsor Response: The Sponsor acknowledges the Agency's feedback regarding the choice of endpoints in the Study DAY101-001/PNOC026 (FIREFLY-1) trial, noting that the primary endpoint was discussed by the Agency in the Type B End of Phase 1 Meeting Preliminary Comments dated 27 April 2020 (Ref ID 4598461). At the time, the Agency agreed that a single-arm trial evaluating ORR based on radiographic response as assessed by RANO-HGG criteria and per IRC assessment with a clinically meaningful response duration may support an application seeking marketing approval. As such, the trial enrollment criteria required patients to have measurable enhancing disease at baseline.

The Majority of Pediatric Low-Grade Gliomas Have Contrast Enhancement on T1-Gd+ Imaging Sequences

Although the Agency contends that contrast enhancement is variable in low-grade glioma (LGG), pediatric low-grade gliomas are fundamentally different than adult low-grade gliomas. While it is correct that the majority of adult low-grade gliomas are non-enhancing, the literature indicates that this is not the case for pediatric low-grade gliomas. The term "pediatric low-grade glioma" encompasses a variety of histologically and biologically distinct subtypes. The most common histologic subtypes, pilocytic astrocytoma and ganglioglioma, which represent approximately 85% of BRAF-altered pediatric low-grade gliomas (Table 1), are nearly universally enhancing (Provenzale 2010, [Collins 2015](#), [Zaky 2018](#), [Resende 2021](#)). In addition, case series of pleomorphic xanthoastrocytomas (PXAs) and pilomyxoid astrocytomas have shown that the overwhelming majority have contrast enhancement ([Komotar 2008](#), [Rao 2010](#), [Moore 2014](#), [Alkonyi 2015](#)). For pediatric diffuse astrocytomas, our review of the limited literature on this subset indicates that diffuse astrocytomas most often have limited or no contrast enhancement ([Bag 2021](#)), however it should also be noted that these less common pediatric-type diffuse low-grade gliomas are far less likely to have a KIAA1549:BRAF fusion, with the most common alterations being BRAF V600E mutations and non-BRAF alterations (MYB/MYBL1 and FGFR). All of the subjects enrolled on Study FIREFLY-1 were required to show measurable evidence of increasing contrast enhancement as evidence of disease progression, prior to initiation of therapy with tovorafenib (DAY101).

Table 1: Complete Prevalence of BRAF-Altered Pediatric Low-Grade Gliomas, US 2019, Ages 0–18 Years

Morphology	Complete Prevalence, Ages 0–18 Years	Gadolinium Enhancement
Pilocytic astrocytoma	7657	Majority enhancing
Ganglioglioma	1601	Majority enhancing

Morphology	Complete Prevalence, Ages 0–18 Years	Gadolinium Enhancement
Diffuse astrocytoma	1330	Frequently none, or partial enhancement
Pleomorphic xanthoastrocytoma	211	Majority enhancing
Desmoplastic infantile astrocytoma and ganglioglioma	212	Majority enhancing (partial or complete)
Dysembryoplastic neuroepithelial tumor	0	
Total	11,011	

Note: The SEER*STAT program was used to calculate 42-year limited duration prevalence of LGG morphologic subtypes in the US for 2017, the latest data available in SEER. The resulting limited duration prevalence was run through the ProjPrev and ComPrev software programs to determine the nationally representative complete prevalence of LGG morphologic subtypes in the US. These data were stratified by single year of age and sex and applied to the US population stratified by age and sex in July 2019 using data from the US Census Bureau ([2020](#)).

Enhancement in Pediatric Low-Grade Glioma is Reflective of Underlying Tumor Biology

It is well acknowledged that the biologic processes that lead to increases in contrast enhancement in brain tumors are an intrinsic function of underlying tumor biology leading to dysregulation of the normal astrocyte/endothelial interaction, in addition to tumor-induced microvascular proliferation. Low-grade (Grade 2) diffuse astrocytomas are less likely to enhance, although longitudinal studies of diffuse astrocytomas show an increased likelihood to exhibit contrast enhancement upon recurrence or progression ([Pallud 2009](#), [Smith 2021](#)).

It follows that the effect of MAPK inhibitors, such as tovorafenib, on contrast enhancement reflects its effect on intrinsic tumor biology. Given the lack of appreciable anti-VEGFR2 activity of tovorafenib at the doses administered, and exposures achieved, in Study FIREFLY-1, there is no evidence that the reduction in contrast enhancement observed is due to a direct effect on endothelial cells. Furthermore, if the effect of tovorafenib was a non-specific effect on endothelial cells, the decrease in contrast enhancement would be, like steroids or anti-angiogenic agents, more generalized (that is, not seen in only 62% of patients) and also would likely be associated with the effects of non-specific anti-VEGFR agents (eg, hypertension, proteinuria, impaired wound healing). Most importantly, if the effect of tovorafenib on contrast enhancement was non-specific, it would not be associated with a decrease in the size of the lesion visible on T2 sequences.

As demonstrated below, with the exception of 4 patients, all patients who had an objective response (CR or PR) by RANO-HGG criteria had a reduction in the area of T2 signal by RANO-LGG criteria (Figure 1). It is important to note that the

RANO-LGG evaluations were not used to determine whether patients remained on treatment in the FIREFLY-1 study. As such, these 4 patients who met the criteria for objective response by RANO-HGG with an increased signal on T2/FLAIR remain on treatment with no evidence of clinical progression. The increase in T2/FLAIR signal in these 4 patients occurred at the initial (3 month) scan, and lead to a determination of PD by RANO-LGG, after which subsequent scans were not included in the determination of best overall response by RANO-LGG. However as indicated in the spider plot below, all four of these patients showed *decreases* in T2 signal in subsequent scans (Figure 2) and have continued on treatment for more than 1 year. Taken together, the concordance of the T1-Gd+ and T2/FLAIR imaging data supports the conclusion that the decrease in contrast enhancement observed with tovorafenib is directly related to reductions in tumor size rather than an indirect effect.

Figure 1 Waterfall Plot for SPPD Best Percent Change from Baseline (RANO-HGG vs RANO-LGG by IRC) - Arm 1

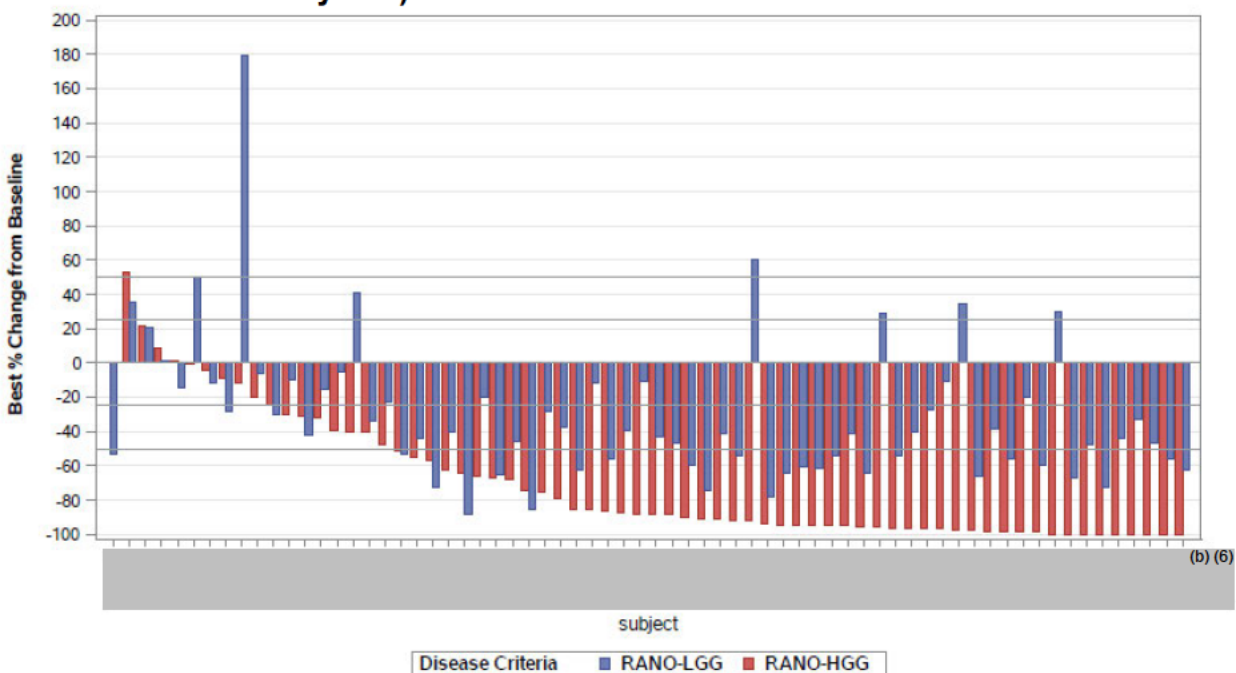
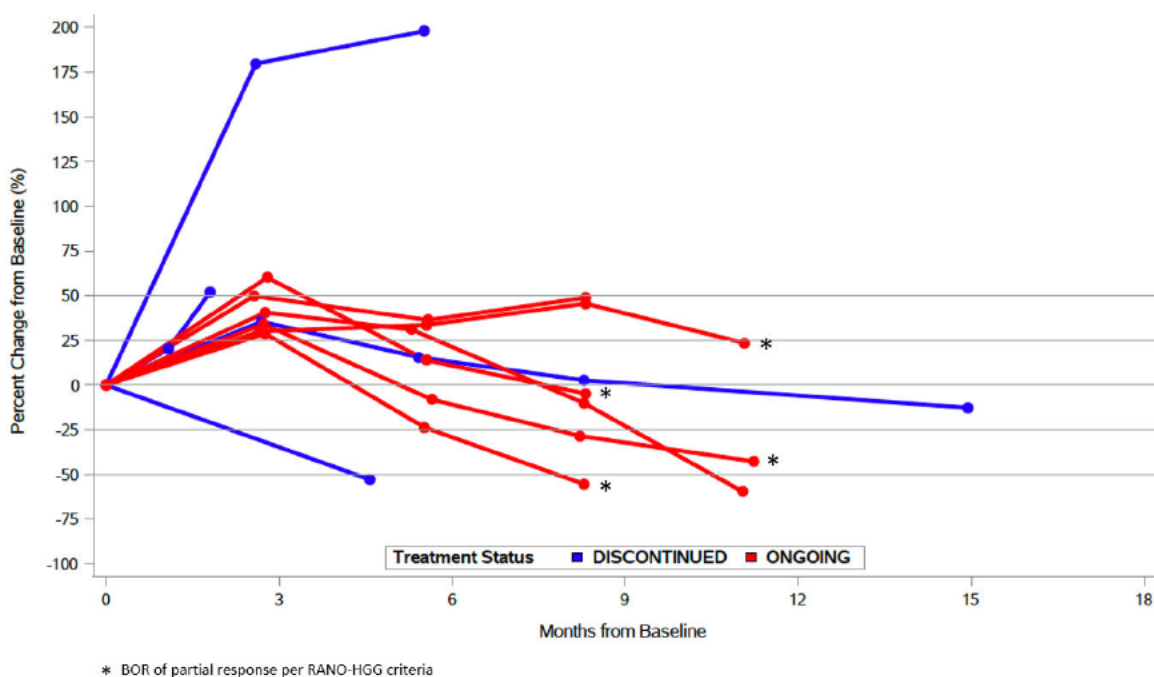


Figure 2 Spider Plot for SPPD % Change from Baseline by IRC Based on RANO-LGG Criteria For Patients with PD by RANO-LGG (as of December 2022)



Reliance on Modified RANO-LGG as the Sole Measure of Response for Pediatric Low-Grade Glioma is Insufficient to Characterize Clinical Benefit

Applying a single imaging criteria (RANO-HGG or RANO-LGG) to pediatric low-grade glioma does not completely assess tumor response. RANO-HGG criteria rely primarily, but not exclusively, on T1-weighted sequences with contrast enhancement, as most drug development efforts, at the time these criteria were published, were focused on high grade tumors in adults, which typically enhance. It is important to note that RANO-HGG criteria require an evaluation of T2/FLAIR response as part of the assessment criteria and a response by RANO-HGG requires that the T2/FLAIR signal is stable or decreasing. Progression in RANO-HGG criteria based on T2/FLAIR requires a “significant” increase in T2/FLAIR to be considered progression in the absence of an increase in enhancement.

RANO-LGG reflected a set of criteria to specifically accommodate adult IDH1-mutant low-grade gliomas, which typically do not enhance at baseline ([van den Bent 2011](#)) but are visible on T2/FLAIR weighted sequences. Because some adult LGGs do have areas of enhancement, RANO-LGG criteria includes measurement of contrast enhancement in assessing response. To be considered a response, the enhancement in an adult LGG should not have increased. New or dramatic increase in enhancement in adult LGG cases often suggests transformation, progression, and a worse prognosis. (b) (4)

In the original 2011 publication of RANO-LGG criteria, the authors state that they do not expect the responses to effective therapies to be as robust in T2-weighted and FLAIR imaging as they have poor specificity in detecting both response and progression in LGG. Because T2 imaging is highly sensitive to changes in the brain parenchyma, and is not specific to abnormal tumor tissue, it integrates a number of pathologic changes within the region of the tumor including scarring (gliosis), inflammation, and significant peritumoral edema. These changes may resolve slowly, or not at all, particularly within heavily pre-treated patients, but also in response to first-line chemotherapy.

In addition, because T2-weighted signal abnormalities are not tumor-specific, it is expected *a priori* that the size of the T2/FLAIR signal abnormality may not always change as dramatically in response to therapy. It is for this reason that the published RANO-LGG criteria (as well as the more recently published RAPNO-LGG criteria) include a “minor response” category (25-49% reduction in lesion size). The inclusion of minor response was recently, overwhelmingly endorsed by the RANO 2.0 revision working group ([REDACTED] (b) (4) [REDACTED]), as well as the RAPNO working group, specifically because of the frequent and expected lack of a significant decrease of the area with T2/FLAIR signal abnormality in LGG patients, and the fact that frequently in relapsed/refractory LGG, it is not the entire lesion that is growing, but rather that there is a growing portion within a heterogenous region of affected brain tissue. The authors of the RANO-LGG manuscript note that minor response by RANO-LGG criteria is often the best achievable response category and, in contrast with high-grade glioma and other cancers, this category assumes particular importance for LGG where minor response may be associated with significant clinical benefit.

Current Assessment Criteria Are Insufficient to Measure Clinical Response in Pediatric Low-Grade Glioma

Pediatric low-grade glioma straddles both T1- and T2-based assessment criteria with clinically meaningful changes not fully reflected in either RANO-HGG or RANO-LGG criteria. Even within the pediatric oncology community, there has been some difficulty defining when to potentially utilize enhancing disease as a response to treatment. For example, the recently published RAPNO-LGG working group acknowledged that the clinical experience with anterior optic glioma suggests that contrast sequences are critical to assess treatment response because many of these lesions enhance completely, which is relevant to this discussion because optic gliomas made up 50% of patients on the FIREFLY-1 trial, and because more broadly, optic pathway tumors represent a significant proportion of relapsed pediatric low-grade glioma due to their inoperability. Similarly, contrast imaging is important in assessing leptomeningeal disease (10% of the population on this trial) and spinal tumors, and as such, is considered to be a standard required sequence. It is clear that pediatric low-grade glioma experts do equate decrease in enhancement with anti-tumor

activity in these cases, particularly in the context of stabilization or reduction of the T2 component.

The majority of pediatric low-grade glioma enhance because of intrinsic tumor biology, and given the selectivity of tovorafenib, we believe that the reduction in enhancement reflects an impact of tovorafenib on intrinsic tumor biology. Unlike the pseudoresponses seen in T1-Gd+ sequences with antiangiogenic agents such as bevacizumab, the reductions in enhancing disease observed with tovorafenib treatment are associated with decreases in T2/FLAIR-measurable disease (Figure 1). The reduction in the contrast enhancing portion of the tumor is sustained and associated with contemporaneous reduction in the size of the overall lesion on T2/FLAIR. While, as expected, the changes in lesion size measured by T2-weighted sequences are generally more modest and tend to appear later in treatment, the data are, directionally, highly consistent between T1- and T2-weighted imaging techniques and support the conclusion that treatment of tovorafenib offers clinical benefit in pediatric low-grade glioma.

It is noteworthy that this same effect has been seen with the MEK inhibitor selumetinib ([Banerjee 2017](#), Figure 2). In this study, despite the lack of numerical agreement in percent change in tumor volume between the contrast enhancing tumor volume and FLAIR volume, the directional concordance was considered indicative of anti-tumor activity. This has led to an increasing reliance on the off-label use of MEK inhibitors in relapsed/refractory BRAF-altered pediatric low-grade glioma patients by the pediatric neuro-oncology community, especially given the lack of approved therapies for these patients.

Although the Agency has expressed concern regarding a perceived difference between the ORR by RANO-HGG criteria and RANO-LGG, we believe that it is important to recognize that T1-Gd+ and T2/FLAIR sequences reflect different aspects of tumor biology, and that it is the high directional concordance between these two measurements, taken together, that indicates significant anti-tumor activity. In fact, when the data are analyzed per the published criteria, the response rates are highly consistent (Table 2).

Table 2: Summary of RANO-HGG and RANO-LGG Efficacy Results

	RANO-HGG N = 69^a	RANO-LGG N = 76^b	
		CR + PR	CR + PR + MR
Pts with response, N ORR	43 62.3% (95% CI: 49.8, 73.7)	12 15.8% (95% CI: 8.4, 26.0)	34 44.7% (95% CI: 33.3, 56.6)
CR, n (%)	4 (9.3%)	0	0
PR, n (%)	39 (90.7%)	12 (100%)	12 (35.3%)
MR, n (%)	-	-	22 (64.7%)

	RANO-HGG N = 69 ^a	RANO-LGG N = 76 ^b	
		CR + PR	CR + PR + MR
Responders with ≥ 6 months follow-up after response, N	36	11	26
Responders with DOR ≥ 6 mos, N (%)	35 (97%)	11 (100%)	25 (96%)
Median DOR (months)	Not yet reached (95% CI: 9, NE*)	Not yet reached (95% CI: 8.4, NE)	14.4 (95% CI: 8.4, NE)
Median time to response (months)	2.8 months (range: 2.6-8.3)	2.8 months (range: 2.3-6.1)	4.2 months (range: 2.3-11.0)

^a Number of patients evaluable by RANO-HGG criteria at baseline.

^b Number of patients evaluable by RANO-LGG criteria at baseline.

We expect that MRI response assessment criteria will continue to evolve as new data are generated. At present, response in enhancement across all three criteria is recognized as indicative of anti-tumor activity ([van den Bent 2011](#), [Wen 2017](#), [Fangusaro 2020](#)). (b) (4)

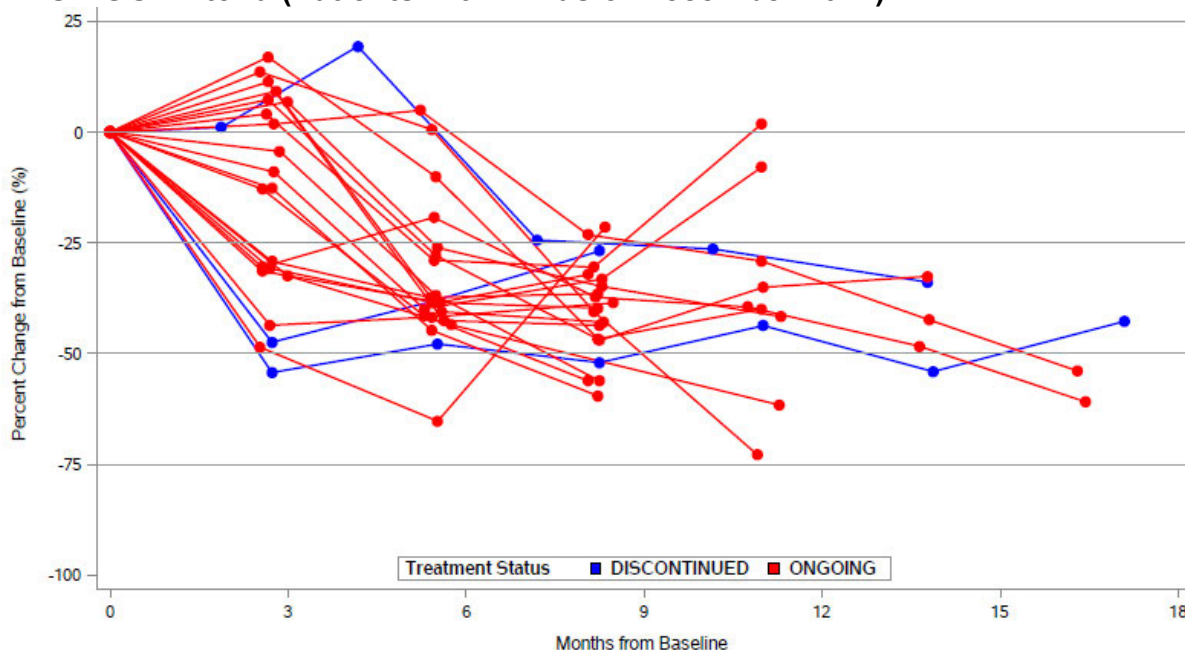
It is well recognized within the neuro-oncology community that MRI findings should always be interpreted in the context of the overall clinical picture, and a definitive conclusion about anti-tumor activity should be based on a comprehensive assessment that includes clinical data and comprehensive radiological data. We believe that the totality of the data, including a significant number of patients having symptomatic stabilization or improvement, is indicative of clinical benefit in this heavily pretreated population – an historically underserved population where the vast majority of patients continue to have no FDA approved options.

Timing of the NDA Submission and Availability of Additional Follow-up

Day One concurs with the Agency regarding the high unmet need in patients with relapsed or refractory pediatric low-grade glioma, in particular for patients with BRAF fusions who have no approved therapies available. The data from Study FIREFLY-1 demonstrate anti-tumor activity on all three imaging endpoints evaluated, including responses in heavily pre-treated patients (3 or more prior systemic therapies), patients with prior MAPK treatment, and patients with BRAF fusions and BRAF V600 mutations. The totality of evidence support the clinical benefit of tovorafenib treatment.

Regarding the Agency's request for additional data to support regulatory decision-making, Day One agrees to submit an additional 6 months of follow-up data beyond the December 2022 data cut. In order to support availability of tovorafenib for patients as soon as possible, Day One proposes to submit this data during the NDA review (data cut in June 2023), together with datasets and an updated Assessment Aid to support the Agency's timely review. Of note, as of the December 2022 data cut, 7 patients currently classified as having had a minor response (MR) have an unconfirmed PR by RANO-LGG criteria, and all remain on study as of this submission (Figure 3). An additional patient classified as having SD had an unconfirmed PR by RANO-LGG as of the December 2022 data cut and this patient remains on treatment as of this submission.

Figure 3 Spider plot for SPPD % Change from Baseline by IRC Based on RANO-LGG Criteria (Patients with MR as of December 2022)



Discussion: FDA acknowledged the complexity and challenges of response assessment in patients with brain tumors.

FDA stated that although a totality of evidence approach would be taken during review of the application, given the consensus of the field that T2/FLAIR-based imaging is most appropriate in this population, ORR and DOR as assessed by LGG imaging criteria will be considered to provide the primary evidence of effectiveness. FDA noted that the substantial number of unconfirmed responses in patients continuing treatment could indicate a higher response rate with additional follow-up time, which would provide a complete picture. FDA also emphasized the importance of DOR in this setting.

FDA stated that the practice of excluding minor responses (MRs) as defined by RANO-LGG criteria from the definition of ORR has been longstanding, and is informed by the uncertainty of the clinical meaningfulness of these responses. FDA stated that they could not commit to including MRs in the calculation of ORR without additional information to support inclusion of these responses. FDA stated that they would commit to review the available clinical data during review of the application, and to that end encouraged DayOne to provide rigorous narratives which incorporated available data on tumor-associated signs and symptoms, any clinical outcome assessment data, as well as imaging findings during treatment on tovorafenib. DayOne stated that they intended to include information on historical scans (prior to treatment with tovorafenib) to establish the trajectory of tumor growth; FDA stated that this information would be helpful, but that historical scans would not need to be IRC-reviewed.

External experts Drs [REDACTED] (b) (4) offered their perspectives supporting the clinical meaningfulness of minor responses in patients with low grade gliomas, and the need to evaluate additional tumor-associated signs and symptoms (e.g., vision) to fully characterize response. DayOne provided the results of an exploratory analysis by patients based on prior MAPK inhibitor receipt, and agreed to provide these results in writing in follow-up to the meeting.

FDA stated that they would have further discussion regarding initiating a rolling review pending the provision of results by the June data cut-off, understanding that the application would not be considered complete until the data from the June data cut-off were provided. DayOne stated that updated datasets, an Assessment Aid, and an CSR addendum could be provided in the September/October 2023 time frame. FDA confirmed that, if based on further discussion, this pathway was acceptable, an addendum to the CSR reflecting the June DCO would be acceptable.

Post-Meeting Addendum:

Please refer to the appended document entitled “RANO-LGG (IRC, Arm 1) ORR by Prior MEK Treatment.pdf,” provided by Day One on Wednesday, April 19th, 2023, by email.

In follow-up to the discussion regarding the planned timing of application submission, please submit a revised plan for rolling review which includes the submission of updated clinical datasets and CSR addendum based on the June 2023 DCO. An NDA submission for tovorafenib will not be considered complete until the data from the June 2023 DCO is submitted, and the fileability of such an application will depend upon the totality of the data, including results of the analyses of ORR and DOR as assessed by RANO-LGG criteria according to BIRC and based on the June 2023 DCO.

In response to these meeting minutes, please also provide a description of your global regulatory strategy as well as the potential impact of any approvals on the enrollment of FIREFLY-2. Additionally, provide an update on the status of enrollment and site activation of FIREFLY-2. We reiterate our expectation that a confirmatory trial be substantially enrolled at the time of an accelerated approval. The status of the proposed confirmatory trial at the time of a potential approval will be a review issue.

We note that the need for a human factors validation study is an outstanding issue. As discussed during the meeting (but not documented in minutes), generally the report of a human factors validation study, if required, would be expected at the time of submission of an application. Refer to Question #9 regarding ongoing correspondence on this topic.

2. Does the Agency agree, given the unmet medical need for pediatric patients with low-grade glioma and the data presented from Study FIREFLY-1, that these data demonstrate a significant clinical benefit and thus that the NDA may be eligible for Priority Review?

FDA Response: Although we acknowledge that pediatric LGG is a serious condition with unmet medical need, in the absence of comprehensive topline data with adequate duration of follow-up using relevant response criteria for LGG, it is premature for us to make a determination on whether the efficacy data from FIREFLY-1 provide sufficient clinical evidence to characterize the benefits and risks of tovorafenib (see Preamble and response to Question 1).

A determination regarding Priority Review will be made by the review team within 60 days of the receipt of an application.

Sponsor Response: The Sponsor acknowledges the Agency's feedback. No further discussion required.

Discussion: There was no discussion for this comment.

3. Does the Agency agree with the cross-reference strategy for the two planned NDAs for tovorafenib tablets and powder for reconstitution (PfR)?

FDA Response: Your plan to include the full NDA (across all modules) in the "parent" NDA 217700 for tablets and house data pertaining to the PfR drug product in Modules 2 and 3 of NDA 218033 while cross-referencing to NDA 217700 for all other NDA content appears reasonable. However, see FDA preamble and response to Question 1.

Sponsor Response: The Sponsor acknowledges the Agency's feedback. No further discussion required.

Discussion: There was no discussion for this comment.

4. Does the Agency agree with the Sponsor's proposed contents and timeline for submission of complete applications, including the submission of certain minor components within 30 days of submission of the original applications?

FDA Response: No. We consider the topline data provided in the briefing package to be incomplete, and as a result, cannot comment on whether rolling review is suitable for your planned NDA submission. As noted in our response to Question 1, we request additional efficacy analyses as per RAPNO-LGG or RANO-LGG with sufficient follow-up from onset of response.

Sponsor Response: The Sponsor acknowledges the Agency's feedback. If the Agency and Day One are able to reach agreement on Question 1 and time permits, Day One would like to discuss the proposed request for rolling review.

Discussion: There was no discussion of this comment

5. Based on the enclosed results from Study FIREFLY-1, does the Agency anticipate that the planned tovorafenib NDA will be the subject of an Oncologic Drugs Advisory Committee (ODAC) meeting?

FDA Response: It is premature to make a determination regarding the need for an Oncologic Drug Advisory Committee (ODAC) to discuss the forthcoming tovorafenib NDAs; refer to our response to Question 1.

Sponsor Response: The Sponsor acknowledges the Agency's feedback. No further discussion required.

Discussion: There was no discussion of this comment

6. Based on the proposed indication for the treatment of patients 6 months of age and older with relapsed or refractory pediatric low-grade gliomas harboring a BRAF fusion or rearrangement or BRAF V600 mutation, and the information provided within this submission, does the Agency agree that the planned tovorafenib NDA meets the statutory criteria for a rare pediatric disease product application?

FDA Response: Please be advised that the Agency does not determine whether a marketing application will be eligible to receive a priority review voucher (PRV) before such an application is approved or licensed. A decision on whether a drug meets the rare pediatric disease PRV eligibility criteria will be made if and when

an associated marketing application is approved, based upon the information submitted in that marketing application and certain facts at the time of approval.

Sponsor Response: The Sponsor acknowledges the Agency's feedback. No further discussion required.

Discussion: There was no discussion of this comment

7. Does the Agency agree with the proposed label text for the PfR formulation as it relates to the quantity of active ingredient per bottle and storage conditions?

FDA Response: The acceptability of the proposed label text for the PfR formulation is a review issue and will be determined at the time of NDA review. However, we have the following comments:

- a. The drug product powder for reconstitution (PfR) is overfilled with (b) (4) mg of the DAY 101 drug substance. In the NDA submission, provide experimental data to demonstrate that the drug product after reconstitution with 14 mL of water can deliver 300 mg of DAY 101 using the intended co-packaged 20 mL syringe per the label instructions.
- b. In compliance with 21 CFR 201.51(g), a gross content specification should be added to the drug product specification to ensure the labeled content is delivered and the residual material is not excessive such as to promote pooling of unused material. Please include a gross content test with upper and lower acceptance criteria reported in mg per vial as a drug product specification. Update 3.2.P.5.1 accordingly. The gross content acceptance criteria should align with your (b) (4) acceptance criteria. Include justification for both your upper and lower gross content limits. The gross content test may be satisfied by the results of the (b) (4) reviewed prior to releasing the batch in lieu of a standalone release test. Please see MAPP 5019.1 (official as of January 28, 2022) for further information.

Sponsor Response: The Sponsor acknowledges the Agency's feedback. No further discussion required.

Discussion: There was no discussion of this comment.

8. Does the Agency require CDISC datasets with the submission of updated safety and efficacy data as part of the 90-day safety update?

Sponsor Response: The Sponsor acknowledges the Agency's feedback. No further discussion required.

Discussion: There was no discussion of this comment.

FDA Response: Yes, please provide the CDISC datasets with the submission of updated safety and efficacy data as part of the 90-day safety update.

9. Does the Agency agree with the Sponsor's assessment that a separate human factors validation study is not required?

FDA Response: We are unable to make a determination regarding a human factors validation study based on the information provided in the meeting package. We refer to our information request dated April 6, 2023. The response to your question will be determined after our review of the requested information.

Sponsor Response: The Sponsor acknowledges the Agency's feedback. A response to the Agency's Information Request dated 06 April 2023 will be submitted to the tovorafenib (DAY101) IND108340 as soon as feasible.

Discussion: There was no discussion of this comment.

Additional Comments

Clinical

10. Your plan to describe the patient experience in clinical efficacy narratives to provide the patient and caregiver's perspective appears reasonable; however, please elaborate on the data you plan to include in these narratives and whether any clinical outcome assessment (COA) data will be included. If you plan to include COA data, please provide a high-level summary of these data including the instruments used to capture this data, if available.

Sponsor Response: Although Patient Reported Outcome (PRO) assessments were administered in the Study FIREFLY-1, unfortunately interpretation of these data will be limited by the high percentage of missing data, and these data will not be included in the clinical efficacy narratives. The clinical efficacy narratives will include relevant information on diagnosis, prior treatment history, and investigator-reported information on functional deficits at baseline (eg, visual deficits, hemiparesis, etc.) from the electronic data capture system. Additionally, through a separate questionnaire, Day One inquired as to whether these deficits improved, remained stable, or worsened during tovorafenib treatment.

Discussion: There was no discussion of this comment.

Clinical Pharmacology

11. Provide your plans for assessing the drug-drug interaction risk for tovorafenib act as a victim and also as a perpetrator given that tovorafenib is primarily metabolized by CYP2C8 and is an inhibitor of CYP2C8.

Sponsor Response: As previously agreed in the Agency's Type B Guidance Meeting Preliminary Comments dated 22 February 2021 (Ref ID 4750968) regarding the drug metabolism and pharmacokinetics (DMPK) and Clinical Pharmacology development programs for tovorafenib, physiologically-based pharmacokinetic (PBPK) modeling will be used to assess the drug-drug interaction risk for tovorafenib as a victim and perpetrator, respectively. This includes the effects of CYP2C8 inhibitors and inducers on tovorafenib, and the effects of tovorafenib on CYP2C8 substrates. These modeling reports will be submitted with the planned NDA.

Discussion: There was no discussion of this comment.

12. Provide your plan to assess the effect of hepatic impairment on the systemic tovorafenib exposure.

Sponsor Response: Per the Agency's Type B Guidance Meeting Preliminary Comments dated 22 February 2021 (Ref ID 4750968) regarding the Clinical Pharmacology program for tovorafenib, the need to conduct studies in subjects with impaired organ function (hepatic/renal) will be based on the results of the human absorption, distribution and metabolism (hAME) mass balance study and assessed during the NDA review.

The hAME study has been completed. It indicates that the major route of elimination is hepatic metabolism and biliary excretion. To further assess the effect of hepatic impairment on tovorafenib exposure, the sponsor plans to test hepatic impairment as a covariate of tovorafenib clearance in the population pharmacokinetic (PopPK) model that includes adult and pediatric PK data pooled from multiple clinical studies. The hAME study report and the PopPK report will be submitted with the planned NDA.

Discussion: There was no discussion of this comment.

13. Provide your plan to assess the effect of renal impairment on the systemic tovorafenib exposure or provide justification for not conducting this assessment.

Sponsor Response: Per the Agency's guidance in the Type B Guidance Meeting Preliminary Comments dated 22 February 2021 (Ref ID 4750968) regarding the Clinical Pharmacology program for tovorafenib, the need to

conduct studies in subjects with impaired organ function (hepatic/renal) will be based on the results of the hAME mass balance study and assessed during the NDA review.

The hAME study has been completed. A minimal contribution of renal excretion to tovorafenib elimination was observed. In addition, the sponsor plans to test renal impairment as a covariate of tovorafenib clearance in the population PK model that includes adult and pediatric PK data pooled from multiple clinical studies. The hAME study report and the PopPK report will be submitted with the planned NDA.

Discussion: There was no discussion of this comment.

14. Clarify if pharmacokinetic (PK) data is available from Study FIREFLY-1 and this data will be included in population PK (PopPK) model. Collect adequate dense PK sampling following single dosing and at steady state in at least 4 patients from age group of 6 months to 2 years and in at least 6 pediatric patients from age groups of ≥ 2 and < 6 years, > 6 and ≤ 12 years and > 12 years of age, respectively to allow adequate characterization of the tovorafenib PK profile in pediatric patients.

Sponsor Response: PK data from Study FIREFLY-1 will be included in the PopPK model and submitted with the planned NDA.

The approximate number pediatric patients with PK data at each age group is the following:

- 6 months to 2 years of age: n=3
- 2 to 6 years of age: n=27
- 6 to 12 years of age: n=66
- 12 to 18 years of age: n=36

Discussion: There was no discussion of this comment.

15. Include integrated dose- and exposure-response analyses using the preliminary and emerging efficacy and safety data to assess the relationships between tovorafenib exposure (e.g., steady state C_{min} or AUC and C_{max}) and efficacy and safety in support of the proposed dosages at the time of NDA submissions.

Sponsor Response: The integrated exposure-response analyses will be performed per the Agency's request and submitted with the planned NDA.

Discussion: There was no discussion of this comment.

Additional clinical pharmacology comments regarding the planned NDA submissions:

The content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support the planned applications should be consistent with FDA Guidance for Industry, "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products –Content and Format" (available at: <https://www.fda.gov/media/74346/download>). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

Address the following questions in the Summary of Clinical Pharmacology:

16. What is the basis for selecting the dose(s) and dosing regimen used in the trials intended to support your marketing application? Identify individuals who required dose modifications and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.
17. What are the exposure-response relationships for efficacy, safety and biomarkers?
18. What is the effect of tovorafenib on the QT/QTc interval?
19. What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?
20. What are the effects of food on the bioavailability? What are the dosing recommendations with regard to meals or meal types? Provide justification for recommendation with regard to meals or meal types.
21. How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure, efficacy, or safety? What dose modifications are recommended?

Sponsor Response to Comments 16 through 21: The Sponsor acknowledges the Agency's feedback and plans to address the above questions in the upcoming NDA submission in the Summary of Clinical Pharmacology

Discussion: There was no discussion of these comments.

Apply the following advice in preparing the clinical pharmacology sections of the original submission:

22. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
23. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation

(and mean $\pm$ standard deviation) and median with minimum and maximum values as appropriate.

24. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
 - a. Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
 - b. Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.
25. Submit the following for the population pharmacokinetic analysis reports:
 - a. Standard model diagnostic plots
 - b. Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line
 - c. Model parameter names and units in tables.
 - d. Summary of the report describing the clinical application of modeling results.

Refer to the following pharmacometric data and models submission guidelines
<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>.

26. Submit the following information and data to support the population pharmacokinetic analysis:
 - a. SAS transport files (*.xpt) for all datasets used for model development and validation
 - b. A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets
 - c. Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model,

and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt)

27. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and safety) relationships in the targeted patient population. Refer to Guidance for Industry for [population PK](#), [exposure-response relationships](#), and [pharmacometric data and models submission guidelines](#).
28. Use the laboratory analysis dataset (adlb.xpt) for the laboratory-based adverse reactions and the adverse event analysis dataset (adae.xpt) for the non-laboratory-based adverse reactions (individual and pooled terms as appropriate) to evaluate the exposure-response relationship for safety and the effect of intrinsic and extrinsic factors on safety based on the maximum toxicity grade compared to baseline.
29. Include a variable that identifies the maximum toxicity grade compared to baseline for laboratory-based adverse reactions in laboratory analysis dataset (adlb.xpt) and for non-laboratory-based adverse reactions (individual or pooled where applicable) in adverse event analysis dataset (adae.xpt) to support these analyses. A description of the pooled non-laboratory-based adverse reactions should be provided in the reviewer guide and consistent with common pooled terms used to inform labeling if applicable.
30. Include the purpose of the simulations, assumptions, detailed process of PBPK model building and verification, summary of model input parameters, version of software, simulation results, and conclusions in the study report.
 - a. Provide the study report as PDF files (screenshots can be incorporated if required).
 - b. Include the model files used to generate the final PBPK simulations. These files should be executable by FDA reviewers using the specified software.
 - c. Include appropriate supporting documentations such as any special instructions and file definitions.
31. Include the following items when you submit your QT study report:
 - a. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
 - b. Electronic copy of the study report
 - c. Electronic or hard copy of the clinical protocol

- d. Electronic or hard copy of the Investigator's Brochure
- e. Annotated CRF
- f. A data definition file which describes the contents of the electronic data sets
- g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses
- h. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)
- i. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
- j. Narrative summaries and case report forms for any:
 - i. Deaths
 - ii. Serious adverse events
 - iii. Episodes of ventricular tachycardia or fibrillation
 - iv. Episodes of syncope
 - v. Episodes of seizure
 - vi. Adverse events resulting in the subject discontinuing from the study
- k. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
- l. A completed Highlights of Clinical Pharmacology Table

Advancing in this field – and possibly reducing the burden of conducting QT studies –depends critically upon obtaining the most comprehensive understanding of existing data. Please consider making your data, at least placebo and positive control data, available for further research purposes; see, for examples, the Data Request Letter at <http://cardiac-safety.org/ecg-database/>.

Sponsor Response to Comments 22 through 31: The Sponsor acknowledges the Agency's feedback and plans to address the above comments in the upcoming NDA submission. The Sponsor notes that the ECG warehouse is no longer accepting uploads of ECG waveforms.

Discussion: There was no discussion of these comments.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. Refer to discussion under Question 1.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- Post-Meeting Addendum: A preliminary discussion was not held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan. A final determination of whether a REMS is needed will be made upon review of a complete application.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.²

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor’s initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD & C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency’s current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating “**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**” These meetings will be scheduled within 30 days of meeting request

² <https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology>

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.³

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information⁴ and Pregnancy and Lactation Labeling Final Rule⁵ websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of

³ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

⁴ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁵ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs,

including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR⁶: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid⁷

18 Page(s) have been Withheld in Full as b4 (CCI/TS)
immediately following this page

⁶ <https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program>

⁷ <https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project>

U.S. Food and Drug Administration

Silver Spring, MD 20993

www.fda.gov

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JACQUELINE J GLEN
05/04/2023 05:56:45 PM



IND 108340

MEETING MINUTES

DOT Therapeutics-1 Inc.
Attention: Jerald Grace, PharmD
Senior Director, Regulatory Science
395 Oyster Point Boulevard, Suite 217
South San Francisco, CA 94080

Dear Dr. Grace:¹

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for DAY101.

We also refer to the teleconference between representatives of your firm and the FDA on October 4, 2021. The purpose of the meeting was to discuss the proposed clinical trial design and statistical assumptions for the planned trial to evaluate the safety and effectiveness of DAY101 in pediatric and adolescent patients with low grade glioma requiring (LGG) harboring an activating RAF alteration (b) (4)

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

¹ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

If you have any questions, call me at (240) 402-9558.

Sincerely,

{See appended electronic signature page}

Jacqueline Glen, MS
Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic
Diseases for DO2
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: October 4, 2021 at 12:00 PM – 1:00 PM, ET
Meeting Location: Teleconference

Application Number: 108340
Product Name: DAY101
Indication: Patients with pediatric low grade glioma harboring an activating RAF alteration (b) (4)
Sponsor Name: DOT Therapeutics-1, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act [

Meeting Chair: Diana Bradford
Meeting Recorder: Jacqueline Glen

FDA ATTENDEES

Martha Donoghue, Deputy Director, Division of Oncology 2 (DO2)
Diana Bradford, Cross Disciplinary Team Leader, DO2
Sonia Singh, Clinical Reviewer, DO2
Marjilla Seddiq, Clinical Reviewer, DO2
Gautam Mehta, Clinical Reviewer, DO2
Emily Wearne, Acting Nonclinical Team Leader, Division of Hematology/Oncology Toxicology (DHOT) Products
Pallavi Mishra-Kalyani, Biometrics Team Leader, Division of Biometrics V (DBV)
Xiaoxue Li, Biometrics Reviewer, DBV
Vishal Bhatnagar, Associate Director for Patient Outcomes, Oncology Center of Excellence (OCE)
Gregory Reaman, Associate Director for Pediatric Oncology, Oncology Center of Excellence
Robert Temple, Deputy Director for Clinical Science, Office of New Drugs
Rosane Charlob Orbach, Clinical Pharmacology Team Leader, Office of Clinical Pharmacology, Division of Translational and Precision Medicine
Jason Moore, Clinical Pharmacology Reviewer, Division of Cancer Pharmacology
Jacqueline Glen, Regulatory Health Product Manager, Division of Regulatory Operations

SPONSOR ATTENDEES

Samuel C. Blackman, MD, PhD, Founder and Chief Medical Officer
Davy Chiodin, PharmD, Chief Development Officer
Mark Kieran, MD, PhD, Vice President, Clinical Development

Michael C. Cox, PharmD, Vice President, Clinical Development

Jerald Grace, PharmD, Senior Director, Regulatory Science

(b) (4), PhD, Statistician (Consultant)

(b) (4)

BACKGROUND

Regulatory History

On August 31, 2020, DAY101 received Breakthrough Therapy Designation for the treatment of pediatric patients with low-grade gliomas (LGGs) harboring an activating RAF alteration that have progressed after one or more prior systemic therapies.

Summary of meetings relevant to this program:

- On April 27, 2020, FDA issued written comments for an End-of-Phase (EOP) 1 meeting to discuss the design of a potential registration study FIREFLY-1, an ongoing, single-arm trial evaluating the safety and efficacy of DAY101 in up to 60 patients, age 6 months to 25 years, with recurrent or progressive LGG harboring a known activating BRAF alteration. FDA stated that a single-arm trial evaluating ORR based on radiographic response as assessed by RANO criteria and per IRC assessment with a clinically meaningful response duration may support an application seeking marketing approval; however, a determination of the significance of the data from a single trial will be based on an analysis of the totality of evidence, including an assessment of the magnitude of clinical benefit, durability of response, and the safety profile of DAY101
- On February 22, 2021, FDA issued written comments for a guidance meeting regarding the proposed drug metabolism and pharmacokinetics (DMPK) and clinical pharmacology packages, and the general companion diagnostic strategy for DAY101 in patients with relapsed or progressive RAF-altered low LGG for a planned new drug application (NDA).
- On July 16, 2021, Day One requested a Type B, EOP meeting to discuss the clinical trial design and statistical assumptions (b) (4)

On March 29, 2021, Day One submitted a (b) (4).
FDA issued an Inadequate (b) (4) letter on July 23, 2021, advising Day One to revise the (b) (4) to include a study, contingent upon the results of FIREFLY-1, that will evaluate (b) (4)

(b) (4). The study proposed in this meeting package is intended to address that (b) (4) deficiency.

DAY101

DAY101 (formerly TAK-580/MLN248) is an oral, small molecule, pan-rapidly accelerated fibrosarcoma (RAF) kinase inhibitor that is being developed for the treatment of low-grade gliomas (LGGs) harboring an activating RAF alteration. The DAY101 drug product is formulated as an immediate-release tablet in 20 mg and 100 mg strengths for oral administration. A pediatric formulation is also being designed as a "powder in bottle" suspension for dosing after reconstitution in water for pediatric patients 6 months of age and older.

Disease Background

LGGs, classified as Grade I and Grade II tumors by the World Health Organization (WHO), are the most common brain tumors in children accounting for 30% of all childhood brain tumors. In the last decade, molecular data has emerged to suggest that the majority of pediatric LGGs (pLGGs) are driven by up-regulation of the RAS/MAPK pathway with the most common genetic alteration being KIAA1549:BRAF wild-type fusions (present in 50-60% of pLGGs). Constitutive activation of the pathway via this fusion has been observed in approximately 80% of pilocytic astrocytomas, the most common subtype of pLGG. BRAF V600E point mutations are less common and have been demonstrated in 15 to 20% of pLGGs.

Treatment Options

Historically, pLGGs have been managed with surgery, multiagent chemotherapy and radiation. Complete resection remains the most favorable predictor of patient outcome and is associated with 10-year overall survival (OS) rates of 90% or greater; however, this is not always feasible for deeply seated or highly infiltrative tumors.

Incompletely resected or unresectable pLGGs have a high rate of disease progression and are associated with significant morbidity and in some cases mortality. Patients with subtotal resections are reported to have a 10-year progression-free survival (PFS) rate of 55%. Progressive residual disease has typically been treated with systemic chemotherapy (e.g., carboplatin and vincristine [CV]; single agent vinblastine; TPCV [thioguanine, procarbazine, lomustine, and vincristine]) or radiation. In the setting of pediatric patients with progressive LGG who are chemotherapy-naïve, the response rate to the commonly used regimen of CV is approximately 30% (Packer et al. 1997), and the response rate to single-agent vinblastine is approximately 20% (Lassaletta et al., 2016).

(b) (4)

Genomics

7. Please provide available data on activity of DAY101 against RAF1 (CRAF) fusions such as SRGAP3-RAF1.

Sponsor Response: In biochemical kinase inhibition assays, DAY101 demonstrated potent inhibition of BRAF V600E mutation as well as wild-type BRAF and CRAF kinases. The biochemical IC₅₀ were 7.1, 0.1 and 0.7 nM for BRAF V600E mutation, wild-type BRAF and CRAF respectively. In cell viability assays, DAY101 inhibited MAPK signaling in cell lines harboring BRAF V600 mutations, which signal as a monomer, as well as cell lines harboring KIAA1549:BRAF

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

mutation which functions as a dimer. This distinguishes DAY101 from type I BRAF inhibitors, such as vemurafenib, which do not inhibit signaling downstream of RAF fusions, which function as RAF dimers.

Two patients with RAF1(CRAF) fusions have been enrolled in the ongoing investigator sponsored trial PNOC014. The first patient is a 12 year old male with disseminated low-grade astrocytoma with piloid features harboring an SRGAP3:RAF1 fusion. After initiation of therapy with DAY101, the MRI performed prior to the start of cycle 3 day 1 demonstrated marked regression of the primary tumor with approximately 91% change from baseline, qualifying as partial response by RANO response criteria. The patient continued therapy up to the protocol specified maximum of two years. The MRI at the completion of therapy confirmed an approximately 99% decrease in tumor burden from baseline.

The second patient is a 14 year old female with pilocytic astrocytoma harboring a SOX6-RAF1 fusion. Treatment is currently ongoing, having received approximately 14 months of therapy with DAY101. On-treatment MRI scans from this patient, who remains on treatment in the ongoing PNOC014 investigator-sponsored trial, have not yet been reviewed by Day One or by an independent neuroradiologist. We anticipate transfer of images from this study, and independent review, will occur over the next few months.

Discussion: There was no discussion of this question.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to [FDA.gov](https://www.fda.gov).²

FDARA REQUIREMENTS

Sponsors may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor’s initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency’s current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided.

Meeting request should be sent to the appropriate review division with the cover letter clearly stating “**MEETING REQUEST FOR PREPARATION OF iPSP MEETING**”

² <https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology>

UNDER FDARA.” These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.³

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.⁴

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data*. This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, as well as email access to the eData Team (cdeler-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page⁵ that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide

³ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

⁴ <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>

⁵ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.⁶

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests

⁶ <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources⁷ and the CDER/CBER Position on Use of SI Units for Lab Tests website.⁸

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*, be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.⁹

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*.

⁷ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

⁸ <https://www.fda.gov/media/109533/download>

⁹ <https://www.fda.gov/media/85061/download>

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

- (1) Study phase
- (2) Statement of whether the study is intended to support marketing and/or labeling changes
- (3) Study objectives (e.g., dose finding)
- (4) Population
- (5) A brief description of the study design (e.g., placebo or active controlled)
- (6) Specific concerns for which you anticipate the Division will have comments
- (7) For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection*

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

of Race and Ethnicity Data in Clinical Trials for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR¹⁰: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid¹¹

¹⁰ <https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program>

¹¹ <https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project>

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JACQUELINE J GLEN
10/28/2021 06:38:21 PM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	108340
Request Receipt Date	July 2, 2020
Product	DAY101
Indication	Treatment of pediatric patients with low-grade glioma harboring an activating RAF alteration that has progressed after one or more prior therapies
Drug Class/Mechanism of Action	Kinase inhibitor
Sponsor	Day One Biopharmaceuticals
ODE/Division	OND/DO2
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	August 31, 2020

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthrough Therapy Designation Determination)** even if the review is attached to the MPC meeting minutes and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):

The sponsor proposes the following indication for DAY101: "for the treatment of pediatric patients with an advanced low-grade glioma harboring an activating RAF alteration who require systemic therapy and who have either progressed following prior treatment or who have no satisfactory alternative treatment options."

The Division proposes the following indication for DAY101: "for the treatment of pediatric patients with low-grade gliomas harboring an activating RAF alteration that have progressed after one or more prior systemic therapies."

2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?

☐ YES ☒ NO

3. Was the BTDR submitted to a PIND?

☐ YES ☒ NO

If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. Consideration of Breakthrough Therapy Criteria:

a. Is the condition serious/life-threatening¹?

☒ YES ☐ NO

¹ For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

If 4a is checked “No,” the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked “Yes”, proceed with below:

- b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?
- ☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
- ☐ Undetermined
- ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):
- i. Only animal/nonclinical data submitted as evidence ☐
 - ii. Insufficient clinical data provided to evaluate the BTDR
(e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
 - iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
 - iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
 - v. No or minimal clinically meaningful improvement as compared to available therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked “No”, BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTDR Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

² For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

- *Information regarding the disease and intended population for the proposed indication.*
- *Disease mechanism (if known) and natural history (if the disease is uncommon).*

Disease Background

Low-grade gliomas (LGGs), classified according to the World Health Organization (WHO) criteria as Grade 1 and Grade 2 tumors, are the most common central nervous system (CNS) tumor among children and account for approximately one-third of pediatric brain tumors; however, pediatric LGGs (pLGGs) are rare cancers that occur at an annual incidence of approximately 1,000-1,600 in the U.S.⁽¹⁾ LGGs encompass different histologies such as astrocytic, oligodendroglial, and mixed glial-neuronal histology, with pilocytic astrocytoma representing the most prevalent.⁽²⁾ Unlike their adult counterparts, which exhibit a more aggressive phenotype, the majority of pLGGs are indolent and do not undergo malignant transformation, often exhibiting a relapsing/remitting clinical course.⁽³⁾ Additionally, these tumors can occur anywhere in the CNS including critical midline structures.

In the last decade, genomic profiling has revealed that aberrations leading to activation of the MAPK pathway are key to oncogenesis in pLGG.⁽⁴⁾ Most of these tumors harbor a single identifiable driver alteration, typically single structural variants or rearrangements that result in the expression of a fusion variant. Rearrangements affecting the genes *KIAA1549* and *BRAF* are the most frequent somatic driver alterations, and the *KIAA1549-BRAF* wild-type fusion is the most commonly identified, found in approximately 50-60% of pLGGs.^(5, 6) The *KIAA1549-BRAF* fusion protein consists of the N'-terminal of the *KIAA1549* protein and the truncated C'-terminal of *BRAF*, which contains the *BRAF* kinase. Loss of the N'-terminal negative regulatory domain of *BRAF* in this fusion results in constitutive activation of the *BRAF* kinase with downstream activation of MAPK signaling.⁽⁷⁾ *BRAFV600E* point mutations are less commonly observed (5-15% of pLGG).⁽⁸⁾

Treatment Options

Historically, pLGGs have been managed with surgery, chemotherapy and radiation. Choice of treatment depends on factors such as patient age, tumor location, surgical resectability and association with neurofibromatosis type 1 (NF1). The mainstay of therapy is complete surgical resection when feasible, and for many patients this may be curative. Although survivors often suffer from functional, neurologic and endocrine complications from their disease or treatment, the prognosis for these patients is generally favorable with 10-year overall survival (OS) of approximately 90%.⁽⁹⁾ Unfortunately, the majority of children with pLGG are unable to undergo complete resection. Patients with unresectable or incompletely resected pLGG have a high rate of disease progression or recurrence, and a 10-year progression free survival (PFS) of 55%.⁽¹⁰⁾ Tumor recurrence is seen in up to 19% of cases.⁽¹¹⁾ These tumors are difficult to treat and associated with poor outcomes.

There are no approved therapies for pLGG, and there is no consensus on a standard treatment approach for progressive or relapsed pLGG. Patients tend to require multiple and potentially multimodal interventions. Chemotherapy, although associated with limited success, is typically used to delay or obviate the need for radiation therapy. The most widely used chemotherapy regimens are carboplatin and vincristine (CV); thioguanine, procarbazine, lomustine, and vincristine (TPCV); and single-agent vinblastine.⁽¹²⁾ In a study of 23 pediatric patients with recurrent LGG treated with CV, there were 7 partial responses (PR) (no complete responses [CR]) yielding an overall response rate (ORR) of 30%.⁽¹³⁾ In a Phase 2 study of vinblastine in 51 pediatric patients with recurrent or refractory LGG, the response rate was 21% (1 CR, 10 PR) with a 5-year PFS of 42%.⁽¹⁴⁾ Radiation therapy is generally reserved for patients with pLGG who are older and for whom less toxic treatments have been exhausted.

There is a high unmet medical need for new treatments for patients with pLGG who are not candidates for complete resection because available treatments (i.e., radiation, systemic chemotherapy) confer a significant risk of long-term sequelae in growing children (e.g., cognitive deficits, blindness, hearing loss, and hormonal disturbance). With improved understanding of the genomic landscape of these tumors, clinical trials with MAPK pathway-directed agents have recently emerged as an alternative treatment option for patients with progressive or relapsed disease.

Although there are no FDA-approved MAPK-pathway targeting agents for LGG, there are several ongoing clinical trials evaluating these agents in patients with LGG. FDA-approved agents that target the MAPK pathway include three Type I RAF inhibitors (vemurafenib, dabrafenib, encorafenib), which specifically inhibit BRAFV600E, and three MEK inhibitors (e.g., trametinib, selumetinib, binimetinib). Type I RAF inhibitors such as vemurafenib, dabrafenib, and encorafenib exert their effect on monomeric forms of BRAF (BRAF V600E/K mutations) and do not inhibit signaling from the *KIAA1549:BRAF* wild-type fusion that functions as dimers and represents the majority of RAF alterations found in pLGGs.^(15, 16) Furthermore, the phenomenon of paradoxical activation of MAPK signaling has been well-described when Type I RAF inhibitors are used to treat tumors harboring *KIAA159:BRAF* wild-type fusion. This class-effect can manifest as accelerated tumor growth and development of pre-malignant and malignant skin lesions (e.g., keratoacanthomas and squamous cell carcinoma).⁽¹⁷⁾

DAY101 Mechanism of Action

DAY101 is described as an oral, CNS-penetrant, small-molecule, Type II RAF kinase inhibitor that inhibits wild-type BRAF and CRAF enzyme equipotently. The sponsor states that DAY101 blocks abnormal signaling resulting from constitutively active BRAF alterations, such as oncogenic BRAFV600 and non-V600 mutations, and wild-type fusions. Reportedly DAY101 does not paradoxically hyperactivate MAPK signaling in tumors harboring BRAF wild-type fusions including the *KIAA1549:BRAF* fusion, as supported by data from nonclinical studies.⁽¹⁸⁾

Relevant Regulatory History

DAY101 was initially developed by Millennium Pharmaceuticals/Takeda Pharmaceuticals and studied in a variety of solid tumors in two adult clinical trials (completed Study C28001 and ongoing Study C28002). These trials have generated exposure data for DAY101 in more than 200 adult patients within the United States and Europe.

Study PNOC014 is an active multicenter Phase 1 dose-escalation trial of DAY101 in patients up to twenty-five years of age with recurrent or progressive non-hematologic malignancies, including CNS tumors, with a genomic mutation resulting in the activation of the RAS/RAF/MEK/ERK pathway. This trial opened in February 2018 and is being conducted in collaboration with the Pacific Pediatric Neuro-Oncology Consortium.

On February 20, 2020, DO2 met with Day One Biopharmaceuticals (Day One) via teleconference for preliminary advice regarding a BTDR submission. DO2 agreed that initial results from 9 patients with pLGG from Study PNOC014 showing durable responses in pediatric patients with heavily pre-treated LGG are encouraging and supportive of further development of DAY101 in pLGG. Although supportive of submission of a BTDR, DO2 encouraged Day One to submit the request after additional patients were enrolled to support the preliminary findings discussed.

On April 14, 2020, Day One submitted an initial Pediatric Study Plan (iPSP).

On April 27, 2020, FDA issued written responses (End-of-Phase 1 [EOP1] meeting) regarding the design of a proposed multicenter, single-arm trial to evaluate DAY101 in pediatric patients with relapsed, refractory or progressive LGGs harboring an activating BRAF fusion or mutation. Day One subsequently requested feedback on this planned registration study from both FDA and EMA through a Common Commentary that was provided after a Pediatric Cluster teleconference held on May 20, 2020. Both Agencies agreed with Day One's plan to pursue a global pediatric program for DAY101. FDA agreed with the proposal to conduct an open-label, single-arm trial.

8. Information related to endpoints used in the available clinical data:

- a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

Day One considers ORR and DOR to be clinically meaningful endpoints for the evaluation of the effectiveness of DAY101. The ORR and DOR data provided to support this BTDR are based on centrally-reviewed radiographic tumor response according to Response Assessment in Neuro-Oncology (RANO) criteria, lending additional support to the data provided.

- b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:
- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
 - *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
 - *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

DO2 agrees that demonstration of a meaningful effect size on durable objective response rate according to RANO criteria for high-grade glioma (HGG) can provide preliminary clinical evidence indicating that the drug may demonstrate substantial improvement on a clinically significant endpoint. There are no standardized response criteria for assessment of brain tumors in clinical trials of pediatric patients.

The RANO criteria were originally developed as an objective tool for radiologic assessment of treatment response in adult patients with high-grade gliomas. The RANO-LGG criteria designed for adults and most recently the Response Assessment in Pediatric Neuro-Oncology (RAPNO) criteria for LGG⁽¹⁹⁾ are response criteria that have been developed specifically to evaluate disease in patients with LGG, but these criteria have not been used as the basis for approval of novel therapies, and the latter (RAPNO LGG) have not yet been clinically validated.

The RANO-HGG criteria were intended to minimize the risk of attributing reduced enhancement observed with antiangiogenic agents as anti-tumor effect (“pseudoresponse”) and to address the phenomenon of pseudoprogression sometimes observed after chemoradiation. Although these issues are less relevant for pLGG, the RANO criteria take into consideration both the T1-weighted/contrast enhancing portion of the tumor as well as T2-weighted-Fluid-Attenuated Inversion Recovery (T2/FLAIR) signal. Pilocytic astrocytomas, the most common LGG diagnosed in pediatric patients, are mostly well demarcated with negligible surrounding vasogenic edema and are described as having heterogenous areas of avid contrast enhancement.⁽²⁰⁾

Although overall survival (OS) and progression-free survival (PFS) have been used to support approval of drugs to treat adult high-grade glioma (glioblastoma) and are more direct measures of clinical benefit, DO2 does not consider these to be feasible endpoints for further evaluation of the effectiveness of DAY101 in pLGG harboring an activating RAF alteration given the rarity of this patient population, lack of satisfactory available treatment in the relapsed or refractory setting, and available clinical data showing durable responses, which is likely to raise questions regarding equipoise.

- c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

Not applicable.

- 9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:**

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

There are no approved treatments for pediatric patients with progressive LGGs. Chemotherapy and radiation therapy are used in clinical practice (see section on “Treatment Options”) but have shown limited success and are associated with long-term morbidity. Table 1 below, reproduced from a publication by Bouffet et al (2012), summarizes radiologic responses and event-free survival in children with LGG including patients with recurrent disease.

Table 1: Objective Radiologic Response and EFS in Previous Clinical Studies Using Chemotherapy for Children with Newly Diagnosed and Recurrent Low-Grade Glioma

Agent or Regimen	No. of Patients	Central Radiology Review	No. of Patients						EFS (%)	Study
			Population	CR	PR+MR	SD	PD	NE		
Carboplatin	81	No	60 ND, 21 R	2	21	46	11	1	64 at 3 years	Gururangan et al ⁶
Vincristine-carboplatin (first line)	78	No	78 ND	4	40	29	5		68 at 3 years	Packer et al ³
SFOP	85	Yes	85 ND	0	51	23	11		34 at 5 years	Laithier et al ⁸
Temozolomide	30	No	11 ND, 19 R	0	3	11	12	4	31 at 4 years	Gururangan et al ⁷
Etoposide-cisplatin	34	No	31 ND, 3R	1	23	10	0		78 at 3 years	Massimino et al ⁴
TPCV	42	No	42 ND	0	15	25	2		45 at 3 years	Prados et al ⁵
Vincristine-carboplatin (recurrent)	18	No	18 R	0	12	5	6		NA	Packer et al ¹⁹
Temozolomide	21	No	21 R		1	10	9	1	NA	Nicholson et al ²¹
Bevacizumab-irinotecan	10	No	10 R	1	6	2		1	NA	Packer et al ^{21a}
Vinblastine	51	Yes	51 R	1	17	19	13	1	42 at 5 years	

Abbreviations: CR, complete response; EFS, event-free survival; MR, minor response; NA, not available; ND, newly diagnosed; NE, not evaluable; PD, progressive disease; PR, partial response; R, recurrent; SD, stable disease; SFOP, alternating courses of carboplatin-procarbazine, etoposide-cisplatin, and vincristine-cyclophosphamide; TPCV, thioguanine, procarbazine, lomustine, and vincristine.

In the setting of advanced disease, response rates to the commonly used chemotherapy regimen of CV, and single-agent vinblastine vary from 20 to 30%. Packer et al. (1993) studied CV in 23 children with recurrent LGG treated with radiotherapy and/or chemotherapy. There were 7 PRs (no CRs) yielding an ORR of 30%. The largest study of chemotherapy (vinblastine) in patients with relapsed or refractory pLGG, previously treated with chemotherapy and/or radiation for incompletely resected or unresectable tumors, showed a response rate of 21% and 5-year PFS of 47%. Chemotherapy is associated with short-term and long-term toxicities such as hearing loss (platinum-based treatment), secondary malignancy and infertility (TPCV regimen), and hypersensitivity reactions (carboplatin).

In the past, focal radiation therapy was considered an alternative adjuvant treatment as it led to an improvement in 10-year PFS with rates ranging from 60 to 65%⁽¹⁾; however, due to the late effects of radiation in survivors of pediatric brain tumors, radiotherapy is avoided when possible, particularly in younger patients. Clinical trials with agents targeting the MAPK pathway (including BRAF inhibitors and MEK inhibitors) are currently ongoing.

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

There have been no prior breakthrough therapy designation requests for pediatric low-grade gliomas.

³ Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

11. Information related to the preliminary clinical evidence:

- a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design⁴, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

Table 2: Studies Supporting the BTDR

Study ID / Design	Population / N	Response Rate	DOR	Other
Study PNOC014 (NCT03429803) Phase 1 dose-escalation study	N= 9 patients with LGG (all evaluable for response)	ORR 55.6% (5/9) CR – 22% (2/9) PR – 33% (3/9)	398 - 620 days (1.1 -1.7 years)	Median time to response: 10.5 weeks (range 8-32 weeks) No responders developed progression

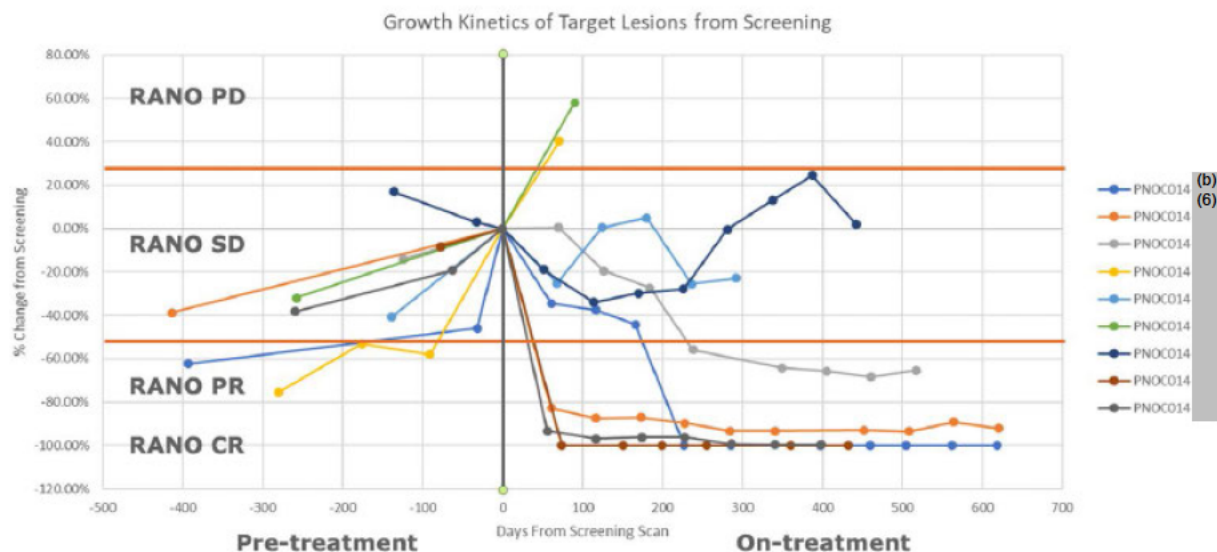
Study PNOC014 is an ongoing multicenter, open-label, dose-escalation study of DAY101 in patients 1 to 25 years of age with radiographically confirmed recurrent or progressive solid tumors, including primary CNS disease, harboring a mutation resulting in the activation of the RAS/RAF/MEK/ERK pathway. DAY101 is administered as an oral tablet once weekly for up to two years. Part A of the study utilized a 3 + 3 design for dose escalation. As of December 20, 2019, nine patients with pLGG enrolled. The median age of these patients is 12 years (range: 4-14); seven of the nine patients (78%) had tumors with KIAA1549:BRAF fusion, one had a SRGAP3-RAF1 fusion and one had NF1 loss-of-function; and all nine had received prior chemotherapy with a median of four lines of prior systemic therapy (range: 2-7). All patients had measurable disease and were evaluable for response assessment using RANO criteria. Pre-treatment and on-treatment MRI scans were collected for all patients and centrally reviewed by an independent neuroradiologist.

The ORR was 56% (95% CI: 21, 86) with two patients exhibiting CR and three patients exhibiting PR. Among patients with a confirmed RAF alteration (excluding the single patient with NF1 loss-of-function), the ORR was 63% (5/8 responses). Of the five responders, four patients had tumors with a KIAA1549:BRAF fusion and one patient had SRGAP3-RAF1 fusion. Duration of response ranged from 398 to 620 days. The median time to response was 10.5 weeks (range 8-32 weeks). Of note, all patients with responses have been on therapy for over 15 months and either remain on study or have completed their 24-month course of therapy. No responders have shown progression.

Figure 1 below (reproduced from the Sponsor's BTDR package) shows growth kinetics of target lesions for each patient prior to enrollment and on study. The left side of the graph shows growth trajectory based on historical scans prior to enrollment. Eight of the nine patients had tumors increasing in size prior to enrollment. The right side of the graph depicts tumor response and time to response. All patients with a confirmed response had an initial response within less than one year of initiation of DAY101, and three of five patients achieved initial response within the first 100 days.

⁴ Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

Figure 1: Tumor Growth Kinetics and Duration of Response in Pediatric Patients Treated with DAY101 Once Weekly (Study PNOC014)



Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; RANO = Response Assessment in Neuro-Oncology; SD = stable disease.

Note: Spider plot representing growth rates prior to, and from, screening, based upon RANO criteria.

*Reviewer Note: PNOC014- (b) (6) (shown in yellow) represents the patient without a confirmed RAF alteration (patient has an optic pathway glioma in the setting of an NF1 mutation).

b. Include any additional relevant information. Consider the following in your response:

- Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.
- Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.
- Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.

Supplemental Data

The BTDR also contains supportive data from two pediatric patients who were treated with DAY101 through expanded access and achieved a best response of stable disease. The first patient is a 14-year old girl with a 12-year history of multiply recurrent diffuse astrocytoma with BRAF alteration who was heavily pre-treated (9 lines of prior therapy including multiple chemotherapy regimens, MEK inhibitor selumetinib and Type I BRAF inhibitor dabrafenib). She initiated treatment with DAY101 in (b) (6) and received 54 cycles of therapy. Due to disease stabilization, she was permitted to enter a "drug holiday" in (b) (6) and is reported to have no evidence of disease progression to date.

A second patient with a 6-year history of multiply relapsed pilocytic astrocytoma harboring a KIAA1549:BRAF wild-type fusion also received DAY101 on a compassionate use basis. Prior therapy for this patient included

chemotherapy and targeted therapy including the MEK inhibitor trametinib. The patient remains on DAY101 to date and is reported to have stable disease following a year of therapy.

Safety Data

All nine patients with pLGG experienced one or more treatment-emergent adverse events (TEAEs). The majority of these events were Grade 1 or Grade 2. No dose limiting toxicities have been reported. The most frequent TEAEs were acneiform rash, anemia, increased aspartate aminotransferase (AST), headache, hypermagnesemia, maculopapular rash, decreased neutrophil count, pruritis, vomiting, decreased white blood cell, achromotrichia, cheilitis, fatigue, anorexia, increased creatinine phosphokinase, dry skin, hyperkalemia, hypophosphatemia, nasal congestion, nevus, and pain in extremity. Additionally, no cutaneous lesions (e.g., keratoacanthoma and squamous cell carcinoma) have been reported.

The overall safety database of DAY101 consists of approximately 200 patients. The most frequently reported TEAEs observed in adult patients with advanced solid tumors treated with single-agent DAY101 on a once-weekly dose schedule (n=39) included fatigue, anemia, nausea, and headache. In addition to these TEAEs, patients who were dosed more frequently also had maculopapular rash, arthralgia, constipation and dyspnea.

12. Division's recommendation and rationale (pre-MPC review):

☒ GRANT:

Provide brief summary of rationale for granting:

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

The data provided in this BTDR indicate that pediatric patients with previously treated, actively progressive LGGs harboring an activating RAF alteration (most frequently the KIAA1549:BRAF fusion) have demonstrated deep, durable responses to DAY101. Progressive pLGGs represent a serious condition with high unmet medical need. Despite being slow-growing, these chronic tumors are associated with significant morbidity and long-term complications secondary to the disease and its treatment. There are no approved therapies for pLGG. Current management with surgery, chemotherapy and radiation has shown limited success in patients with advanced disease and are associated with significant acute and late toxicities.

In the context of a plausible biologic rationale and relevant mechanism of action (Type II RAF inhibition), the observed ORR of 56% (5 of 9 patients) and DOR of greater than one year in patients with progressive pLGGs provide strong preliminary evidence that DAY101 may demonstrate substantial improvement on a clinically significant endpoint over available therapy. Additionally, as patients are able to remain on treatment for long periods, DAY101 appears to have a manageable safety profile (without the paradoxical hyperactive ERK signaling observed with other MAPK-targeting agents). Although the small sample size (n=9) supporting this application confers a degree of uncertainty regarding the observed point estimate of ORR, DO2 considers the totality of evidence strongly supportive of BTDR and considers this sample size acceptable for the purposes of making a BTDR determination based upon the rarity of progressive pLGG harboring an activating RAF alteration. Therefore, DO2 recommends granting BTDR for the treatment of pediatric patients with low-grade glioma harboring an activating RAF alteration that has progressed after one or more prior systemic therapies.

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

13. Division's next steps and sponsor's plan for future development:

- a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The sponsor has interacted with FDA in an EOP1 meeting to discuss a planned multicenter, single arm study of DAY101 in pediatric patients with relapsed, refractory or progressive LGGs harboring an activating BRAF fusion or mutation. Day One is engaging with both FDA and EMA to formulate a global registration strategy in pLGG and has received feedback from both agencies on clinical trial design. FDA provided input on the DAY101 development program during a Pediatric Cluster Call and participated in a Common Commentary with EMA. FDA has also provided the Sponsor with advice on development of a companion diagnostic and recommended a dedicated meeting with CDRH. DO2 will continue to interact with Day One as needed as development progresses.

14. List references, if any:

1. Diwanji TP, Engelman A, Snider JW, et al. Epidemiology, diagnosis, and optimal management of glioma in adolescents and young adults. *Adolesc Health Med Ther.* 2017;8:99-113.
2. Sievert AJ, Fisher MJ. Pediatric low-grade gliomas. *J Child Neurol.* 2009;24(11):1397-1408.
3. Ryall, S., Tabori, U. & Hawkins, C. A comprehensive review of paediatric low-grade diffuse glioma: pathology, molecular genetics and treatment. *Brain Tumor Pathol.* 2017;34:51–61,
4. Zhang J, Wu G, Miller CP, et al. Whole-genome sequencing identifies genetic alterations in pediatric low-grade gliomas. *Nat Genet.* 2013;45(6):602–612.
5. Chen YH, Gutmann DH. The molecular and cell biology of pediatric low-grade gliomas. *Oncogene.* 2014;33(16):2019-26.
6. Jones DT, Kocialkowski S, Liu L, et al. Tandem duplication producing a novel oncogenic BRAF fusion gene defines the majority of pilocytic astrocytomas. *Cancer Res* 2008;68(21):8673-7.
7. de Blank P, Bandopadhyay P, Haas-Kogan D, et al. Management of pediatric low-grade glioma. *Curr Opin Pediatr.* 2019;31(1):21-27.
8. Nicolaides T, Nazemi KJ, Crawford J, et al. Phase I study of vemurafenib in children with recurrent or progressive BRAFV600E mutant brain tumors: Pacific Pediatric Neuro-Oncology Consortium study (PNOC-002). *Oncotarget.* 2020;11(21):1942.
9. Packer RJ, Pfister S, Bouffet E, et al. Pediatric low-grade gliomas: implications of the biologic era. *Neuro Oncol.* 2017;19(6):750-761.
10. Tihan T, Ersen A, Qaddoumi I, et al. Pathologic characteristics of pediatric intracranial pilocytic astrocytomas and their impact on outcome in 3 countries: a multi-institutional study. *Am J Surg Pathol.* 2012;36(1):43-55.
11. Dirven CM, Mooij JJ, Molenaar WM. Cerebellar pilocytic astrocytoma: a treatment protocol based upon analysis of 73 cases and a review of the literature. *Childs Nerv Syst.* 1997; 13:17–23.
12. Raabe E, Kieran MW, Cohen KJ. New strategies in pediatric gliomas: molecular advances in pediatric low-grade gliomas as a model. *Clin Cancer Res.* 2013. 2013; 19(17):4553-4558.
13. Packer RJ, Lange B, Ater J, et al. Carboplatin and vincristine for recurrent and newly diagnosed low-grade gliomas of childhood. *J Clin Oncol.* 1993;11(5):850-856.
14. Bouffet E, Jakacki R, Goldman S, et al. Phase II study of weekly vinblastine in recurrent or refractory pediatric low-grade glioma. *J Clin Oncol.* 2012;30(12):1358-1363.

15. Behling F, Schittenhelm J. Oncogenic BRAF Alterations and Their Role in Brain Tumors. *Cancers (Basel)*. 2019;11(6):794.
16. Schreck KC, Grossman SA, Pratilas CA. BRAF Mutations and the Utility of RAF and MEK Inhibitors in Primary Brain Tumors. *Cancers (Basel)*. 2019;11(9):1262.
17. Karajannis MA, Legault G, Fisher MJ, et al. Phase II study of sorafenib in children with recurrent or progressive low-grade astrocytomas. *Neuro Oncol*. 2014;16(10):1408-1416.
18. Sun Y, Alberta JA, Pilarz C, et al. A brain-penetrant RAF dimer antagonist for the noncanonical BRAF oncoprotein of pediatric low-grade astrocytomas. *Neuro Oncol*. 2017;19(6):774- 85.
19. Fangusaro J, Witt O, Driever PH, et al. Response assessment in paediatric low-grade glioma: recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group. *Lancet Oncol*. 2020;21(6):e305-e316.
20. Chourmouzi D, Papadopoulou E, Konstantinidis M, et al. Manifestations of pilocytic astrocytoma: a pictorial review. *Insights Imaging*. 2014;5(3):387-402.

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☐
 Deny Breakthrough Therapy Designation ☐

Reviewer Signature: { See appended electronic signature page}
 Team Leader Signature: { See appended electronic signature page}
 Division Director Signature: { See appended electronic signature page}

Revised 3/18/19/M. Raggio

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SONIA SINGH
09/30/2020 08:24:08 AM

AMY K BARONE
10/02/2020 07:26:10 AM

MARTHA B DONOGHUE
10/02/2020 07:31:57 AM