CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217700Orig1s000
218033Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	New Drug Application
Application Number(s)	217700, 218033
Priority or Standard	Priority
Submit Date(s)	08/31/2023
Received Date(s)	08/31/2023
PDUFA Goal Date	04/30/2024
Division/Office	DO2/OOD/OND
Review Completion Date	See electronic stamp date
Established Name	Tovorafenib
(Proposed) Trade Name	OJEMDA
Pharmacologic Class	Kinase inhibitor
Code name	DAY101
Applicant	Day One Biopharmaceuticals, Inc.
Formulation(s)	Tablet (NDA 217700), for oral suspension (NDA 218033)
Dosing Regimen	380 mg/m^2 orally once weekly (maximum recommended dosage is 600 mg orally once weekly) with or without food
Applicant Proposed Indication(s)/Population(s)	Treatment of pediatric patients 6 months of age and older with relapsed or refractory pediatric low-grade glioma (LGG) harboring a BRAF fusion or rearrangement, or BRAF V600 mutation.
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of patients 6 months of age and older with relapsed or refractory pediatric low-grade glioma (LGG) harboring a BRAF fusion or rearrangement, or BRAF V600 mutation.

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
OOD=Office of Oncologic Diseases
OCP=Office of Combination Products
OB=Office of Biostatistics
DHOT=Division of Hematology Oncology Toxicology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DMPP=Division of Medical Policy Programs
DRISK=Division of Risk Management
DPV=Division of Pharmacovigilance

Glossary

ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from time 0 to 24 hours
AUC_{0-48}	area under the concentration-time curve from time 0 to 48 hours
AUC_{0-168}	area under the concentration-time curve from time 0 to 168 hours
AUC_{0-inf}	area under the concentration-time curve from time 0 to time infinity
AUC_{0-last}	area under the concentration-time curve from time 0 to the last measured concentration
AUC_{ss}	area under the concentration-time curve at steady state
BCRP	breast cancer resistance protein
BOR	best overall response
BRAF	v-raf murine sarcoma viral oncogene homolog B
BSA	body surface area
CI	confidence interval
CL/F	apparent clearance
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CNS	central nervous system
CPK	creatine phosphokinase
CR	complete response
CRAF	v-raf murine sarcoma viral oncogene homolog C
CT	computed tomography
CYP	cytochrome P450
DLT	dose-limiting toxicity
DOR	duration of response
DSMB	Data Safety Monitoring Board
eCRF	electronic case report form
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOT	end of treatment
E-R	exposure-response
FDA	Food and Drug Administration
GD	gestational day

GLP	Good Laboratory Practice
hERG	human ether-à-go-go related gene
HGG	high-grade glioma
HLGT	high level group term
IC_{50}	concentration required for 50% inhibition
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IRC	Independent Radiology Review Committee
IV	intravenous
LGG	low-grade glioma
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated protein kinase kinase
MR	minor response
MRI	magnetic resonance imaging
MTD	maximum-tolerated dose
NCI	National Cancer Institute
NDA	New Drug Application
NE	not evaluable
NOAEL	no observed adverse effect level
NRAS	neuroblastoma ras viral oncogene homolog
ORR	overall response rate
OS	overall survival
pcVPC	prediction-corrected visual predictive check
pERK	phosphorylated-ERK
PfOS	powder for oral suspension
PfR	powder for reconstitution
PFS	progression-free survival
PK	pharmacokinetic(s)
PK-PD	pharmacokinetic-pharmacodynamic
PO	*per os*, orally
PR	partial response
Q2D	every other day
QD	once daily
QW	once weekly
RAF	rapidly accelerated fibrosarcoma
RANO	Response Assessment in Neuro-Oncology
RAPNO	Response Assessment in Pediatric Neuro-Oncology
RAS	rat sarcoma virus
RECIST	Response Evaluation Criteria in Solid Tumours

RP2D	recommended Phase 2 dose
QW	once weekly
SAE	serious adverse event
SD	standard deviation
SF	shortening fraction
SMQ	Standardised MedDRA Query
SOC	system organ class
SPPD	sum of product of perpendicular diameters
$t_{1/2}$	half life
TEAE	treatment-emergent adverse event
TFST	time to first subsequent anti-cancer therapy
T_{max}	time to maximum plasma concentration
ULN	upper limit of normal
US	United States
Vc/F	apparent central volume of distribution
WHO	World Health Organization
WT	wild type

1. Executive Summary

1.1. Product Introduction

Tovorafenib is an orally administered, CNS-penetrant Type II RAF kinase inhibitor of mutant BRAF V600E, wild-type BRAF, and wild type-CRAF kinases. Tovorafenib is not currently FDA approved for any indication.

The Applicant is seeking FDA approval of tovorafenib for the treatment of pediatric patients 6 months of age and older with relapsed or refractory pediatric low-grade glioma (LGG) harboring a BRAF fusion or rearrangement, or BRAF V600 mutation. The Applicant's proposed dosage regimen is (b) (4) mg/m^2 orally once weekly with a maximum recommended dosage of 600 mg once weekly.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The data submitted by the Applicant provide substantial evidence of effectiveness to support the accelerated approval of tovorafenib as described in 21 CFR part 314.510 Subpart H for the treatment of patients 6 months of age and older with relapsed or refractory pediatric LGG harboring a BRAF fusion or rearrangement, or BRAF V600 mutation. The recommended dosage regimen for tovorafenib is 380 mg/m^2 orally once weekly with a maximum recommended dosage of 600 mg once weekly.

The recommendation for accelerated approval is based on the results of FIREFLY-1 (NCT04775485), a single-arm, open-label, multicenter clinical trial that included 76 patients 6 months to 25 years of age with relapsed or refractory LGG with an activating BRAF alteration. Eligible patients were required to receive at least one prior systemic therapy and have documented evidence of radiographic progression. Patients received tovorafenib as a single agent once weekly at the recommended Phase 2 dose (RP2D) of 420 mg/m^2 (not exceeding 600 mg) in 28-day cycles for up to 26 cycles or until radiographic progression, unacceptable toxicity, or loss of clinical benefit. The primary endpoint was overall response rate (ORR) according to blinded independent central review (BICR) as per the Response Assessment in Neuro-Oncology (RANO) criteria; a secondary endpoint was ORR according to BICR as per Response Assessment in Pediatric Neuro-oncology (RAPNO) LGG (RAPNO-LGG) criteria. In alignment with current scientific consensus on the measurement of these tumors, FDA considered that the RAPNO-LGG criteria, which assess response based on T2 flair signaling rather than contrast enhancement in high grade glioma (HGG)-based response criteria, were most appropriate as the primary means to assess responses in pediatric LGG, which are largely non-contrast enhancing.

Efficacy was evaluated in 76 patients with pediatric LGG harboring an activating BRAF alteration, including KIAA1549:BRAF fusions and BRAF V600E mutations, and with measurable

disease at baseline enrolled in Arm 1 (a non-randomized cohort). Treatment with tovorafenib resulted in an overall response rate of 51% (95% CI: 40, 63), including complete, partial, and minor responses, with a median duration of response (DOR) of 13.8 months (95% CI: 11.3, not estimable [NE]), according to BICR as per RAPNO criteria; response rates were similar across subgroups defined by BRAF alteration type.

The response rate and duration of response observed with tovorafenib, coupled with the once-weekly dosage schedule and oral route of administration, provide a meaningful advantage over available therapy. Available therapies include chemotherapy (e.g., carboplatin in combination with vincristine or vinblastine as a single agent), which requires intravenous infusion, while dabrafenib in combination with trametinib, approved for patients with BRAF V600E mutations, requires administration of two oral agents once or two times daily. In the pediatric population, the dosage schedule and route of administration for tovorafenib may be beneficial in limiting disruptions to school attendance and decreasing caregiver burden. Furthermore, the safety profile of tovorafenib may offer an advantage over the toxicities associated with commonly used chemotherapy agents for patients with pediatric LGG (e.g., severe myelosuppression, neurotoxicity).

The review team considers the ORR, which is large in magnitude, and the durability of responses observed in FIREFLY-1 to be clinically meaningful and supportive of accelerated approval in patients with relapsed or refractory pediatric LGG with the indicated BRAF alterations. Importantly, tovorafenib is the first targeted agent to be approved for the treatment of patients with pediatric LGG harboring BRAF fusions or rearrangements, including the KIAA1549:BRAF fusion which is the most common molecular alteration in pediatric LGG.

The results of FIREFLY-1, an adequate and well-controlled trial, with the provided confirmatory evidence, meet the statutory standard for substantial evidence. Confirmatory evidence includes additional clinical data from PNOC014, an investigator-sponsored dose-finding study of tovorafenib in patients 1 to 25 years of age with recurrent or progressive non-hematologic malignancies, including CNS tumors, that harbor a genomic mutation resulting in the activation of the RAS/RAF/MEK/ERK pathway, and preclinical studies demonstrating strong mechanistic data. The application is also supported by evidence of effectiveness of other drugs from a related pharmacologic class for a related indication.

The submitted evidence meets the statutory evidentiary standard for accelerated approval through demonstration of an effect on an endpoint reasonably likely to predict clinical benefit. Treatment with tovorafenib resulted in a large, clinically meaningful, and durable overall response rate in patients with relapsed or refractory pediatric LGG harboring a BRAF fusion or rearrangement, or BRAF V600 mutation.

Therefore, based on a favorable benefit:risk assessment, the review team recommends accelerated approval of tovorafenib for the treatment of patients with relapsed or refractory pediatric LGG harboring a BRAF fusion or rearrangement, or BRAF V600 mutation.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Pediatric low-grade gliomas (LGGs) comprise 30% of all childhood brain tumors with approximately 1,000 to 1,600 new cases occurring annually in the United States (Diwanji et al., 2017; de Blank et al., 2019). These tumors encompass various histologies and are characterized by activation of the MAP kinase pathway as highlighted in the 2021 World Health Organization Classification of Tumors of the Central Nervous System (Louis et al., 2021). Most tumors harbor a single identifiable driver alteration, with BRAF alterations occurring in up to 70% of pediatric LGG (Ryall et al., 2020; Zhang et al., 2013). The canonical KIAA1549:BRAF fusion is most common, identified in approximately 35% of tumors, and the BRAF V600E mutation is found in approximately 15% of tumors (Ryall et al., 2020). Although these tumors are slow-growing with a 10-year overall survival (OS) rate that exceeds 90%, they can display clinically heterogeneous behavior with some patients experiencing multiple progression events that are associated with morbidity and potentially mortality (Sievert, 2009). Pediatric LGGs are traditionally treated with surgery, chemotherapy, and radiation therapy. In the relapsed or refractory setting, regimens include carboplatin and vincristine and single agent vinblastine which result in an overall response rate (ORR) of approximately 35 to 52%, including minor responses (Packer et al., 1993; Bouffet et al., 2012). In a cohort of 36 patients with relapsed/refractory LGG (n=34) and HGG with BRAF V600E mutations treated with dabrafenib and trametinib, an ORR of 25% (95% CI: 12, 42) according to RANO-LGG criteria was observed, with 78% of patients demonstrating a DOR of at least 6 months (Tafinlar United States Prescribing Information [USPI]). Notably, there are no approved treatments for patients with BRAF fusions including the KIAA1549:BRAF fusion that is the most frequent oncogenic driver in pediatric LGG.

Tovorafenib is an oral, CNS-penetrant Type II RAF inhibitor of mutant BRAF V600E, wild-type BRAF, and wild type-CRAF kinases. The effectiveness of tovorafenib for the treatment of patients 6 months of age and older with relapsed or refractory pediatric LGG harboring a BRAF fusion or rearrangement, or BRAF V600 mutation was established based on data from 76 patients in Arm 1 of FIREFLY-1, a single-arm, open-label, multicenter trial that included patients 6 months to 25 years of age with relapsed or refractory LGG with an activating BRAF alteration. Eligible patients were required to receive at least one prior systemic therapy and have documented evidence of radiographic progression. Patients received tovorafenib as a single agent once weekly at the recommended Phase 2 dose (RP2D) of 420 mg/m^2 (not exceeding 600 mg) orally once weekly. Patients were treated in 28-day cycles for up to 26 cycles or until radiographic progression, unacceptable toxicity, or loss of clinical benefit. The primary endpoint was ORR according to blinded independent central review (BICR) as per the Response Assessment in Neuro-Oncology (RANO Criteria) with a secondary endpoint of ORR according to BICR as per Response Assessment in Pediatric Neuro-oncology (RAPNO) LGG (RAPNO-LGG) criteria (Wen et al., 2017; Fangusaro et al., 2020). In alignment with current scientific consensus on the measurement of these tumors, the FDA considered RAPNO-LGG criteria, which assess response based on T2 flair signaling rather than contrast

enhancement in HGG-based response criteria, to be the most appropriate as the primary means to assess responses in LGG, which are largely non-contrast enhancing.

Treatment with tovorafenib resulted in an ORR of 51% (95% CI: 40, 63), inclusive of complete, partial, and minor responses with a median duration of response (DOR) of 13.8 months (11.3, not estimable [NE]), according to BICR as per RAPNO-LGG criteria; response rates were similar across subgroup analyses based on BRAF alteration type (KIAA1549:BRAF fusion vs. BRAF V600E mutation status vs. "other" BRAF alterations including BRAF rearrangement and duplication). The observed response rate was also similar among patients regardless of the number of prior lines of systemic therapy and prior exposure to a RAF and/or MEK inhibitor. The FDA has previously considered only partial and complete responses in its calculation of ORR given uncertainties regarding the clinical meaningfulness of these responses. However, in consideration of current scientific consensus regarding appropriate measurement and response criteria for pediatric LGG, and of data provided in the application supporting the clinical meaningfulness of minor responses in pediatric LGG, the FDA determined that inclusion of minor responses in the response rate calculation to be appropriate.

The safety of tovorafenib was assessed primarily in the safety population of 137 patients ranging from 11 months to 24 years of age with relapsed or refractory pediatric LGG harboring the protocol-specified RAF alterations who received tovorafenib once weekly at the recommended Phase 2 dose (RP2D) of 420 mg/m^2 (maximum dose 600 mg) with actual dose administered ranging from 0.76 to 1.25x the approved dosage (range: 290 to 476 mg/m^2). Among these 137 patients, the median duration of exposure was approximately 12 months (range: 22 to 722 days) with 86% receiving tovorafenib for at least 6 months and 49% receiving tovorafenib for at least 12 months.

The approved dose of tovorafenib (380 mg/m^2 orally once weekly) is supported by submitted data demonstrating a lack of clinically significant differences in exposure-response relationships (E-R) for ORR observed over the actual dose range administered in Arm 1 of FIREFLY-1 and an improved safety profile based on positive trends of E-R relationships for Grade 2 and higher adverse reactions. Finally, analyses suggest that a modest dose reduction may mitigate the impact of tovorafenib on growth, resulting in an improved benefit-risk profile with the dose of 380 mg/m^2 orally once daily compared to 420 mg/m^2 orally once daily.

A pooled safety population including all patients from FIREFLY-1 (n=140) and adult patients from Study C28001 (n=32), a study investigating tovorafenib in patients with advanced solid tumors including melanoma, comprised an overall safety database of 172 patients who received tovorafenib at the RP2D of 420 mg/m^2 orally once weekly. The warnings and precautions in the USPI for tovorafenib are based on the pooled safety population and include hemorrhage, skin toxicity/photosensitivity, hepatotoxicity, effect on growth, embryo-fetal toxicity, and potential for increased growth of NF1-associated tumors. Intracranial hemorrhage was a clinically relevant safety signal that occurred at a rate of 11% in

the target population and included a Grade 5 treatment-emergent adverse reaction. In general, the safety profile is similar to that observed with other in-class products.

The most common adverse reactions in Arm 1 of FIREFLY-1 (≥ 30%) were rash, hair color changes, fatigue, viral infection, vomiting, headache, hemorrhage, pyrexia, dry skin, constipation, nausea, dermatitis acneiform, and upper respiratory tract infection. The most common Grade 3 or 4 laboratory abnormalities (≥2%) were decreased phosphate, decreased hemoglobin, increased creatinine phosphokinase, increased alanine aminotransferase, decreased albumin, decreased lymphocytes, decreased leukocytes, increased aspartate aminotransferase, decreased potassium, and decreased sodium.

Although safety data was not available for patients less than 11 months of age, the FDA determined that the inclusion of patients 6 months to 1 year of age in the indication statement was appropriate based on the totality of the data, including the ability to extrapolate pharmacokinetic data from patients 1 year of age to 6 months of age, in consideration of the maturation of relevant drug metabolizing enzymes and the extent of hepatic and renal clearance of the drug. Given that there is a high unmet medical need in this population; in the context of a favorable benefit-risk assessment, inclusion of these patients in the indication statement is warranted.

The risks of tovorafenib are considered acceptable in the indicated population due to the serious and potentially life-threatening nature of relapsed or refractory pediatric LGG. The safe use of tovorafenib can be adequately implemented in the post-market setting through instructions for surveillance and actions to mitigate risk as described in product labeling. No additional risk management strategies are recommended.

In conclusion, the submitted data meets the statutory standard for demonstration of substantial evidence of effectiveness, and tovorafenib has a favorable benefit-risk profile for the treatment of patients 6 months of age and older with relapsed or refractory pediatric LGG harboring BRAF fusion or rearrangement, or BRAF V600 mutation. The large in magnitude and durable response rate observed with tovorafenib is clinically meaningful and similar to other therapies available in the relapsed setting, and the route and frequency of administration offer a meaningful advantage over available therapy. Tovorafenib is the first targeted agent to be approved for the treatment of patients with pediatric LGG harboring KIAA1549:BRAF fusions, the most frequently occurring genomic subtype of pediatric LGG. Based on the favorable benefit-risk assessment for this population with a serious, life-threatening disease, accelerated approval is recommended for the following indication:

OJEMDA is a kinase inhibitor indicated for the treatment of patients 6 months of age and older with relapsed or refractory pediatric LGG harboring a BRAF fusion or rearrangement, or BRAF V600 mutation.

The recommended dosage regimen for tovorafenib is 380 mg/m^2 orally once weekly with a maximum recommended dosage of 600 mg once weekly. As a condition of accelerated approval, a post-marketing requirement will be issued to obtain the additional data necessary to verify the clinical benefit of tovorafenib. To fulfill the PMR, the Applicant plans to submit data, including response rate, duration of response and progression-free survival results, from the FIREFLY-2 trial, an international, open-label, randomized, controlled clinical study in the front-line setting comparing tovorafenib to physician's choice of chemotherapy in patients with pediatric LGG with RAF fusions, rearrangements or V600 mutations who require systemic therapy. At the time of the anticipated accelerated approval, FIREFLY-2, which initiated enrollment in 2023, is ongoing with reasonable progress in enrollment. A post-marketing commitment will be issued for the Applicant to provide adequate analytical and clinical validation results from clinical trial data to support labeling of a companion diagnostic test to detect BRAF alterations to identify patients with pediatric LGG who may benefit from tovorafenib.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pediatric LGGs comprise 30% of all childhood brain tumors with an annual incidence of 1,000 to 1,600 in the US (Diwanji et al., 2017). These tumors encompass various histologies with pilocytic astrocytoma representing the most common subtype and are characterized by genomic alterations that activate the MAP kinase pathway as highlighted in the 2021 World Health Organization Classification of Tumors of the Central Nervous System (Louis et al., 2021). • Most tumors harbor a single identifiable driver alteration with BRAF alterations occurring in up to 70% of pediatric LGG (Ryall et al., 2020). BRAF alterations are typically single structural variants or rearrangements that result in the expression of a fusion variant (de Blank et al., 2019). Rearrangements affecting the genes KIAA1549 and BRAF are the most frequent somatic driver alterations, and the canonical KIAA1549:BRAF fusion is the most commonly identified, present in approximately 35% of tumors (Ryall et al., 2020). Other BRAF alterations include the BRAF	Pediatric LGG is a serious and potentially life-threatening disease with limited treatment options available for patients with BRAF alterations including the KIAA1549:BRAF fusion that is the leading genomic alteration in these tumors. Additionally, patients with relapsed or refractory pediatric LGG are at risk for significant morbidity including neurocognitive impairment, vision/hearing loss, endocrinopathies and other complications which may result from tumor location or from traditionally administered treatments.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	V600E mutation which is found in approximately 15% of tumors (Lassaletta et al., 2017). • Unlike adult LGG, the majority of pediatric LGG are indolent and do not undergo malignant transformation, resulting in a 10-year overall survival rate exceeding 90% (Sievert et al., 2009); however, clinical behavior of tumors can vary significantly. In addition, patients with LGG are at risk for significant morbidity including neurocognitive impairment, vision/hearing loss, endocrinopathies and other complications which may result from tumor location or from traditionally administered treatments. • The most favorable predictor of survival in patients with pediatric LGG is complete resection, whereas poorer outcomes are noted in patients with deep-seated or highly infiltrative tumors, such as those in the optic pathway/hypothalamus for which surgery is not feasible. The latter can be difficult to treat and more commonly exhibits disease progression or recurrence. The 5-year progression-free survival (PFS) rate for patients with pediatric LGG is approximately 50% (de Blank et al., 2019); patients may experience multiple progression events associated with substantial morbidity that may ultimately be fatal. • Pediatric LGGs with BRAF V600E mutation tend to have a poorer response to chemotherapy and are observed to have shorter PFS and OS (Bouffet et al., 2023). In contrast, the KIAA1549:BRAF fusion predicts better clinical outcomes, as this alteration is most commonly associated with pilocytic astrocytomas and these tumors tend to be more surgically accessible (e.g., located in the cerebellum), making them more amenable to complete resection (Ryall et al., 2020). • In summary, there is a wide spectrum of disease severity in patients with pediatric LGG who are vulnerable to multiple progression	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	events and a host of complications (e.g., functional, neurologic, endocrine) from either worsening of their underlying disease or morbidity from treatments administered in the relapse setting (e.g., surgical re-resection, radiation therapy).	
Current Treatment Options	• The mainstay of treatment of pediatric LGG is complete surgical resection when possible. Although there is no clear consensus for progressive or recurrent tumors without a targetable genomic alteration, chemotherapy is generally administered as front-line adjuvant treatment and is used to delay or obviate the need for radiotherapy. The most commonly used agents in this setting include the combination of carboplatin and vincristine which result in an overall response rate (ORR) of approximately 52% (Packer et al., 1993), and single-agent vinblastine which has an ORR of approximately 35% (Bouffet et al., 2012). The response criteria used in these studies relied upon contrast-enhanced imaging, and the cited response rates incorporate minor responses. Further, the response rates include patients irrespective of BRAF alteration status; response rates to chemotherapy by specific BRAF alteration type are not well characterized. • Second-line radiation treatment may be used but is associated with more frequent and significant neurocognitive, endocrine, and other long-term toxicities that can be particularly debilitating in younger children. • The targeted therapies dabrafenib, a BRAF inhibitor, and trametinib, a MEK inhibitor, are approved in combination for the treatment of pediatric patients 1 year of age and older with LGG harboring a BRAF V600E mutation who require systemic therapy. The approval of this regimen was based on the results of a randomized trial evaluating dabrafenib and trametinib compared to carboplatin and vincristine, which demonstrated improvement in ORR and PFS (Tafinlar USPI). In the dabrafenib and trametinib arm, an	Pediatric LGG is typically treated with surgical resection, chemotherapy and/or radiation therapy. Complete resection is attempted when feasible. Although approved treatment options are available for patients with BRAF V600E mutations, there are no FDA-approved targeted treatments for pediatric LGG with wild-type BRAF fusions, representing an important subset of patients with high unmet medical need. Safe and effective treatments for this highly morbid disease are needed.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	ORR of 47% (95% CI: 25, 59) as assessed by RANO-LGG criteria (defined as CR+PR) was observed, with a median DOR of 24 months (95% CI: 15, NE) (Bouffet et al., 2023). • In a pediatric cohort from Study CTMT212X2101, which included 34 patients with relapsed or refractory pediatric LGG treated with dabrafenib and trametinib, a response rate of 25% (95% CI: 12, 42) as assessed by RANO-LGG criteria (CR + PR), was observed, with DOR of at least 12 months in 56% of responders (Tafinlar USPI). • There are no approved targeted therapies for the treatment of pediatric LGG with BRAF fusions, representing a patient population with high unmet medical need. • Approved Type I BRAF inhibitors including dabrafenib do not inhibit signaling from the KIAA1549:BRAF fusion, the most common oncogenic driver in these tumors and which functions as dimers (Behling, 2019; Schreck, 2019).	
Benefit	• The primary efficacy data supporting these applications are derived from 76 patients enrolled in FIREFLY-1, a single-arm, open-label, multicenter trial conducted globally in patients 6 months to 25 years of age with relapsed or refractory LGG with an activating BRAF alteration or RAF fusion, or locally advanced or metastatic solid tumor with an activating RAF fusion. • The primary endpoint was overall response rate according to BICR as per Response Evaluation in Neuro-oncology (RANO) criteria, which are used to evaluate response in high-grade glioma based on contrast enhancement, with ORR assessed by the Response Assessment in Pediatric Neuro-oncology (RAPNO) LGG (RAPNO-LGG) criteria per BICR as a secondary endpoint.	Substantial evidence of effectiveness supporting accelerated approval was demonstrated for tovorafenib in the indicated patient population based on results of Arm 1 (n=76) of FIREFLY-1. The observed ORR, which is large in magnitude, and the durability of responses observed, are clinically meaningful for patients with relapsed or refractory pediatric LGG harboring BRAF alterations. Responses were observed in patients with KIAA1549:BRAF fusion, BRAF V600E mutation, and patients with BRAF rearrangements and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The results from Arm 1, a non-randomized cohort of 76 patients with BRAF-altered pediatric LGG with measurable disease at baseline that served as the key efficacy population for this trial, demonstrated an ORR of 51% (95%: 40, 63), inclusive of minor, partial, and complete responses with a median DOR of 13.8 months (95% CI: 11.3, NE) according to BICR as per RAPNO-LGG criteria. • The response rate was generally similar in patients regardless of BRAF alteration (52% among patients with KIAA1549:BRAF fusion, 50% among patients with BRAF V600E mutation, and 50% among patients with BRAF rearrangements or duplications, according to BICR as per RAPNO-LGG criteria), prior use of BRAF and/or MEK inhibitor, and number of prior lines of systemic therapy. • All patients in the efficacy set with BRAF V600 mutations (n=12) harbored BRAF V600E mutations; however, the proposed indication for tovorafenib includes patients with BRAF V600 mutations, encompassing the rarer mutation types V600K and V600D. Preclinical data was submitted to support the activity of tovorafenib against BRAF V600D mutations in addition to BRAF V600E mutations. • Review of patient experience data that was investigator-reported and compiled in patient efficacy narratives indicated preliminary signals of improvement in tumor associated signs or symptoms in some patients treated with tovorafenib who demonstrated minor responses.	duplications, as well patients who received multiple lines of prior therapy including BRAF and/or MEK inhibitor. Preclinical data, tovorafenib's established mechanism of action and review of the scientific literature describing relevant BRAF V600 mutations in pLGG supported inclusion of rare BRAF V600 mutation subtypes in the indication statement. The FDA determined that it was most appropriate to rely upon response as assessed by the RAPNO-LGG criteria as the primary efficacy outcome measure given the non-enhancing nature of pediatric LGG. The FDA has historically only considered partial and complete responses in the calculation of ORR given uncertainties regarding the clinical meaningfulness of minor responses; however, consistent with current scientific consensus and based upon review of data provided in the application supporting the clinical meaningfulness of minor responses in pediatric LGG, the FDA determined that inclusion of MRs in calculation of the response rate in this patient population is appropriate. Confirmation of clinical benefit will be

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		obtained in a post-marketing trial. A post-marketing requirement to obtain the information needed to verify the clinical benefit of tovorafenib in patients with pediatric LGG harboring RAF fusion or rearrangement or BRAF V600 mutation will be issued to obtain additional data to further characterize ORR, DOR and to assess PFS observed with tovorafenib treatment in a randomized trial. At the time of the anticipated accelerated approval, FIREFLY-2, which initiated enrollment in 2023, is ongoing with reasonable progress in enrollment (refer to Section 3.1).
Risk and Risk Management	• The primary safety population for these applications consisted of the 137 patients enrolled to Arms 1 and 2 of FIREFLY-1 with relapsed or refractory RAF-altered pediatric LGG. Additionally, a pooled safety population including all patients from FIREFLY-1 (n=140) and adult patients from Study C28001 (n=32), a study investigating tovorafenib in patients with advanced solid tumors including melanoma, comprised an overall safety database of 172 patients who received tovorafenib at the recommended Phase 2 dose of 420 mg/m^2 orally once weekly. • The warnings and precautions for the USPI for tovorafenib include hemorrhage, skin toxicity/photosensitivity, hepatotoxicity, effect on growth,	The treatment-emergent adverse reactions observed with tovorafenib treatment in FIREFLY-1 and the pooled safety population were similar to those observed with other in-class products. While tovorafenib can cause significant toxicities, these toxicities are generally acceptable in the context of a serious disease and are adequately addressed by information in the Warnings and Precautions section and the dose modification recommendations in product labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	embryo-fetal toxicity and potential for increased growth of NF1-associated tumors. Intracranial hemorrhage was a clinically relevant adverse reaction that occurred at a rate of 11% in the target population and included a Grade 5 treatment-emergent adverse reaction. • In the pediatric LGG safety population (n=137), serious adverse reactions occurred in 45% of patients including viral infection (9%), pneumonia (4%) and sepsis (4%). • The most common adverse reactions in Arm 1 of FIREFLY-1 (≥ 30%) were rash, hair color changes, fatigue, viral infection, vomiting, headache, hemorrhage, pyrexia, dry skin, constipation, nausea, dermatitis acneiform, and upper respiratory tract infection. • The most common Grade 3 or 4 laboratory abnormalities (≥2%) were decreased phosphate, decreased hemoglobin, increased creatinine phosphokinase, increased alanine aminotransferase, decreased albumin, decreased lymphocytes, decreased leukocytes, increased aspartate aminotransferase, decreased potassium, and decreased sodium.	Limited clinical data is available from patients less than 1 year of age (the youngest patient enrolled in FIREFLY-1 was 11 months old). The acceptability of including patients as young as 6 months of age in the proposed indication for tovorafenib is based upon the ability to extrapolate pharmacokinetic data from patients 1 year of age to 6 months of age, in consideration of the maturation of relevant drug metabolizing enzymes and the extent of hepatic and renal clearance of the drug. The FDA also considered that all patients initiating treatment with tovorafenib will be closely monitored, and infants in particular will be closely monitored for toxicities associated with the drug. Finally, the FDA considered that although few patients less than one year of age will be eligible for tovorafenib based on disease rarity and the need for prior treatment, there is a high unmet medical need in this population; in the context of a favorable benefit-risk assessment, inclusion of these patients in the indication statement is warranted. The clinical review team determined that it is in the best interest of U.S. patients to approve tovorafenib before a companion diagnostic

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		assay is available. Since an application for an in vitro companion diagnostic device was not submitted for contemporaneous approval with this NDA, the approved labeling will state that there is no FDA-approved test for selecting patients for treatment with tovorafenib. The Applicant has committed to a PMC to provide adequate analytical and clinical validation results from clinical trial data to support labeling of a companion diagnostic test to detect BRAF alterations for identifying patients with pediatric LGG who may benefit from tovorafenib. There were no significant safety concerns identified during NDA review requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS). Given the anticipated chronic use of tovorafenib, post-marketing requirements (PMRs) to address safety in the pediatric population will be issued to characterize the known serious risk of long-term adverse effects of the drug on growth and development, including growth plate abnormalities, as well as the potential for

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		gonadal toxicity given based on nonclinical studies. PMRs to address the impact of drug-drug interactions will also be issued.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

			Section where discussed, if applicable
X	The patient experience data that was submitted as part of the application, include:		
	□	Clinical outcome assessment (COA) data, such as	[e.g., Section 6.1 Study endpoints]
		□ Patient reported outcome (PRO)	
		□ Observer reported outcome (ObsRO)	
		□ Clinician reported outcome (ClinRO)	
		□ Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□	Patient-focused drug development or other stakeholder meeting summary reports	
	□	Observational survey studies designed to capture patient experience data	
	□	Natural history studies	
	□	Patient preference studies (e.g., submitted studies or scientific publications)	
	X	Other: (Please specify) Refer also to efficacy narratives discussed in Section 8.1.2.15.	
X	Patient experience data that was not submitted in the application but was considered in this review. See Section 8.1.2.14.		

X

Cross-Disciplinary Team Leader

2. Therapeutic Context

2.1. Analysis of Condition

Applicant's Position

Low-grade gliomas are the most common brain tumors in children (Ostrom 2019). They can occur anywhere in the central nervous system (CNS) and can comprise multiple different tumor histologies. Pediatric low-grade gliomas have a generally favorable prognosis with 10-year overall survival (OS) between 85% to 96% (Bandopadhayay 2014; Bergthold 2014, Krishnatry 2016) and, in contrast to adult low-grade gliomas, rarely undergo malignant transformation (Broniscer 2007). However, even histologically benign tumors can be associated with significant morbidities or be life-threatening because of their space-occupying effects within the cranium and effects of local infiltration (McKinney 2004). Many patients suffer profound tumor- and treatment-associated morbidities, including cognitive, physical, neurological, and endocrinological deficits, leading to disability and poorer socioeconomic outcomes (Ris 2019; Strother 2002). Pediatric low-grade gliomas typically become quiescent, or senescent, as patients enter the third decade of life, underscoring the need for treatments that control tumor growth while reducing long-lasting side effects that may compromise the quality of life and of survivorship.

Depending on the location of the tumor, children can present with signs of hydrocephalus (headache, nausea, and vomiting), ataxia (cerebellar glioma), vision loss (optic glioma), endocrine dysfunction (hypothalamic glioma), motor dysfunction (brainstem/deep midline glioma). Patients may commonly experience a constellation of these symptoms. Tumors usually do not present with metastatic disease.

BRAF alterations are the most common oncogenic drivers in pediatric low-grade glioma and occur in up to 70% of cases (Ryall 2020a; Ryall 2020b; Faulkner 2015). These genomic alterations result in increased BRAF kinase activity independent of extracellular stimuli or rat sarcoma virus (RAS)-guanosine triphosphate as well as constitutive signaling that drives cell proliferation and tumor growth (Davies 2002; Jones 2008).

The most common BRAF alteration found in pediatric low-grade glioma is the KIAA1549:BRAF fusion, found in approximately 65% of BRAF-altered pediatric low-grade glioma. Although rare, other oncogenic BRAF fusions have been identified in pediatric low-grade glioma, all of which consist of an N-terminal dimerization domain from another protein and the C-terminal kinase domain of BRAF. The canonical BRAF V600E mutation is found in approximately 30% of BRAF-altered pediatric low-grade glioma. (Ryall 2020b; Schreck 2019; Schreck 2023; Zwaig 2022).

The FDA's Assessment

The FDA agrees with the Applicant's summary and has the following additional comments. Pediatric LGG account for an estimated 30% of all childhood brain tumors with an annual incidence in the United States of 1000 to 1600 cases (de Blank et al., 2019). These tumors encompass different histologies such as astrocytic, oligodendroglial, and mixed glial-neuronal histology, with pilocytic astrocytoma as the most prevalent subtype. Pediatric LGGs are characterized by activation of the RAS/MAP kinase pathway with the majority exhibiting a single identifiable driver alteration. BRAF alterations occur in up to 70% of pediatric LGG and are typically single structural variants or rearrangements that result in the expression of a fusion variant (Ryall et al., 2020). The canonical KIAA1549:BRAF fusion represents the most frequent alteration, present in approximately 35% of tumors, and is significantly enriched in pilocytic astrocytomas (Penman et al., 2015). Other BRAF alterations include the BRAF V600E mutation which is found in 15% of tumors (Ryall et al., 2020).

Although considered benign by pathology with rare occurrence of malignant transformation, pediatric LGGs are clinically heterogeneous. Most tumors are slow-growing with a 10-year overall survival rate exceeding 90% (Sievert, 2009) with the longest survival rates observed in patients whose tumors can be completely resected. In contrast, patients with highly infiltrative tumors or those for which surgery is not possible due to location have a high rate of disease progression or recurrence. Overall, 5-year progression free survival (PFS) is approximately 50% (Packer et al., 2017), and patients may experience multiple progression events associated with significant morbidity and possibly death. Accordingly, there is a wide spectrum of disease severity in patients with pediatric LGG.

2.2. Analysis of Current Treatment Options

The preferred initial management of pediatric low-grade glioma is surgical resection, with complete resection being the most favorable predictor of patient outcome. For approximately one-half of patients, a single surgical approach is curative (Tihan 2012). However, complete resection is not always feasible, especially for highly infiltrative or deep-seated tumors which have a high risk of functional impact. Patients with tumors that cannot be completely resected or are unresectable experience disease progression or recurrence, with a 5-year progression-free survival (PFS) of approximately 50% (Wisoff 2011).

For patients whose disease recurs after surgery or for whom surgery was not an option, chemotherapy is usually offered as first-line systemic therapy. No approved chemotherapy regimens for pediatric low-grade glioma exist, but carboplatin and vincristine is a widely used combination (Ater 2012, Gnekow 2019) as well as single-agent vinblastine (Lassaletta 2016).

For patients with relapsed or recurrent pediatric low-grade glioma, chemotherapy may be attempted again, or a targeted therapy may be offered. The largest study of chemotherapy in the recurrent/refractory population was performed with single-agent vinblastine, which

resulted in an overall response rate (ORR; complete response [CR] + partial response [PR]) of 21% (11/51 patients), and a 5-year PFS of 42.3%±7.2% (Bouffet 2012).

The Type I BRAF inhibitors dabrafenib and encorafenib, and the mitogen-activated protein kinase (MEK) inhibitors selumetinib, trametinib, and binimetinib, have been studied in patients with pediatric low-grade gliomas, however none have been approved for use as single agents for the treatment of pediatric low-grade glioma. Type I BRAF inhibitors are effective only on BRAF V600 mutations and do not inhibit signaling from the KIAA1549:BRAF fusions representing the majority of RAF genomic alterations found in pediatric low-grade gliomas (Sun 2017). Importantly, as a class, Type I BRAF inhibitors also increase the risk of tumor growth due to paradoxical activation resulting from transactivation of RAF in the presence of activated RAS (Sievert 2013). Available MEK inhibitors lack adequate CNS penetrance and have a number of significant class-associated toxicities including ophthalmologic toxicities (retinal vein obstruction, central serous retinopathy), and cardiac toxicities (decreased left ventricular ejection fraction/ cardiomyopathy), as well as a high frequency of dermatologic adverse events and moderate to severe gastrointestinal toxicities. Thus, long-term use of MEK inhibitors can be challenging for some patients.

The combination of dabrafenib plus trametinib recently (March 2023) received approval for the subset of pediatric patients 1 year of age and older with low-grade glioma harboring a BRAF V600E mutation who require systemic therapy. The majority of patients with BRAF-altered pediatric low-grade glioma still have no approved therapy.

Radiotherapy is typically reserved as a last resort for older patients in the salvage setting, as radiation has been associated with cognitive decline, endocrine deficiencies, secondary malignancies, vascular damage, and growth abnormalities in survivors of pediatric brain tumors (De Blank 2019).

Table 1. Summary of Treatments for Pediatric Low-Grade Glioma and BRAF V600E/K Inhibitors

Product(s) Name and Indication/ Enrolled Patient Population	Year and Type of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA-approved treatments for pediatric low-grade glioma				
Dabrafenib + trametinib Indication: 1 year of age and older with LGG with a BRAF V600E mutation Data source: Mekinist (trametinib) Package Insert Tafinlar (dabrafenib) Package Insert	2023 Full	D: BID T: QD orally; based on body weight	According to modified RANO-LGG criteria (IRC, Wen, 2017); n = 73 **ORR (n, %)**: 46.6% (95% CI: 34.8, 58.6) **DOR (months)**: 23.7 (95% CI: 14.5, NE) **PFS (months)**: 20.1 (95% CI: 12.8, NE) Note: modified RANO-LGG ORR includes confirmed PR/CR only	Of the 166 patients who received D+T, adverse reactions occurring at >25% were pyrexia, rash, headache, vomiting, musculo-skeletal pain, fatigue, dry skin, diarrhea, and nausea. AEs leading to: Dose reduction: 48% Dose interruption: 73% Discontinuation: 4% Warnings and precautions include new primary malignancies (cutaneous and non-cutaneous), tumor promotion in BRAF wild-type tumors, hemorrhage, cardiomyopathy, eveitis, serious febrile reactions, serious skin toxicities, hyperglycemia, G6PD deficiency, and embryo-fetal toxicity.
Dabrafenib + trametinib Indication: unresectable or metastatic solid tumors with BRAF V600E mutation in patients ≥6 years Study enrolled recurrent or refractory pLGG with BRAF V600E mutation (2nd line or later)	2022 Accelerated	D: BID T: QD orally; based on body weight	According to modified RANO-LGG criteria (IRC, Wen, 2017); n = 36: **ORR (n, %)**: 9, 25% (95% CI: 12.1, 42.2) **DOR (months)**: 33.6 (95% CI: 11.2, NR). **PFS (months)**: 36.9 (95% CI: 36, NR) Note: 32/36 (89%) of patients had not received prior targeted therapy (ie, MAPKi naïve); modified RANO-LGG ORR includes	Of the 36 patients receiving D+T, treatment related adverse events occurring at >25% were pyrexia, dermatitis acneiform, fatigue, rash, diarrhea, vomiting, and nausea AEs leading to: Dose reduction: 31% Dose interruption: 72% Discontinuation: 22%

Product(s) Name and Indication/ Enrolled Patient Population	**Year and Type of Approval**	**Dosing/ Administration**	**Efficacy Information**	**Important Safety and Tolerability Issues**
Data source: Mekinist (trametinib) Package Insert Tafinlar (dabrafenib) Package Insert			confirmed PR/CR only	
Standard-of-care treatment				
Vinblastine monotherapy Study enrolled recurrent or refractory pLGG; MAPK pathway aberration not required (Bouffet et al, 2012)	N/A	Weekly for 52 weeks, IV; based on body weight or BSA depending on age	According to modified Macdonald criteria, primarily T1 Gd+ (IRC), n = 50 evaluable, 48 centrally reviewed **ORR (n, %)**: 11, 23% **DOR (months)**: NR **5-year Event-free Survival**: 35.7% ± 7.6%	38 of 51 patients (75%) experienced Grade 3/4 AEs, most commonly hematologic.
Investigational targeted therapies				
Selumetinib monotherapy Recurrent or progressive optic pathway and hypothalamic LGG; BRAF/MEK inhibitor naïve only (Fangusaro et al, 2021)	N/A	BID, orally, based on BSA	According to T2/FLAIR imaging per the local institution; n = 25 **ORR (n, %)**: 6, 24% **DOR (months)**: NR **2-year PFS (months)**: 73.8 ± 9.3% **VA improved**: 4/19 (21%) **VA stable**: 13/19 (68%) **VA worsening**: 2/19 (11%)	Attributable toxicities included Grade 1/2 CPK elevation, anemia, diarrhea, headache, nausea, emesis, fatigue, ALT and AST increase, hypoalbuminemia, and rash AEs leading to: Dose reduction: 44% Dose interruption: NR Discontinuation: 16%

Product(s) Name and Indication/ Enrolled Patient Population	**Year and Type of Approval**	**Dosing/ Administration**	**Efficacy Information**	**Important Safety and Tolerability Issues**
Trametinib monotherapy Progressive or refractory pLGG with MAPK pathway activation (NF-1, KIAA1549:BRAF fusion, and other with activation of the MAPK/ErK pathway); MEKi naïve only (Perreault et al, 2022)	N/A	QD, orally, based on body weight	According to T2 imaging per the local institution; n = 40 LGG with MAPK/ERK activation evaluable **ORR (n, %):** 5, 15% **Minor response (n, %):** 13, 33%	Safety not reported
Vemurafenib monotherapy Recurrent or progressive BRAF V600E mutant glioma; BRAFi naïve only (Nicolaides et al, 2020)	N/A	BID, orally, based on BSA	According to modified RANO (T2/FLAIR including cysts, where applicable, centrally reviewed); n = 19 **ORR**: 6 (32%) (95%CI: NR **DOR**: NR **PFS**: NR	Limited reporting; most common treatment-related toxicities were maculopapular rash and other skin and subcutaneous tissue disorders
Mirdametinib monotherapy Recurrent or progressive pLGG with MAPK pathway activation; MEKi naïve only (Vinitsky et al, 2022)	N/A	BID, orally, based on BSA	n = 6 **Minor response**: 4/6 (67%)	N = 11 No dose-limiting toxicities reported; only Grade 1/2 treatment-related AEs reported; no MEK-related retinopathy or cardiopathy reported

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; BRAF = v-raf murine sarcoma viral oncogene homolog B; BSA = body surface area; D = dabrafenib; CI = confidence interval; CPK = creatine phosphokinase; CR = complete response; DOR = duration of response; FDA = Food and Drug Administration; FGFR = fibroblast growth factor receptor; G6PD = glucose-6-phosphate dehydrogenase; IRC = Independent Radiology Review Committee; IV = intravenous; LGG = low-grade glioma; MAPK = mitogen-activated protein kinase; MEK = mitogen-activated protein kinase kinase; N/A = nor applicable; NE = not estimable; NF-1 = neurofibromatosis type 1; NR = not reported; ORR = overall response rate; PFS = progression-free survival; pLGG = pediatric low-grade glioma; PR = partial response; QD = once daily; RANO = Response Assessment in Neuro-oncology; T = trametinib; VA = visual acuity.

The FDA's Assessment

The FDA agrees with the Applicant's assessment of current treatment options; however, selumetinib, vemurafenib, and mirdametinib are investigational therapies and not approved in the US for the treatment of pediatric LGG.

Pediatric LGGs have historically been treated 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 (e.g., cognitive deficits, blindness, hearing loss, and hormonal disturbance) from their disease or treatment, the prognosis for these patients is generally favorable with 10-year overall survival (OS) of approximately 90% (Sievert, 2009).

There is no consensus on a standard treatment approach for progressive pediatric LGG. Patients tend to require multiple and potentially multimodal interventions. Chemotherapy is typically used to delay or obviate the need for radiation therapy. Carboplatin and vincristine have traditionally been used in patients with progressive pediatric LGG and demonstrate an ORR of approximately 52% based primarily on contrast-enhanced CT and/or MRI results in a study of 23 pediatric patients with recurrent LGG. The responders included 7 patients (30%) whose tumors demonstrated greater than 50% reduction in tumor size and 5 patients (22%) with minor responses defined as greater than 25% but less than 50% reduction in tumor size (Packer et al., 1993). Single-agent vinblastine has been more recently implemented in clinical practice with an ORR of approximately 35% (including 21% of patients who had tumor shrinkage of at least 50%) based on a study of 51 pediatric patients with recurrent or refractory LGG; in this study, responses were based primarily on contrast-enhanced imaging results, and for non-enhancing lesions, measurements were performed on T2 or fluid-attenuated inversion recovery images (Bouffet et al., 2012). Due to the relatively recent use of genomic profiling in pediatric LGG, earlier studies evaluating chemotherapy for the treatment of relapsed or refractory LGG did not select for patients based on molecular alterations in tumors; therefore, understanding of the effectiveness of these chemotherapy regimens is within the context of an unselected patient population. In addition, response criteria have evolved over time, further limiting direct comparisons to contemporary studies.

The treatment landscape for BRAF-mutant pediatric LGG is most notable for the combination of dabrafenib and trametinib, which is approved for the first-line treatment of pediatric patients 1 year of age and older with LGG with a BRAF V600E mutation who require systemic therapy. This approval was based on improvements in ORR and PFS in a randomized trial; an overall response rate of 47% (95% CI: 25, 59) and duration of response of 24 months (95% CI: 15, NE) was observed in patients treated with dabrafenib and trametinib in Study CDRB43G2201 with a PFS HR of 0.31 (95% CI: 0.17, 0.55) (Tafinlar USPI). Responses in this trial were assessed by

RANO-LGG criteria, with ORR defined as CR +PR. In Study CTMT212X2101, dabrafenib and trametinib was evaluated in a cohort of 36 pediatric patients with relapsed or refractory pediatric LGG harboring a BRAF V600E mutation (n=34) and two patients with high-grade glioma (HGG) (Tafinlar USPI). The ORR of the combination treatment in this subset of patients is 25% (95% CI: 12, 42) with duration of response of at least 12 months in 56% of responders. Although somewhat limited by the inclusion of patients with high-grade tumors, the ORR in this cohort provides general insight into the effectiveness of dabrafenib and trametinib in patients with relapsed or refractory disease.

Importantly, there are no approved targeted therapies for the treatment of pediatric LGG with tumors harboring BRAF fusions, representing a patient population with high unmet medical need. Type I BRAF inhibitors exert their effect on monomeric forms of BRAF (e.g., BRAF V600E/K mutations) and do not inhibit signaling from the KIAA1549:BRAF fusion that functions as dimers and is the most common oncogenic driver in these tumors (Schreck et al., 2019). Furthermore, the phenomenon of paradoxical activation of MAPK signaling has been well-described when Type I BRAF inhibitors are used to treat BRAF wild-type tumors harboring alterations such as the KIAA1549:BRAF fusion (Sievert et al., 2013).

3. Regulatory Background

Applicant's Position

Day One Biopharmaceuticals, Inc. (Day One, the Sponsor) acquired tovorafenib in December 2019 from Takeda Pharmaceuticals, which evaluated the molecule in a variety of solid tumors in Study C28001 (NCT01425008) and Study C28002 (NCT02327169). These studies generated exposure data for tovorafenib in more than 200 adult patients from the US and Western Europe. Sponsorship of IND 108340 was transferred from Takeda to the Sponsor on 23 January 2020. The Sponsor resumed full global development of tovorafenib in solid tumors including pediatric low-grade gliomas.

Tovorafenib is being developed for commercial use as two formulations: 1) an immediate-release tablet and 2) powder for oral suspension (PfOS). The Sponsor plans to submit two complete applications for both formulations 1) New Drug Application (NDA) 217700 for tablets; and 2) NDA 218033 for PfOS.

The FDA's Assessment

The FDA agrees with the Applicant's position. The FDA received the applications for both formulations of tovorafenib on August 31, 2023.

3.1. U.S. Regulatory Actions and Marketing History

Tovorafenib (DAY101) is not currently registered or approved in the US or any other part of the world.

The FDA's Assessment

The FDA agrees with the Applicant's position.

3.2. Summary of Presubmission/Submission Regulatory Activity

Following the Type B Pre-NDA meeting held on 19 April 2023, Day One submitted a revised table with content and timing of a complete application for rolling review. The Agency provided agreement on the revised rolling review table on 13 May 2023 (Ref ID 5173698). Table 2 outlines the regulatory history of IND 108340 in preparation for the submissions of Original NDAs 217700 (tablets) and 218033 (PfOS).

Table 2. Regulatory History of Tovorafenib Referencing FDA Interactions and Agreements Under IND 108340 and Other Important Items of Note

Date	Application Number	Presubmission Activities, Decisions, and Advice
23 Jan 2020	IND 108340	Sponsorship of IND 108340 was transferred from Takeda Pharmaceuticals to Day One Biopharmaceuticals, Inc.
27 Apr 2020	IND 108340	FDA Type B End of Phase 1 Meeting (FIREFLY-1): Discussion on the design of the Phase 2 study (FIREFLY-1) intended to serve as the registration trial of tovorafenib, and the suitability of the overall data package in support of the planned NDA.
31 Aug 2020	IND 108340	Breakthrough Therapy Designation granted by FDA in the treatment of pediatric patients with low-grade glioma harboring an activating RAF alteration who have progressed after one or more therapies.
24 Sep 2020	IND 108340	Orphan Drug Designation granted by FDA for tovorafenib for the treatment of malignant glioma.
22 Feb 2021	IND 108340	FDA Type B Meeting (FIREFLY-1): Discussion on proposed drug metabolism and pharmacokinetics, clinical pharmacology, and companion diagnostics development programs for tovorafenib and to confirm acceptability of the plans in support of a planned NDA
23 Feb 2021	IND 108340	FDA agreed Initial Pediatric Study Plan was received.
26 July 2021	IND 108340	Rare Pediatric Disease Designation granted for tovorafenib for the treatment of low-grade gliomas harboring an activating RAF alteration disproportionately affecting children.
05 Dec 2021	IND 108340	FDA Type B End of Phase 2 Meeting (CMC, Clinical Pharmacology): Preliminary Meeting Minutes Discussion of the CMC and Clinical Pharmacologinformation for tovorafenib in preparation for an anticipated NDA filing in recurrent or progressive pediatric low-grade glioma.
25 Apr 2022	IND 108340	FDA Type B Content and Format Meeting: Discussion of the proposed content and format of the forthcoming NDA filing in recurrent or progressive pediatric low-grade glioma. Discussion focused on the clinical, clinical pharmacology, nonclinical pharmacology, toxicology, and statistical sections of the NDA.
20 May 2022	IND 108340	FDA Type B Content and Format Meeting, Written Responses Only: Discussion of proposed content and format of the CMC sections of the forthcoming NDA.
1 Nov 2022	IND 108340	Informal FDA Teleconference: Discussion of FDA's Advice/information request dated 22 Sep 2022 regarding Day One's Request for Advice on NDA 217700 rolling review, pooled ISS, population PK, and exposure-response data.
19 Apr 2023	IND 108340	FDA Type B Pre-NDA Meeting: Discussion on the topline data obtained from Study DAY101-001/PNOC026 (FIREFLY-1) and submission timeline supporting the two NDAs planned for tovorafenib.

Date	Application Number	Presubmission Activities, Decisions, and Advice
19 May 2023	NDA 217700	Submission to FDA of Tier 1 of 3 for tovorafenib (tablets). Components include: Available administrative documents – cover letter and forms (partial Module 1) Nonclinical summary documents including the nonclinical overview and written/tabulated summaries (partial Module 2) All nonclinical pharmacology, pharmacokinetic and toxicology reports (Module 4)
06 Jun 2023	IND 108340	(b) (4)
21 Jun 2023	NDA 217700	Presubmission to Rolling Submission (Tier 2 of 3) to FDA for tovorafenib (tablets). Components include: Remaining administrative documents (remaining Module 1) Quality and clinical summary documents (remaining Module 2) All chemistry and quality data related to tovorafenib drug substance and te immediate-release tablet formulation (Module 3) All clinical data (Module 5)
21 Jun 2023	NDA 218033	Presubmission to Rolling Submission (Tier 1 of 2) to FDA for tovorafenib PfOS. Components include: Quality summary documents pertaining to tovorafenib PfOS (Module 2) All chemistry and quality data specific to tovorafenib PfOS formulation (Modules 3 and 5)
31 Aug 2023	NDA217700	Original application Tier 3 of 3 of Rolling Submission to FDA for tovorafenib tablets. Components include: Applicable administrative documents – cover letter and form (Module 1) Study FIREFLY-1 CSR Addendum (June data cut) and corresponding datasets (Module 5)
31 Aug 2023	NDA 218033	Original application Tier 2 of 2 of Rolling Submission to FDA for tovorafenib PfOS. Components include: Applicable administrative documents – cover letter and form (Module 1)

Source: Applicant-provided table.

Abbreviations: CMC = Chemistry, Manufacturing, and Controls; CSR = clinical study report; FDA = Food and Drug Administration; IND = Investigational New Drug (application); ISS = Integrated Summary of Safety; NDA = New Drug Application; PfOS = powder for oral suspension; PK = pharmacokinetics; (b) (4)

The FDA's Assessment

The FDA agrees with the Applicant's regulatory timeline and overview of pre-submission interactions. The FDA provides the following additional comments regarding select milestones and key discussion that occurred at specific meetings regarding regulatory submissions.

Breakthrough Therapy Designation – August 31, 2020

On July 2, 2020, the Applicant submitted a breakthrough therapy designation request (BTD) 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 BTDR was based on clinical data from Study PNOC014, an ongoing multicenter dose-escalation trial of DAY101 in patients 1 to 25 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 was conducted in collaboration with the Pacific Pediatric Neuro-Oncology Consortium (PNOC). DAY101 was administered once weekly for up to two years.

The Applicant's package to support the BTDR included nine patients with multiply relapsed or refractory pediatric LGG who were confirmed to have measurable disease and were evaluable for response assessment using Response Assessment in Neuro-Oncology (RANO) criteria for high-grade glioma (HGG). The ORR was 56% (95% CI: 21, 86) with two patients exhibiting complete response (CR) and three patients exhibiting partial response (PR). Among patients with a confirmed RAF alteration (excluding a 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. At the time of data submission, no responders had shown progression.

The data provided in the BTDR indicated that pediatric patients with previously treated, progressive LGGs harboring an activating RAF alteration (most frequently the KIAA1549:BRAF fusion) had a substantial response rate and demonstrated durable responses to DAY101. The FDA subsequently granted BTD to DAY101 for the treatment of pediatric patients with LGG harboring an activating RAF alteration that have progressed after one or more prior systemic therapies.

Pre-NDA Meeting – April 19, 2023

Notable discussion at this meeting included the FDA's recommendation to evaluate efficacy in FIREFLY-1 using response criteria specifically devised for LGG (i.e., RAPNO-LGG and RANO-LGG), which are preferred over RANO-HGG as LGG is a radiographically distinct tumor from HGG. FDA communicated that they 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 the target patient population.

(b) (4)

(b) (4)

Midcycle Communication Meeting – January 31, 2024

Relevant discussion at this meeting included updates provided by the Applicant regarding the enrollment status of the FIREFLY-2 trial. The Applicant noted that at the time, (b) (4)

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4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

Refer to the Clinical Inspection Summary, dated February 9, 2024, for full details. Briefly, three clinical investigators, Drs. Lindsay Kilburn (Site # 1014), Daniel Landi (Site # 1019), and Dong Khung Quang (Site # 61002), as well as the imaging Contract Research Organization (CRO) Imaging Endpoints II, LLC and the study sponsor, Day One Pharmaceuticals, Inc (Day One), were selected for inspection. Inspections of the CIs, (Drs. Kilburn, Landi, and Quang), the Applicant, and the imaging CRO revealed no discrepancies or regulatory violations. Based on these inspections, Study DAY101-001 (FIREFLY-1) appears to have been conducted adequately and the data generated by the inspected clinical investigators and the imaging CRO and submitted by the applicant, Day One, appear acceptable in support of the proposed indication.

4.2. Product Quality

For a full discussion of product quality review issues, refer to the OPQ Integrated Quality Assessments uploaded in DARRTs on April 12, 2024 (NDA 217700 and NDA 218033). The product quality review team recommends approval for these NDAs. The Applicant has provided adequate CMC information for tovorafenib tablets and the powder for reconstitution. Drug substance, drug product manufacturing and testing facilities were found to be acceptable. For both formulations, a PMC has been agreed upon with the Applicant to submit additional dissolution profile (multi time-point) data generated from commercial batches using the final dissolution method (USP apparatus II, 65 rpm, 900 mL 0.1 N HCl with 0.25% SDS at 37^{o}C) and the interim acceptance criterion of Q= (b) (4) % in 45 minutes until the appropriate acceptance criterion for the dissolution test of the drug product is finalized.

4.3. Clinical Microbiology

Refer to the OPQ Integrated Quality Assessments uploaded in DARRTS on April 12, 2024 (NDA 217700 and NDA 218033) for additional details regarding the microbiology assessment. There are no clinical microbiology issues that would preclude approval.

4.4. Devices and Companion Diagnostic Issues

In FIREFLY-1, assessment of RAF alteration was determined by local molecular assays as routinely performed at CLIA or other similarly certified laboratories. Based upon prior correspondence with the Applicant, the development of a companion diagnostic (CDx) for the selection of patients with pediatric LGG who have BRAF fusion or rearrangement, or BRAF V600 mutation is currently in progress. The Applicant is collaborating with Foundation Medicine, Inc. (FMI) to expand the intended use of the FoundationOne® CDx (F1CDx) to include a CDx

indication for the indicated patient population.

Since a CDx is not available for concurrent approval with tovorafenib, the FDA will include a PMC in the approval letter for tovorafenib. Per the PMC, the CDx will be validated through an appropriate analytical and clinical validation study using clinical trial data that demonstrates the device is essential to the safe and effective use of tovorafenib for the treatment of patients 6 months of age and older with relapsed or refractory pediatric LGG harboring a BRAF fusion or rearrangement, or BRAF V600 mutation.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Tovorafenib is a small molecule inhibitor of rapidly accelerated fibrosarcoma (RAF) kinases (BRAF, CRAF). The established pharmacological class for tovorafenib is kinase inhibitor. BRAF V600 mutations and BRAF fusion proteins drive tumorigenic potential through hyperactivation of downstream signaling of the mitogen-activated protein kinase (MAPK) pathway.

X-ray crystallography studies support that tovorafenib is a Type II pan-RAF kinase inhibitor, showing that it binds to the inactive RAF kinase (DFG-out) conformation of the kinase domain indicating that it can bind both monomeric wild-type and mutant Raf kinases and dimeric fusion protein RAF kinases. Pharmacological assessment of tovorafenib showed inhibitory activity against BRAF V600E mutant kinase, wild-type (WT) BRAF kinase, and WT CRAF kinase in enzymatic assays and antiproliferative activity against BRAF V600E and V600D mutations in cellular assays (IC_{50}s 0.7 to 10.1 nM). Tovorafenib also inhibited phosphorylation of the downstream effector ERK (pERK) in cell lines containing BRAF V600E and V600D mutations. Tovorafenib had antiproliferative activity against neuroprogenitor cells (p53-/-) transduced with constructs for BRAF V600E or KIAA1549:BRAF (a truncation/fusion BRAF oncoprotein which functions as a dimer and is found in pediatric low grade astrocytoma) with IC_{50} values of 248 and 190 nM, respectively. Tovorafenib also inhibited pERK in these transduced cells. Of note, Sun et al. 2017 states that these 2 models do not emulate the pediatric tumors at the genetic or histopathologic levels. In vivo, tovorafenib had antitumor activity in subcutaneous xenograft mouse models bearing melanoma tumors with the AGK-BRAF fusion, BRAF V600E and V600D mutations, BRAF WT, and in colorectal cancer tumors with BRAF V600E mutations. In addition, tovorafenib had antitumor activity in mice bearing intracranial neuroprogenitor (p53-/-) BRAF V600E or KIAA1549:BRAF expressing tumors. Tovorafenib increased survival time in mice bearing these intracranial tumors compared to control treated animals. Overall, tovorafenib has activity against BRAF WT, V600E and V600D mutants, and KIAA1549 and AGK BRAF fusion proteins.

In vitro, tovorafenib increased phosphorylation of ERK at clinically relevant concentrations in cells with neurofibromatosis Type-1-loss of function (NF1-LOF) suggesting activation, rather than inhibition, of the MAP kinase pathway. In a genetically engineered mouse model of NF1-associated plexiform neurofibroma (PFN) lacking a BRAF alteration, tovorafenib did not reduce proximal nerve tumor volume or tumor number per mouse after 12 weeks of daily treatment compared to a vehicle control. Non-significant increased tumor volume occurred in 2 out of 12 mice (~17%) with PFN when treated with tovorafenib. Because NF1 patient populations are at risk of developing low grade gliomas and based on these nonclinical findings demonstrating activation/tumor growth and lack of effectiveness in NF1 models, the clinical and nonclinical team agreed to include a warning and precautions in the label stating that tovorafenib may

promote tumor growth in patients with NF1 tumors.

Secondary targets of tovorafenib included Abl, Arg, DDR2, and EphA with IC_{50} values of 16, 1, 50, and 221 nM which are considered clinically relevant concentrations (vs. 340 nM; unbound Cmax in patients at the proposed clinical dose).

Tovorafenib inhibited human ether-à-go-go related gene (hERG) potassium channel current with an IC_{50} of 8.9 µM in a safety pharmacology assessment, which is approximately 26-fold higher than the human free steady-state Cmax of 340 nM. In clinical trials conducted, QTc prolongation was not observed in patients treated with tovorafenib. Additional safety pharmacology assessments conducted in cynomolgus monkeys and beagle dogs revealed transient, dose-dependent increase in heart rate. Dogs and monkeys in the highest dosed groups (125 mg/kg in dogs and 60 mg/kg in monkeys) also exhibited transient increase in blood pressure. Tovorafenib had no effect on the central nervous system (CNS) in rats, as demonstrated in a functional observational battery (FOB), and no effect on respiratory function in rats.

Tovorafenib was widely distributed throughout rat tissues within an hour of oral dosing. The highest concentrations were found in the small intestine, adrenal gland, liver, esophagus, kidney, brown adipose tissue, stomach, cecum, pancreas, Harderian gland, eye (uveal tract), salivary gland, and heart, while the lowest concentrations were found in the brain, spinal cord, seminal vesicles, testis, and eye lens. The major route of excretion of tovorafenib was feces with minor excretion via the urinary route in rats, with 73 to 87% of radioactive tovorafenib recovered after 8 h of oral dosing in intact and bile duct cannulated rats. In consultation with the FDA clinical pharmacology team, animal to human exposure multiples were calculated using the model-predicted steady-state AUC of 70538 ng*h/mL (493767 ng*h/mL following once weekly administration, divided over 7 days for estimation of mean daily exposure) in humans. In addition, considering that animals in the general repeat-dose toxicology studies were given tovorafenib once every 2 days, the animal AUC was divided by 2 for estimation of mean daily exposure to compare with human exposures.

The Applicant evaluated the safety of tovorafenib administered orally once every 2 days in 28-day and 91-day GLP-compliant general toxicology studies using Sprague Dawley rats and cynomolgus monkeys. The oral administration is consistent with the intended clinical route of administration. All animals survived when administered tovorafenib in the 28- or 91-day rat studies or the 28-day monkey study. Tovorafenib led to a significant number of mortalities in the 91-day monkey study due to anemia and bone marrow suppression. Thus, the mid and high dose groups were euthanized after 2 months of treatment. Hematology and chemistry lab findings indicated that tovorafenib caused anemia and bone marrow suppression in both rats and surviving monkeys. In the rat, male reproductive organs and female ovaries were target organs of toxicity noted at doses approximately ≤0.3-fold the human exposure at the recommended clinical dose. The clinical team noted concerns about hemorrhage based on

safety data from the clinical study reports. Findings of hemorrhage in the rats included thymus, mesenteric and submandibular lymph nodes, and bone (femur) in the 4-week study, and bone (femur, tibia, sternum), ovary, and liver in the 3-month study. Finding of hemorrhage in the monkeys included esophagus and colon in the 4-week study and rectum, thyroid, lymph node, and uterus in the 3-month study. Hemorrhage in animals may be secondary to inflammation; however, considering all the nonclinical data, there was no mechanistic rationale for the hemorrhage observed in the clinic. Overall, tovorafenib related adverse findings in animal toxicology studies included: gastrointestinal, epidermal (including skin), hematologic, and hepatotoxicity; pro-inflammatory events leading to findings in the thyroid and parathyroid and changes in levels of hormones, calcium, and phosphorus. Toxicities were observed in reproductive organs in the general toxicology studies and included reversible increased thickness of the vaginal mucosa, increased size and/or numbers of corpora hemorrhagicum, and hemorrhage, and non-reversible cystic follicles, decreased corpora lutea, and interstitial cell hyperplasia in ovaries in female rats, and reduced weights of epididymis and testes, which correlated with reversible tubular degeneration/atrophy of the testes and reduced epididymal sperm in male rats.

Tovorafenib was negative for genotoxicity in the following studies: in vitro bacterial reverse mutation (Ames) assay, in vitro micronucleus assay in human lymphocytes, and in vivo bone marrow micronucleus assay in rats. Tovorafenib was positive in the in vitro chromosomal aberration assay; this occurred at a single concentration that was associated with drug precipitation. Because of the potential for prolonged treatment and long-term survival in the proposed patient population, it is important to address the carcinogenicity potential of tovorafenib. Two post-marketing requirements (PMRs) to conduct carcinogenicity studies in mice and rats were communicated to the Applicant. Of note, the Applicant submitted a special protocol assessment for a (b) (4) on July 7, 2023, under IND 108340 for DAY101.

A preliminary GLP-compliant dose range-finding embryo-fetal development study was conducted in pregnant rats to assess the effect of tovorafenib on fetal development. Once daily oral dosing for 12 days, between gestation days (GD) 7 and 17 during the period of organogenesis, resulted in total litter loss at the lowest dose of ≥37.5 mg/kg/day which is approximately 0.8 times the recommended clinical dose of 380 mg/m^2 once weekly based on AUC. Treated dams had no clinical signs at doses as high as 150 mg/kg/day. Due to the discernable embryofetal toxicity signal, the FDA agreed that an additional study was not likely warranted. A GLP-compliant fertility and early embryonic development study was conducted in male and female rats to assess the effect of tovorafenib on fertility and embryonic development parameters. Once daily oral administration of tovorafenib in rats at doses of 37.5, 75, or 150 mg/kg/day for 64 days beginning 29 days before mating had no effect on male reproductive success (mating) or fertility parameters (sperm density, or sperm motility). However, females administered the same doses for 14 days prior to cohabitation through GD 6 demonstrated significantly impaired reproductive and fertility parameters at the same dose

levels. Females had significantly lower numbers of pregnancies, corpora lutea, implantations, and live embryos. Considering these findings, the review team recommends an embryofetal toxicity warning. Based on FDA guidance, "Oncology Pharmaceutical: Reproductive Toxicity Testing and Labeling Recommendations," for embryofetal toxic drugs that are non-genotoxic drugs, considering a half-life is 48 hours for tovorafenib and that the FDA clinical pharmacology team identified tovorafenib to be a CYP3A inducer, which may compromise the efficacy of hormonal contraception, the FDA recommends advising females of reproductive potential to use effective non-hormonal contraception during treatment with tovorafenib and for 28 days after the last dose to account for drug clearance (i.e., 2 weeks) plus an additional 14 days for CYP3A induction to normalize (i.e., total 28 days after the last dose). FDA recommends advising males of reproductive potential to use effective contraception during treatment with tovorafenib and for 2 weeks after the last dose. In addition, due to the potential for serious adverse reactions in breastfed children from tovorafenib, the FDA recommends advising lactating women not to breastfeed during treatment with tovorafenib and for 2 weeks following the last dose.

The nonclinical data are adequate to support the approval of tovorafenib for the proposed indication.

5.2. Referenced NDAs, BLAs, DMFs

Applicant's Position

There are no referenced NDAs, Biologics License Applications, or Drug Master Files related to nonclinical pharmacology or toxicology for tovorafenib.

The FDA's Assessment

The FDA agrees.

5.3. Pharmacology

Applicant's Position

Tovorafenib (designated as DAY101, TAK-580, MLN2480, BSK-1369, BSK-001369, and BIIB024 at various points during development) is a Type II RAF kinase inhibitor that has been characterized by both *in vitro* and *in vivo* studies to support the potential therapeutic benefits in human cancers harboring specific genomic alterations. Tovorafenib is an oral, CNS-penetrant, selective, small-molecule Type II RAF kinase that inhibits RAF monomers and dimers. It has been developed for treatment of patients with pediatric low-grade glioma harboring an activating BRAF fusion or rearrangement or BRAF V600 mutation that has progressed after one or more prior systemic therapies.

5.3.1. Primary Pharmacology

In biochemical assays, tovorafenib inhibited both the oncogenic BRAF V600E mutation and the wild-type (WT) BRAF and WT v-raf murine sarcoma viral oncogene homolog C (CRAF) kinases, with the concentration required for 50% inhibition (IC_{50}) values of 7.1 nM, 10.1 nM, and 0.7 nM, respectively. Tovorafenib inhibited a small subset of kinases in addition to RAF in a similar potency range, including Abl, Arg, Frk, Lck, EphA2, EphA8, DDR2, and SAPK2a. Tovorafenib showed a high degree of selectivity in a large non-kinase screening panel of 169 receptors, transporters, and channels. Tovorafenib also inhibits phosphorylated-ERK (pERK) and cell proliferation in a broad panel of *in vitro* cancer cell lines, with BRAF mutant cancer cells being most sensitive to tovorafenib's antiproliferative effects, and several RAS mutant cell lines showing moderate sensitivity to tovorafenib.

Tovorafenib has been shown to inhibit the kinase activity of BRAF in the context of BRAF fusions with various 5' gene partners, most notably fusion with the KIAA1549 gene. KIAA1549:BRAF fusion kinase activity is inhibited by tovorafenib with comparable potency to inhibition of BRAF V600E in cell model systems, without the paradoxical activation of the MAPK pathway reported for Type I BRAF inhibitors. Importantly, in contrast to Type I BRAF inhibitors, tovorafenib does not result in paradoxical activation of MAPK signaling in BRAF fusion expressing cells, which limits the use of Type I BRAF inhibitors in that setting (Sun 2017).

In vivo, tovorafenib demonstrated strong and sustained inhibition of pERK in pharmacokinetic-pharmacodynamic (PK-PD) studies in mice bearing either BRAF mutant or RAS mutant xenograft tumor models following a single oral dose. Similarly, in a neuroblastoma ras viral oncogene homolog (NRAS)-mutant xenograft tumor model, following two consecutive doses, tovorafenib showed strong and sustained pERK inhibition. These data support the conclusion that tovorafenib is a potent Type II RAF inhibitor *in vivo*.

The *in vivo* anti-tumor activity of tovorafenib was evaluated in five different tumor xenograft models with oral dosing on either once daily (QD), every other day (Q2D), or twice weekly dosing schedules. Four of these models were tested both in *vitro* and *in vivo* with tovorafenib. The tumor models included models of melanoma and colon cancer, and tovorafenib showed anti-tumor activity in all of these BRAF-mutant and BRAF-fusion tumor xenograft models. BRAF-mutant tumor models were sensitive to tovorafenib, with regressions of large, established tumors observed in two melanoma models: WM-266-4 (BRAF V600D) and A375 (BRAF V600E). In all the models in which tovorafenib was efficacious, tumors regrew once dosing was stopped, indicating that continued dosing is required to maintain efficacy in these models. Tumors that regrew were sensitive to a second dosing cycle of tovorafenib. Furthermore, tovorafenib was assessed in a melanoma patient-derived xenograft model harboring a BRAF fusion that demonstrated striking antitumor activity *in vivo*. Activity against both BRAF mutant and BRAF fusion tumor models provides further support that tovorafenib is a Type II Type II RAF inhibitor.

The FDA's Assessment

The Applicant uses terminology such as "potent," "strong," or "high degree of selectivity" to describe study results; such terms should be avoided as they are vague, subjective, and promotional.

The Applicant submitted study results from conducted pharmacology studies and cited research data from scientific literature to support the primary pharmacology of tovorafenib. The information presented from literature and cited by the Applicant is descriptive and is not relied upon for approval of NDAs 217700 and 218033 or for labeling recommendations.

The FDA generally agrees with the Applicant's conclusions on the pharmacology of tovorafenib, with additional pertinent details below. In vitro, tovorafenib had kinase inhibitory activity against BRAF V600E mutant kinase, wild-type (WT) BRAF kinase, and WT CRAF kinase, with the concentration required for 50% inhibition (IC_{50}) values of 7.1, 10.1, and 0.7 nM, respectively. Evaluation of the binding mode of tovorafenib using crystallography showed that tovorafenib binds to the inactive conformation of the BRAF kinase domain or the DFG-out conformation consistent with a pan-RAF kinase inhibitor or a Type II inhibitor. Evaluation of antiproliferative activity and effects on downstream phosphorylated ERK (pERK) signaling in various cancer cell lines indicated that tovorafenib had greater activity in cell lines containing BRAF V600E and V600D mutations with WT Ras with EC_{50} values ranging from 0.17 to 1.5 µM (2-fold lower to 4-fold higher vs. unbound Cmax of model predicted values in patients at the indicated dose of 380 mg/m^2; Table 3). Tovorafenib had moderate activity against specific cell lines with WT BRAF and K-Ras, N-Ras, or WT Ras status (EC_{50} values ranging from 2.4 to 10 µM); however, in additional cell lines with WT BRAF plus WT or mutant Ras, tovorafenib had no antiproliferative activity (Figure 1) or effect on pERK levels (data not shown in review). The Applicant cited Sun et al 2017, which showed that in vitro tovorafenib had antiproliferative activity against neuroprogenitor cells (p53-/-) transduced with constructs for BRAF V600E or KIAA1549:BRAF (a truncation/fusion BRAF oncoprotein which functions as a dimer and is found in pediatric low grade astrocytoma) with IC_{50} values of 248 and 190 nM, respectively. Tovorafenib also inhibited pERK in these transduced cells. Of note, the paper states that these 2 models do not emulate the pediatric tumors at the genetic or histopathologic levels.

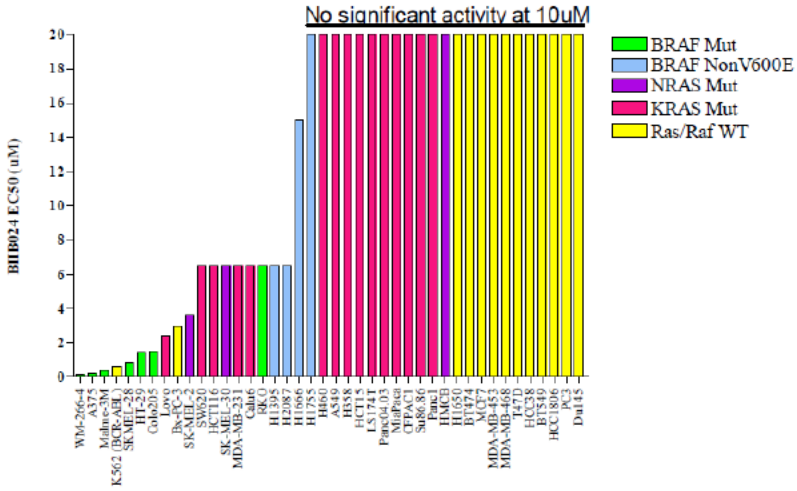
Table 3. Antiproliferative Activity and Inhibition of pERK by Tovorafenib in Cancer Cell Lines With BRAF Mutations and WT Ras

Cell Line	Tumor Type	BRAF Status	Ras Status	Antiproliferation EC_{50} (μM)	Inhibition of pERK EC_{50} (μM)
WM-266-4	Melanoma	V600D	WT	0.17	0.014
A375	Melanoma	V600E	WT	0.24	0.065
Malme-3M	Melanoma	V600E	WT	0.4	ND
SK-MEL-28	Melanoma	V600E	WT	0.85	ND
K562 (BCR-ABL)	CML	WT	WT	0.63	None
HT-29	Colon	V600E	WT	1.4	0.11
Colo-205	Colon	V600E	WT	1.5	0.1

Source: Reviewer-generated table.

ND = not determined.

Figure 1. Antiproliferative Activity of Tovorafenib Grouped by Cell Line BRAF/Ras Mutation Status

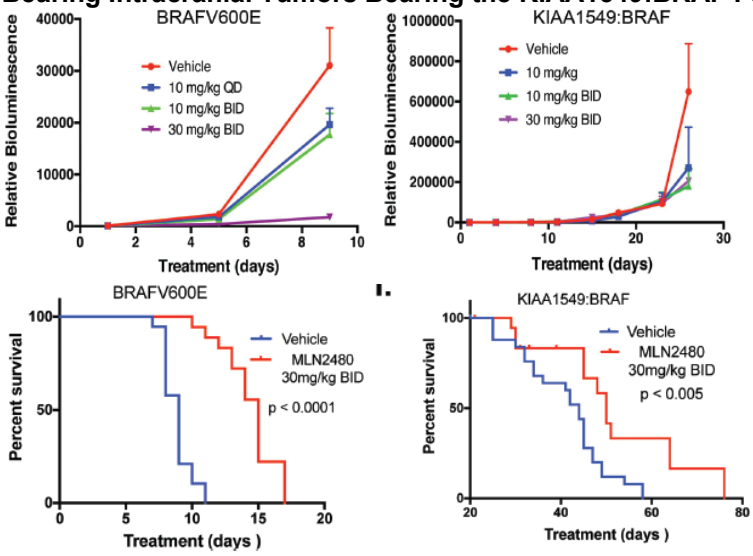


Source: Excerpted from Applicant's Study #rsch-2010-009

Evaluation of antitumor activity was conducted in several subcutaneous xenograft models and one intracranial model. Tovorafenib had antitumor activity in xenograft mouse models bearing subcutaneous melanoma tumors with the AGK-BRAF fusion, BRAF V600E or V600D mutations, and BRAF WT when administered orally ranging from once daily to once every 4 days. Similar antitumor activity was observed in subcutaneous mouse models of colorectal tumors bearing BRAF V600E mutations and pancreatic tumors with BRAF WT. Tovorafenib antitumor activity peaked around a dose of 12.5 mg/kg with lower or higher doses having less antitumor activity when given orally once daily or once every 2-3 days for up to 28 days. Tovorafenib led to inhibition of phosphorylation of ERK in the tumor tissue harvested from these treated mice. In mice bearing intracranial tumors of KIAA1549:BRAF model cells or BRAF V600E model cells (both p53-/- neuroprogenitor cells) expressing luciferase, treatment with tovorafenib dose-dependently decreased luciferase signaling indicating tovorafenib crossed the blood brain barrier and had antitumor activity against cells bearing the KIAA1546::BRAF fusion or BRAF

V600E mutation. Tovorafenib also increased survival in these intracranial tumor bearing mice compared to vehicle control (Sun et al 2017).

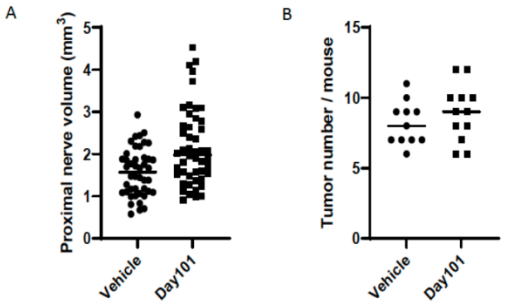
Figure 2. Tovorafenib Had Antitumor Activity (top) and Increased Survival (bottom) in Mice Bearing Intracranial Tumors Bearing the KIAA1549:BRAF Fusion or V600E Mutation



Source: Excerpted from Sun et al 2017.

In a genetically engineered $NF1^{flox/flox}$, postn-Cre^{+} mouse model of NF1-associated plexiform neurofibroma (PNF) without BRAF alterations, mice developed PNFs similar to human tumors by 4 months of age. Treatment of these mice with tovorafenib orally once daily at 25 mg/kg starting at 4 months of age for 12 weeks showed that tovorafenib did not reduce proximal nerve tumor volumes compared to the vehicle control group. In addition, tovorafenib did not reduce the number of tumors found per mouse when compared to the vehicle control group. Increased tumor size occurred in 2 out of 12 mice (17%; n=5 [3 tumors from one mouse and 2 tumors from a different mouse]) in the tovorafenib treated group; however, this was not statistically significant compared to the vehicle control group.

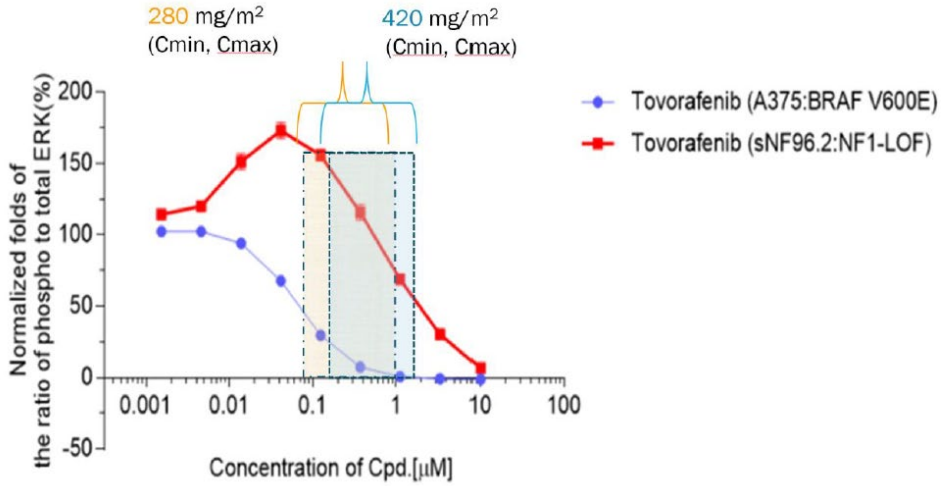
Figure 3. Tovorafenib Did Not Reduce Proximal Nerve Tumor Volume (A) or Tumor Number (B) in a Mouse Model of Nf1-Associated Plexiform Neurofibroma



Source: Excerpted from Study DAY101-prc-ivp-001

In vitro studies further evaluating the activity of tovorafenib in NF1-models measured phosphorylated ERK (pERK) levels in tumor cells lines containing NF1-LOF (sNF96.2, MeWo and NCI-H1838 cells) or BRAF V600E (A375 cells). The data showed tovorafenib inhibited pERK in a concentration-dependent manner in a BRAF V600E cell line. In contrast, tovorafenib had a bell curve effect on pERK levels in NF1-LOF expressing cell lines, increasing pERK levels at lower concentrations. When these results were super-imposed with protein binding adjusted to a clinically relevant exposure (human C_{max} and C_{min}) for tovorafenib, a higher increase in pERK in NF1-LOF cell line was observed compared to cells expressing the BRAF V600E mutation at the minimal and maximum Cmax exposure range.

Figure 4. pERK Levels Super-Imposed Mean Protein Binding Adjusted Clinically Relevant Exposure Range at 280 and 420 mg/m² Tovorafenib



Source: Excerpted from Applicant's information request response

5.3.2. Secondary Pharmacology

Applicant's Position

Tovorafenib showed a high degree of selectivity in a large non-kinase screening panel of 169 receptors, transporters, and channels. Tovorafenib only inhibited ligand binding to 3 of the 169 receptors, transporters, and channels by > 50% at 10 μM: Adenosine A_{2A} (75%), Adenosine A_3 (51%) and glutamate/N-methyl-D-aspartic acid/polyamine (65%). The IC_{50} values were assessed and all were > 1.0 μM which is considerably higher than the IC_{50} values for mutant BRAF, WT BRAF, and WT CRAF kinases. In addition to the relatively weak inhibitory activity in comparison to RAF kinases, these receptors are unlikely to be inhibited clinically based on clinical exposure. Tovorafenib is highly protein bound and the free maximum plasma concentration (C_{max}) is approximately 0.28 μM, which is approximately 4-fold lower than the most potent IC_{50} observed for these non-kinase receptors. Tovorafenib did not inhibit any of the 5 cytochrome P450 (CYP) enzymes at > 50% at 10 μM.

The FDA's Assessment

The FDA generally agrees with the Applicant's conclusions on the secondary pharmacology of tovorafenib, with additional pertinent details below. The Cmax of unbound tovorafenib was calculated by the FDA clinical and nonclinical team to be 0.34 µM (340 nM) at the recommended dose of 380 mg/m^2 once weekly. Additional secondary kinase targets inhibited by tovorafenib at clinically relevant concentrations are listed in Table 4.

Table 4. Secondary Kinase Targets for Tovorafenib at Clinically Relevant Concentrations

Target	Tovorafenib IC_{50} (nM)
Abl	34
Arg	3
DDR2	23
EphA2	28
EphA8	20
Lck	16
PTK5	1
SAPK2a	50
SAPK2b	221

Source: Reviewer-generated table.

5.3.3. Safety Pharmacology

Applicant's Position

Safety pharmacology studies as specified in the International Council for Harmonisation (ICH) guidelines were conducted in compliance with Good Laboratory Practice (GLP) regulations to investigate effects of tovorafenib on the CNS, respiratory system, and cardiovascular system. *In vitro*, the IC_{50} for the inhibitory effect of tovorafenib on human ether-à-go-go related gene (hERG) potassium current was 8.9 µM, which is 32-fold higher than the unbound C_{max} value in humans of 0.28 µM. When tovorafenib was orally administered to rats, no effects on the CNS were observed at doses up to 1500 mg/kg. In the respiratory safety pharmacology study, nonadverse effects on tidal volume, minute volume, and respiratory rate were observed at doses of 500 to 1500 mg/kg; 1500 mg/kg was considered the no-observed-adverse-effect level (NOAEL). In beagle dogs and cynomolgus monkeys, nonadverse dose-dependent effects were observed on heart rate, with expected concurrent shortening of the PR, QRS, and QT intervals. At higher doses (125 mg/kg in beagle dogs and 60 mg/kg in cynomolgus monkeys), increased blood pressure was also observed. The NOAEL in the GLP cynomolgus monkey cardiovascular

safety pharmacology study was 60 mg/kg.

The FDA's Assessment

In general, the FDA agrees with the Applicant's position on safety pharmacology. Cmax of unbound tovorafenib was calculated by the FDA clinical and nonclinical team to be 0.34 µM at the recommended human dose. Therefore, the 8.9 µM IC_{50} for hERG channel inhibition corresponds to a 26-fold exposure multiple.

5.4. ADME/PK

Applicant's Position

The pharmacokinetics (PK) of tovorafenib has been well characterized *in vitro, in vivo,* and in the preclinical animal species used for nonclinical toxicity studies.
Tovorafenib *in vitro* passive permeability was high, yet tovorafenib has low aqueous solubility. The low aqueous solubility and high permeability of tovorafenib suggest that solubility-limited absorption would be expected, especially at high dose levels. Tovorafenib demonstrated good oral absorption in all animal species evaluated (mouse, rat, dog, and monkey) with absolute bioavailability following solution or suspension dosing of 18.1% in dog, 27.4% in monkey, up to 95.4% in mouse, and up to 100% in rat at 3 or 5 mg/kg orally (PO). (b) (4) Upon repeat dosing in rats, the plasma exposure of tovorafenib increased in a less than dose-proportional manner with increasing doses, while in monkeys, exposure increases were roughly proportional to dose. In both species, there was little accumulation with repeated dosing on a Q2D schedule in GLP toxicology studies. In rats, a gender difference was observed in exposure to tovorafenib, with female rats having exposure approximately 2-fold higher than male rats; in monkeys, there were no significant gender differences in exposure.

Tovorafenib had low systemic clearance (<10% of the liver blood flow) in nonclinical species following intravenous (IV) administration, and the volume of distribution was generally larger than the volume of total body water in animal species, suggesting that tovorafenib is distributed into peripheral tissues. The plasma half-life of tovorafenib ranged from approximately 3.6 to 10.7 hours in mice, rats, and dogs, but was much longer (approximately 17.8 hours) in monkeys following intravenous (IV) administration.

Tovorafenib exhibits high plasma protein binding from all species tested (mean of 2.5 to 5.3% unbound) and is well distributed in the body. Tovorafenib was highly bound to human serum albumin and moderately bound to α1-acid glycoprotein. *In vivo,* tovorafenib was well distributed to rat tissues, including the brain, with brain:plasma area under the concentration-

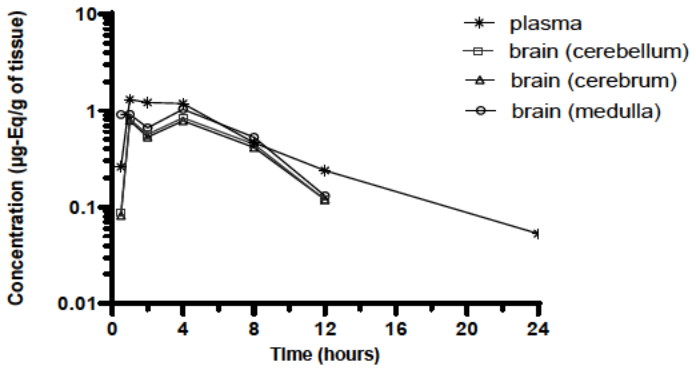
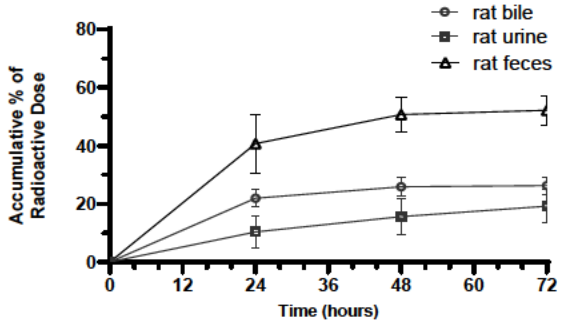
time curve (AUC) ratio of tovorafenib-derived radioactivity of approximately 0.57 in rats, indicating that tovorafenib-derived radioactivity penetrated the blood-brain barrier. Tovorafenib undergoes oxidative metabolism mediated by aldehyde oxidase and several CYP isoforms. Overall, the metabolic profiles of tovorafenib in isolated hepatocytes from rats and cynomolgus monkeys, but not dogs, were comparable to humans and no unique *in vitro* human metabolites were detected. Tovorafenib was extensively metabolized in rats following IV administration, with less than 3% of the dose eliminated as unchanged drug in bile or urine. The major biotransformation pathways of [^{14}C]-tovorafenib were hydrolysis of the thiazole carboxamide moiety (M10), oxidative N-dealkylation of the pyrimidine carbamoyl moiety (M6), and a combination of these 2 pathways (M9). Minor metabolites observed were a result of oxidation (M3, M15), N-acetyl cysteine conjugation (M5), reduction of M6 (M13), oxidative de-chlorination of M13 (M11), and further glucuronidation of M3, M11, and M13.

In the mass balance study in rats using radiolabeled [^{14}C]-tovorafenib, approximately 17.2%, 26.3%, and 52.2% of radioactivity was excreted in urine, bile, and feces, respectively; approximately 20.7% and 76.1% of radioactivity was excreted in urine and feces in intact rats. Therefore, biliary-fecal excretion was identified as the major elimination pathway.

Table 5. ADME Studies With Tovorafenib

<table>
<tr><th>Type of Study</th><th>Major Conclusions</th></tr>
<tr><td colspan="2">Protein Binding</td></tr>
<tr><td>Assessment of protein binding of tovorafenib by equilibrium dialysis (Studies: PD09-27 and DOT1-DMPK-003)</td><td>Tovorafenib exhibits high plasma protein binding from all species tested (mean value in the range from 2.5 to 5.3% unbound). Tovorafenib was highly bound to human serum albumin (95.3%) and moderately bound to α1-acid glycoprotein (42%).
<table>
<tr><th>Species</th><th>% unbound at 1 µM</th><th>% unbound at 10 µM</th><th>Mean</th></tr>
<tr><td>Human</td><td>2.54</td><td>2.51</td><td>2.5</td></tr>
<tr><td>Dog</td><td>2.06</td><td>3.57</td><td>2.8</td></tr>
<tr><td>Monkey</td><td>3.73</td><td>4.86</td><td>4.3</td></tr>
<tr><td>Rat</td><td>3.62</td><td>6.92</td><td>5.3</td></tr>
<tr><td>Mouse</td><td>2.26</td><td>3.52</td><td>2.9</td></tr>
</table></td></tr>
<tr><td colspan="2">Absorption</td></tr>
<tr><td>Single-dose PK of tovorafenib in mice, rats, dogs and monkeys (Studies: P024-10-04, P024-10-05, P024-08-01 and P024-08-02)</td><td>Tovorafenib in vitro passive permeability was high, yet tovorafenib has low aqueous solubility. The low aqueous solubility and high permeability of tovorafenib suggest that solubility limited absorption would be expected, especially at high dose levels.
Tovorafenib had low systemic clearance (< 10% of the liver blood flow) in nonclinical species following IV administration, and the volume of distribution was generally larger than the volume of total body water.</td></tr>
</table>

<table>
<tr><td>Type of Study</td><td>Major Conclusions</td></tr>
<tr><td></td><td>
<table>
<tr><th>Species</th><th>CL (L/h/kg)</th><th>V_z, or V_{ss} (L/kg)</th><th>IV, $t_{1/2}$ (h)</th><th>Oral T_{max} (h)</th><th>IV, $AUC_{0-\infty}$ (ng*h/mL)</th><th>Oral F%</th></tr>
<tr><td>BALB/c mouse</td><td>0.19</td><td>1.70</td><td>6.30</td><td>5.00</td><td>26100[a]</td><td>95.4[b]</td></tr>
<tr><td>Rat</td><td>0.16</td><td>0.52</td><td>3.60</td><td>4.00</td><td>31970[a]</td><td>41.4[b]</td></tr>
<tr><td>Dog</td><td>0.102</td><td>1.49</td><td>10.7</td><td>3.00</td><td>10500[a]</td><td>18.1[c]</td></tr>
<tr><td>Monkey</td><td>0.0845</td><td>2.18</td><td>17.8</td><td>3.81</td><td>11900[a]</td><td>27.4[c]</td></tr>
</table>
[a] Dosed at 5 mg/kg in rodent species and 1 mg/kg in non-rodent species.
[b] Oral vehicle in 10% solutol,10% ethanol, 10% PEG400 and 70% water.
[c] Oral vehicle in 1% sodium carboxymethyl cellulose, 0.2% Polysorbate 80 suspension.
Upon repeat dosing in rats, the plasma exposure of tovorafenib increased in a less than dose-proportional manner with increasing doses, while in monkeys, exposure increases were roughly proportional to dose. In both species, there was little accumulation with repeated dosing on a Q2D schedule in GLP toxicology studies. In rats, there was a gender difference in exposure to tovorafenib, with female rats having exposure approximately 2-fold higher than male rats; in monkeys, there were no significant gender differences in exposure.
</td></tr>
<tr><td>Distribution</td><td></td></tr>
<tr><td>Quantitative whole-body autoradiography in male Long Evans rats after a single oral administration of [14C]-tovorafenib (Study: 96N-1209)</td><td>Tissue distribution was evaluated in male LE rats following a single oral administration of 5.23 mg/kg of [^{14}C]tovorafenib (189 µCi/mg). Quantitative whole-body radiography was evaluated for up to 72 hours postdose.
[^{14}C]-tovorafenib was well distributed into rat tissues at 0.5 hours through 72 hours postdose. Tissue concentrations declined steadily over the course of the study and most concentrations were near or below the lower limit of quantitation, 0.009 µg-Eq/g) at 72 hours. The highest concentrations of tovorafenib-derived radioactivity among all tissues were at 1 hour postdose in the following tissues: small intestine, adrenal gland, liver, esophagus, kidney cortex, adipose brown, stomach, kidney medulla, cecum, pancreas, Harderian gland, eye uveal tract, salivary gland, and heart.
The C_{max} of tovorafenib-derived radioactivity in brain ranged from 0.791 to 1.03 across the cerebellum, cerebrum, and medulla, with T_{max} in brain occurring between 1- and 4-hours postdose. Measurable concentrations of [^{14}C]-tovorafenib were present in the brain tissues up to 12 hours after dosing. The brain:plasma AUC ratio of tovorafenib-derived radioactivity was approximately 0.57, indicating that tovorafenib-derived radioactivity penetrated the blood-brain barrier.</td></tr>
</table>

Type of Study	Major Conclusions
	 The blood:plasma ratio of tovorafenib-derived radioactivity in rat was 1.03, suggesting distribution of radioactivity to red blood cells.
Metabolism	
Identification of tovorafenib metabolites in rat plasma, urine, bile and fecal samples (studies: PD09-30 and MLN2480-11638)	Tovorafenib undergoes oxidative metabolism mediated by aldehyde oxidase and several CYP isoforms. Overall, the metabolic profiles of tovorafenib in isolated hepatocytes from rats and cynomolgus monkeys, but not dogs, were comparable to humans and no unique in vitro human metabolites were detected. *In vivo*, tovorafenib was extensively metabolized in rats following IV administration, with < 3% of the dose eliminated as unchanged drug in bile or urine. The major biotransformation pathways of [^{14}C]tovorafenib were hydrolysis of the thiazole carboxamide moiety (M10), oxidative N-dealkylation of the pyrimidine carbamoyl moiety (M6), and a combination of these 2 pathways (M9). Minor metabolites observed were a result of oxidation (M3, M15), N-acetyl cysteine conjugation (M5), reduction of M6 (M13), oxidative de-chlorination of M13 (M11), and further glucuronidation of M3, M11, and M13.
Excretion	
[^{14}C]-tovorafenib excretion and mass balance of radioactivity in intact and bile-duct cannulated rats following a single oral dose (Study: TAK-R3401)	In the mass balance study in rats using radiolabeled [^{14}C]-tovorafenib, approximately 17.2%, 26.3%, and 52.2% of radioactivity was excreted in urine, bile, and feces, respectively; approximately 20.7% and 76.1% of radioactivity was excreted in urine and feces in intact rats.  Biliary-fecal excretion was identified as the major elimination pathway.

Source: Applicant-provided table.

ADME = absorption, distribution, metabolism, and excretion; AUC = area under the concentration-time curve; CL = clearance; C_{max} = maximum plasma concentration; GLP = Good Laboratory Practice; IV = intravenous; LE = Long Evans; PK = pharmacokinetics; QD = once every other day; $t_{1/2}$ = half-life; T_{max} = time to maximum plasma concentration; Vss = volume of distribution at steady state; Vz = volume of distribution in the terminal state.

The FDA's Assessment

The FDA generally agrees with the Applicant's conclusions on pharmacokinetics, with notable exceptions below. Tovorafenib bound comparably to α1-acid glycoprotein at 10 µM (39%) and 1 µM (42%). Following exposure of a single oral dose of [^{14}C]-tovorafenib in rats, distribution to brain tissue was ≤1.0 µg equiv/g at Tmax. The brain:plasma AUC ratio of radiolabeled tovorafenib in cerebellum, cerebrum, and medulla was 0.57, 0.54, and 0.67, respectively.

5.5. Toxicology

5.5.1. General Toxicology

Applicant's Position

The nonclinical assessment program included repeat-dose oral toxicity studies with durations of treatment up to 3 months in Sprague-Dawley rats and cynomolgus monkeys in accordance with ICH S9 for an anticancer drug. The Sprague Dawley rat and cynomolgus monkey were chosen as the toxicology species for tovorafenib based on comparison of metabolite profiles generated by isolated hepatocytes from mice, rats, dogs, rabbits, cynomolgus monkeys, and humans. The rat and monkey most closely aligned with the metabolic profile of humans. Further, monkeys and rats were shown to be sensitive to tovorafenib toxicity in early dose ranging toxicology and/or PK studies. Additionally, systemic exposures of tovorafenib in dogs were several-fold lower than in cynomolgus monkeys. Toxicokinetic measurements were performed for most of the repeat dose toxicity studies, with validated bioanalytical methods utilized for the GLP studies. Additional- evaluations in the nonclinical toxicology program for tovorafenib included a battery of *in vitro* and *in vivo* genotoxicity studies as well as reproductive and developmental toxicity studies that included assessments on fertility, early embryonic development and embryo-fetal development in rats. The nonclinical safety assessment program for tovorafenib also incorporated GLP safety pharmacology studies including *in vitro* evaluation of the hERG potassium channel, CNS and respiratory system assessments in rats, and cardiovascular system evaluation in dogs and monkeys.

The formulations used in the toxicity studies were 100% polyethylene glycol 400 for monkeys and 1% sodium carboxymethylcellulose with 0.2% Tween® 80 (ie, polysorbate 80) in water for rats. Oral administration of tovorafenib was used for all toxicity studies to align with the intended commercial use of the drug product. Tovorafenib is to be dosed orally once weekly (QW) until disease progression or unacceptable toxicity.

Repeat-dose pivotal toxicity studies are shown in Section 19.3, Table 57.

The FDA's Assessment

In general, the FDA agrees with the Applicant's assessment of the repeat-dose toxicology studies, except for the Applicant's 3-month monkey histopathology data listed in Applicant table 29. Rats were treated once every 2 days with 0, 50, 150, or 500 mg/kg of tovorafenib for 3 months with no drug-related mortalities. Monkeys were treated once every 2 days with 0, 3, 10, or 20 mg/kg of tovorafenib. Due to excessive toxicity, both male and female monkeys dosed with 10 or 20 mg/kg were only treated for 2 months, with death rates of 60% (3/5) and 40% (2/5), respectively. Clinical signs in moribund monkeys included lethargy, GI toxicity, weakness, hypothermic, pale mucous membranes, body weight loss, and dehydration. Cause of death in monkeys was anemia and bone marrow suppression. Tovorafenib led to decreased body weight gain in rats (up to 15%) and body weight loss in surviving monkeys (up to 12%) which correlated with decreased food consumption in both species. There were several dose-dependent changes in hematology parameters in both rats and monkeys that were indicative of anemia and bone marrow suppression, all of which recovered after the recovery period in surviving animals. Mild changes in serum chemistry parameters occurred in both species without any histopathological correlates in corresponding tissues. Note that the Applicant did not include the early euthanasia animals in the data analysis for the 3-month monkey study hematology or clinical chemistry findings listed in applicant table 29; however, the results in early death animals were similar to surviving animals.

Target organs in the rat included epididymis, testis, ovary, thyroid gland, thymus, lymph nodes, and spleen as listed in the applicant table 29. Additional target organs identified by the FDA in the rat were bone (femur), bone marrow, and pancreas, and additional findings in spleen include dose-dependent increases in pigmented macrophages in the red pulp (minimal to mild). For the rat histopathology, findings in bone, bone marrow, pancreas, and male reproductive organs recovered but were still present in ovaries, thyroid gland, lymph nodes, and spleen by the end of the recovery period. Testes organ weights were still decreased in rats at the 150 and 500 mg/kg doses but without microscopic correlates. Of note, heart weights were significantly increased at the end of the dosing period in female rats dosed at 500 mg/kg with increases ranging from 34.9 to 44.1% of the control values but without any microscopic correlates. These findings were still apparent in female rats at 500 mg/kg (10.9 to 20.4% of the control values) with additional findings of increased heart weight in female rats at 150 mg/kg ranging from 13.6 to 18.6% of controls. For the 3-month monkey study, the Applicant did not include the histopathology from the early death animals and several findings in the terminal necropsy animals listed in the study report in applicant table 29; thus, a comprehensive table with all target organs was added by the FDA (see Table 6). Findings in the esophagus and thyroid of the monkeys did not recover after a 4-week recovery period. Exposure in female rats was approximately 1.6 to 2.2-fold higher for Cmax and AUC compared to male rats at every dose level. Exposure in the monkeys was similar between males and females.

A 4-week study in rats treated with tovorafenib (BIIB024) with the same doses and schedule as the 3-month study showed similar hematological findings indicating anemia and bone marrow suppression. New findings in the 3-month study included male reproductive organs. Potential bone resorption was noted in the 4-week study based on clinical chemistry assessments and findings of hemorrhage (medullary cavity; moderate) in the femur occurred in 10% of males at the 500 mg/kg dose. In addition, hemorrhage (diaphysis) was noted in 20% of females dosed at 500 mg/kg in the 3-month study indicating long bone is a potential target organ of tovorafenib. Femur samples were not evaluated in the low or mid dose animals in the 3-month study. Similarly, females had 2- to 3-fold higher exposure to tovorafenib in the 4-week study compared to males. In a 4-week monkey study, animals were treated with the same dose and schedule as the 3-month study, but no mortalities occurred. The mortalities in the 3-month monkey study occurred during Weeks 7 to 9. Similar toxicities and target organs were noted for the monkeys in both studies. Full review of the 4-week studies was conducted under IND 108340.

The clinical team noted concerns about hemorrhage based on safety data from the clinical study reports. Findings of hemorrhage in the rats included thymus, mesenteric and submandibular lymph nodes, and bone (femur) in the 4-week study, and bone (femur, tibia, sternum), ovary, and liver in the 3-month study. Finding of hemorrhage in the monkeys included esophagus and colon in the 4-week study and rectum, thyroid, lymph node, and uterus in the 3-month study.

Table 6. 3-Month Monkey Histopathology

Dose (mg/kg)		0 mg/kg		3 mg/kg		10 mg/kg		20 mg/kg	
Sex		M	F	M	F	M*	F#	M*	F#
# animals (main, recovery)		4/2	4/2	4/2	4/2	4/2	4/2	4/2	4/2
Bone marrow									
Decreased hematopoiesis	Minimal	-	-	1	-	-	-	-	-
Increased myeloid to erythroid ratio	Minimal	-	-	2	1	-	2	-	-
	Mild	-	-	-	-	-	1	-	1
	Moderate	-	-	-	-	-	-	1	1
Atrophy, femur, adipose tissue, serous	Moderate	-	-	-	-	-	-	-	1
Esophagus									
Degeneration, epithelial	Minimal	-	-	-	-	1	-	-	1
	Mild	-	-	-	-	-	-	-	1
Erosion	Minimal	-	-	-	-	-	-	-	2
Hemorrhage, submucosal	Minimal	-	-	-	-	-	-	-	1
Inflammation, mixed cell, submucosal	Mild	-	-	-	-	2	-	-	2
Infiltration, mononuclear cell; submucosal	Minimal	-,2	-,1	-	-	1,1	-,2	-,1	-,1
	Mild	-	-	-	-	-	-	-,1	1
Edema, submucosal	Mild	-	-	-	-	-	-	-	1
Salivary gland, sublingual									
Inflammation, mixed cell	Minimal	-	-	-	-	-	2	-	2
	Mild	-	-	-	-	-	-	-	1

Dose (mg/kg)		0 mg/kg		3 mg/kg		10 mg/kg		20 mg/kg	
Sex		M	F	M	F	M*	F#	M*	F#
# animals (main, recovery)		4/2	4/2	4/2	4/2	4/2	4/2	4/2	4/2
Vacuolation	Minimal	-	-	-	-	-	-	-	1
Adrenal gland									
Depletion, zona fasciculata	Minimal	-	-	-	-	-	2	-	1
Thyroid									
Depletion; colloid	Minimal	-,1	-,1	-	-	-	-,1	-,1	-,2
	Mild	-	-	-	-	-	-	-	2
Infiltration, mononuclear cell	Minimal	-,1	-,1	-	-	1,1	-	-	-,2
	Mild	-	-	-	-	-	-	-	1
Large intestine, colon									
Infiltration, eosinophilic	Minimal	-	-	-	-	-	-	1	1
Erosion	Mild	-	-	-	-	-	1	-	-
	Moderate	-	-	-	-	-	1	-	-
Inflammation, neutrophilic	Minimal	-	-	-	1	1	-	-	-
	Mild	-	-	-	-	-	-	-	1
	Marked	-	-	-	-	-	1	-	-
Hemorrhage	Mild	-	-	-	-	1	-	-	-
Large intestine, cecum									
Erosion	Minimal	-	-	-	-	-	1	-	-
Inflammation, neutrophilic	Minimal	-	-	-	-	-	1	-	-
	Moderate	-	-	-	-	-	1	-	-
Edema	Moderate	-	-	-	-	-	1	-	-
Infiltration, eosinophilic	Minimal	-	-	-	-	1	-	1	1
Large intestine, rectum									
Erosion	Mild	-	-	-	-	-	1	-	-
	Moderate	-	-	-	-	-	1	-	-
Inflammation, neutrophilic	Minimal	-	-	-	-	1	1	-	-
	Mild	-	-	-	-	-	-	-	1
	Moderate	-	-	-	-	-	1	-	-
	Marked	-	-	-	-	-	1	-	-
Accumulation, macrophage submucosal	Mild	-	-	-	-	-	1	-	-
Abscess; crypt	Minimal	-	-	-	-	-	1	-	-
Liver									
Infiltration, mononuclear cell	Minimal	-	-	-	-	-	2	-	-
Lymph node, mandibular									
Accumulation, macrophage, subcapsular sinus	Minimal	-	-	-	-	-	2	-	1
Infiltration, neutrophilic	Minimal	-	-	-	-	-	1,1	-	-
Lymph node, mesenteric									
Accumulation; macrophage, medullary sinus	Minimal	-	-	-	-	-	1,1	-	1
Edema	Mild	-	-	-	-	-	1	-	-
Ovary									
Mineralization	Minimal	-	1	-	4	-	2	-	1
Skin									
Inflammation, mixed cell	Severe	-	-	-	-	-	1	-	-
Hyperplasia; epidermal	Mild	-	-	1	-	-	-	-	-
Stomach									

Dose (mg/kg)		0 mg/kg		3 mg/kg		10 mg/kg		20 mg/kg	
Sex		M	F	M	F	M*	F#	M*	F#
# animals (main, recovery)		4/2	4/2	4/2	4/2	4/2	4/2	4/2	4/2
Vacuolation; mucosal	Minimal	-	-	-	-	-	1	-	-
	Mild	-	-	-	-	-	-	-	1
Atrophy, mucosal	Mild	-	-	-	-	-	1	-	-
Small intestine, duodenum									
Infiltration, eosinophilic	Minimal	-	-	-	-	-	-	-	1
Thymus									
Atrophy	Minimal	-	-	-	1	-	1	-	1
	Mild	-	-	-	-	-	-	1	-
	Moderate	-	-	-	-	-	1	-	1
	Marked	-	-	-	-	-	2	-	-
Vagina									
Inflammation, mononuclear cell	Minimal	-	1,1	-	-	-	1	-	3,1

Source: Reviewer-generated table.

* Necropsy Day 72.

Necropsy Day 70; includes early euthanasia monkeys Days 47, 61, 63. All others necropsy Day 92 3 mg/kg. Recovery necropsy Days 100 or 98 (no low dose recovery animals).

5.5.2. Genetic Toxicology

Applicant's Position

Tovorafenib was negative in both a non-GLP compliant screening and GLP-compliant Ames bacterial reverse mutation assay, indicating that tovorafenib is not mutagenic.

Tovorafenib was negative in the rat bone marrow micronucleus assay at doses up to 2000 mg/kg (Report P024-08-17). Tovorafenib was also negative for inducing chromosomal aberrations in cultured human lymphocytes without metabolic activation (all concentrations) and was negative with metabolic activation (S9) at ≤ 172 µg/mL (initial assay) and ≤ 150 µg/mL (confirmatory assay) (Report P024-08-16). Tovorafenib was positive in the chromosomal aberration assay in the presence of S9 at a single, high precipitating dose in the initial assay (200 µg/mL) and the confirmatory assay (245 µg/mL) (Report P024-08-16). Any biological relevance of this single positive result in the presence of a drug precipitate is unclear. Based on a weight of evidence evaluation, tovorafenib is not expected to be clastogenic based on the results of the rat micronucleus and chromosomal aberration assays (Table 7).

Table 7. Genetic Toxicology Studies

Study Number/ Study Type/ GLP Compliant	Study Title	Test System	Key Findings	eCTD Location
P024-07-02/ Reverse mutation in bacterial cells/ No	BSK-1355 and BSK-1369 Bacterial Mutation Test (Screening Version)	phenobarbital and 5,6-benzoflavone induced male Sprague-Dawley rat liver S9 mix	**Cytotoxic Effects:** at 5000 µg/plate in TA1535 and WP2 uvrA, ≥ 158 µg/plate in TA1537, and TA100, ≥ 1581 µg/plate in TA98, without metabolic activation and at ≥ 500 µg/plate in TA1537 and TA100 and ≥ 1581 µg/plate in TA98 with metabolic activation. **Genotoxic Effects**: none	4.2.3.3.1
P024-08-15/ Reverse mutation in bacterial cells/ Yes	Bacterial Reverse Mutation Assay with a Confirmatory Test	Aroclor™ 1254 induced male Sprague-Dawley rat liver S9 mix	**Cytotoxic Effects**: Cytotoxicity at ≥ 1000 µg/plate in TA100 without metabolic activation and at 5000 µg/plate in WP2 uvrA and ≥ 667 in TA100 with metabolic activation in a separate dose range-finding assay. **Genotoxic Effects**: none	4.2.3.3.1
P024-08-16 Test for induction of chromosomal aberrations/ Yes	Chromosomal Aberrations in Cultured Human Peripheral Blood Lymphocytes	Aroclor™ 1254 induced male Sprague-Dawley rat liver S9 mix	**Cytotoxic Effects**: ≥ 50% mitotic index reduction seen at ≥ 350 µg/mL without and with S9 in initial assay and ≥ 40 µg/mL without S9 and 250 µg/mL with S9 in confirmatory assay **Genotoxic Effects**: 200 and 245 µg/mL with metabolic activation	4.2.3.3.1
P024-08-17/ Test for induction of micronuclei/ Yes	In Vivo Rat Bone Marrow Micronucleus Assay	Rat/Sprague-Dawley Polychromatic erythrocytes (PCEs)	Toxic/Cytotoxic Effects: none. Genotoxic Effects: none.	4.2.3.3.2

Source: Applicant-provided table.

Abbreviations: eCTD = electronic common technical document; GLP = Good Laboratory Practice.

The FDA's Assessment

The FDA generally agrees with the Applicant's conclusions that tovorafenib was not genotoxic in the performed genotoxicity studies. Tovorafenib was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay and was not clastogenic in an in vivo bone marrow micronucleus

assay in rats. Tovorafenib induced chromosomal aberrations in cultured human lymphocytes with metabolic activation at 200 and 245 µg/mL in the definitive and follow-up assay, respectively; however, due to precipitation at these doses and the lack of concentration dependent effect, and that tovorafenib was not clastogenic in the in vivo micronucleus assay, the overall weight of evidence suggests that tovorafenib is not genotoxic.

5.5.3. Carcinogenicity

Applicant's Position

Carcinogenicity studies are in progress, as a post-marketing requirement, per Food and Drug Administration (FDA) feedback from the Type B (End of Phase 1) Meeting held on 27 April 2020. The carcinogenicity studies (b) (4)

The FDA's Assessment

The FDA agrees that carcinogenicity studies in mice and rats are warranted to determine the risk of carcinogenicity from tovorafenib for chronic use given the long-life expectancy of the proposed population. Two nonclinical PMRs for rodent carcinogenicity studies were communicated to the Applicant. The Applicant submitted a special protocol assessment for a (b) (4) on July 7, 2023, under IND 108340 for DAY101. The protocol was reviewed by the FDA, including the Executive Carcinogenicity Assessment Committee with recommendations sent to the Applicant on August 17, 2023.

5.5.4. Reproductive and Developmental Toxicology

Applicant's Position

The ovary (increased size and/or numbers of corpora hemorrhagicum and hemorrhage after 1 month of Q2D dosing with findings of cystic follicles, decreased corpora lutea, and interstitial cell hyperplasia after 3 months of Q2D dosing), vagina (increased thickness of the vaginal mucosa), testes (tubular degeneration/atrophy), and epididymis (reduced luminal sperm) were noted as target organs in repeat-dose toxicity studies in the rat. The vaginal findings in rats appeared to occur secondarily to the ovarian effects. The ovarian findings were present at all doses, suggestive of reproductive senescence, and were still present after 4 and 2 weeks of recovery in female rats dosed for 1 and 3 months Q2D, respectively. Microscopic effects on the reproductive system in male rats in the 3-month repeat-dose toxicity study included tubular degeneration/atrophy in the seminiferous tubules of the testes and reduced luminal sperm in the epididymis at ≥ 50 mg/kg Q2D, which correlated with dose-related decreases in organ weights of both tissues. Although testes weights at ≥ 150 mg/kg were lower (dose-related) than controls at the end of the 2-week recovery period, there were no microscopic changes in either the testes or epididymis at recovery. Reproductive organ findings were not observed in the monkey.

A GLP preliminary, dose range-finding embryo-fetal development study of tovorafenib in rats by oral gavage has been completed. Tovorafenib was administered QD by oral gavage to timed-mated female rats at 37.5, 75, or 150 mg/kg/day from gestational day (GD) 7 through GD 17. All rats survived to scheduled euthanasia on GD 21. There were no clinical observations observed at any dose level.

Overall, mean maternal body weight gain was 20%, 20%, and 15% of controls in the 37.5-, 75-, and 150-mg/kg/day dose groups for the interval of GD 7 to 21, respectively. The reduced mean maternal body weight gains observed in the tovorafenib-treated groups were considered secondary to increases in early resorptions that resulted in total litter loss at all dosages. Based on this outcome, the NOAEL for embryo-fetal development could not be established. FDA agreed that further embryofetal studies were not required.

Fertility was evaluated in Crl:CD(SD) male and female rats administered tovorafenib orally at dose levels of 0, 37.5, 75, and 150 mg/kg/day. There were no tovorafenib related effects on any male reproductive parameters, including mating or fertility, sperm motility and density, or male reproductive organ weights. In females, there were tovorafenib-related effects on fertility parameters at all dose levels, including fewer pregnancies, corpora lutea, implantation sites, and live embryos. Additionally, post-implantation loss was increased in tovorafenib treated females. The NOAEL for male reproductive performance was 150 mg/kg/day, and the NOAEL for female reproductive performance was less than 37.5 mg/kg/day.

Table 8 outlines the non-pivotal reproductive and developmental toxicity studies. Table 9 outlines the fertility and early embryonic development study.

Table 8. Reproductive and Developmental Toxicity: Non-Pivotal Studies

Report Title: A Preliminary Dose Range-Finding Embryo-fetal Development Study of DAY101 by Oral (Gavage) in Rats			**Test Article:** Tovorafenib	
Design similar to ICH 4.1.3? Yes[1]	**Duration of Dosing:** GD7 to GD17		**Study No.:** 20282867	
Species/Strain: Rat/Sprague-Dawley	**Day of Mating:** GD 0			
Initial Age: 63 to 79 days old	**Day of C-Section:** GD 21		**Location in CTD:** 4.2.3.5.2	
Date of First Dose: 12 Jan 2021	**Method of Administration:** Oral gavage			
Special Features: none	**Vehicle/Formulation:** 1% NaCMC with Tween 80 in water		**GLP Compliance:** Yes	
No Observed Adverse Effect Level:	**F_0 Females:** 150 mg/kg/day		**F_1 Litters:** Not determined (<37.5 mg/kg)	
Dose (mg/kg)	**0 (Control)**	**37.5**	**75**	**150**
Dams/Does: Toxicokinetics: AUC_{0-24}	NA	57,500	59,800	87,800

Report Title: A Preliminary Dose Range-Finding Embryo-fetal Development Study of DAY101 by Oral (Gavage) in Rats			**Test Article:** Tovorafenib	
No. Pregnant	8	8	8	8
No. Died or Sacrificed Moribund	0	0	0	0
No. Aborted or with Total Resorption of Litter	0	8	8	8
Clinical Observations	-	-	-	-
Necropsy Observations	-	-	-	-
Body Weight, Day 21 (%)[2,3]	367.6 g	-27.6	-29.2	-28.0
Food Consumption, GD 7 to GD 21 (%)[2]	22.3 g/animal/day	-17.3	-25.4	-20.4
Mean No. Corpora Lutea	12.3	12.9	13.4	13.0
Mean No. Implantations	11.3	11.6	12.4	11.1
Mean % Preimplantation Loss	7.88	8.00	6.25	12.45
Litters:				
No. Litters Evaluated	8	0[4]	0[4]	0[4]
No. Live Fetuses	11.1	0	0	0
Mean No. Resorptions	0.1	11.6	12.4	11.1
No. of Litters with Dead Fetuses	0	0	0	0
Mean % Postimplantation Loss	0.96	100	100	100
Mean Fetal Body Weight (g)	5.947	ND	ND	ND
Fetal Sex Ratios (% males)	53.78	ND	ND	ND
Fetal Anomalies:				
Gross External	None detected	ND	ND	ND
Visceral Anomalies	None detected	ND	ND	ND
Skeletal Anomalies	Not evaluated	ND	ND	ND
Total Affected Fetuses (Litters)	0 (0)	ND	ND	ND

Source: Applicant-provided table.

[1] Similar to a preliminary EFD study more so than definitive EFD study; less dams/group than required for a definitive study and no fetal skeletal evaluations performed.

[2] For controls, group means are shown. For treated groups, percent differences from controls are shown.

[3] Lower body weight in tovorafenib-treated dams was due to total resorption of litters.

[4] Due to 100% resorptions, no litters were available for evaluation from tovorafenib-treated dams.

Abbreviations: AUC = area under the concentration-time curve; EFD = embryo-fetal development; GD = gestation day; NaCMC = carboxymethyl cellulose sodium salt; ND = no data.

Table 9. Reproductive and Developmental Toxicity: Fertility and Early Embryonic Development to Implantation

Report Title: A Fertility and Early Embryonic Development Study of DAY101 Administered by Oral Gavage in Male and Female Rats				**Test Article:** Tovorafenib
Design similar to ICH 4.1.1? Yes	**Duration of Dosing:** Male: 64 days beginning 29 days before mating; Female: 15 days before cohabitation through GD 6			**Study No.:** 20314033
Species/Strain: Rat/Sprague-Dawley	**Day of Mating:** GD 0			**Location in CTD:** 4.2.3.5.1
Initial Age: Male: 131 days; Female: 82 days	**Day of C-Section:** GD 13			
Date of First Dose: 27 Sep 2021 (females); Date 07 Nov 2021 (males)	**Method of Administration:** Oral gavage			**GLP Compliance:** Yes
Special Features: Treated females paired with untreated males; treated males paired with untreated females; sperm analysis	**Vehicle/Formulation:** 1% NaCMC with 0.2% Tween® 80 in water			
No Observed Adverse Effect Level:				
F_0 Males: 150 mg/kg/day				
F_0 Females: 150 mg/kg/day (for systemic toxicity); not determined for reproductive performance				
F_1 Litters: not determined (<37.5 mg/kg)				
Dose (mg/kg)	**0 (Control)**	**37.5**	**75**	**150**
Treated Males				
Toxicokinetics	NA	ND	ND	ND
No. Evaluated	22	22	22	22
No. Died or Sacrificed Moribund	0	0	1[1]	0
Clinical Observations	-	-	-	-
Necropsy Observations	-	-	-	-
Body Weight	-	-	-	-
Body Weight Gain (Day 29 to Day 64) (%)[2]	45.4 g	-25*	-29**	-36**
Food Consumption	-	-	-	-
Mean No. Days Prior to Mating	2.5	2.9	2.4	2.4
No. of Males that Mated with untreated females	22	22	22	22
No. of Fertile Males	18	20	20	20
Sperm motility and density	-	-	-	-
Untreated females mated with treated males	-	-	-	-
Treated Females				

Report Title: A Fertility and Early Embryonic Development Study of DAY101 Administered by Oral Gavage in Male and Female Rats				**Test Article:** Tovorafenib
Toxicokinetics: AUC	NA	57,500[3]	59,800[3]	87,800[3]
No. Evaluated	22	22	22	22
No. Died or Sacrificed Moribund	0	0	0	0
Clinical Observations	-	-	-	-
Necropsy Observations	-	-	-	-
Premating Body Weight (%)[2]	281.2 g	-0.7	-1.1	-2.7
Gestation Body Weight (%)[2]	347.9 g	-4.8*	-4.8*	-5.3⁑
Premating Food Consumption (%)[2]	19.8 g/animal	-6.2	-10.2*	-13.7⁑
Gestation Food Consumption (%)[2]	23.10 g/animal	-3.70	-6.87	-5.85
Mean No. Estrous Cycles/14 days	-	-	-	-
Mean No. Days Prior to Mating	2.2	2.0	2.3	2.7
No. of Females Sperm Positive	22	22	22	22
No. of Pregnant Females	22	20	14**[4]	18
No. Aborted or with Total Resorption of Litter	0	0	0	0
Mean No. Corpora Lutea	18.4	15.0^	14.9^^	12.6^^
Mean No. Implantations	15.5	12.9^	12.4^^	10.4^^
Mean % Preimplantation Loss	14.07	14.02	14.80	19.42
Mean No. Live Conceptuses	14.7	7.1^^	4.9^^	5.4^^
No. Dead Conceptuses	0.8	5.8^^	7.4^^	4.9^^
Postimplantation Loss - Embryo	5.26	44.86^^	65.51^^	53.47^^

Source: Applicant-provided table.

* significantly different than the corresponding vehicle control, P ≤ .05 ANOVA and Dunnett

⁑ significantly different than the corresponding vehicle control, P ≤ .01 ANOVA and Dunnett

** significantly different than the corresponding vehicle control, P ≤ .01 Fisher's exact test

^ significantly different than the corresponding vehicle control, P ≤ .05 Kruskal-Wallis and Dunn

^^ significantly different than the corresponding vehicle control, P ≤ .01 Kruskal-Wallis and Dunn

– No noteworthy findings

[1] Euthanized Day 46 due to gavage error

[2] For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

[3] Data from the embryofetal development study of dams dosed on GD 7 through GD 17 (study 20282867)

[4] Statistical significance is for female fertility index and female pregnancy index (both are 63.3%; 14/22)

Abbreviations: GD = gestation day; NA = not applicable; ND= no data.

The FDA's Assessment

The FDA generally agrees with the Applicant's assessment of the effects of tovorafenib on reproductive and developmental toxicity with additional pertinent details below. In the 3-month monkey general toxicology study, the ovaries were target organs with findings of increased incidences of mineralization at doses ≥3 mg/kg.

In the Preliminary Dose Range-Finding Embryo-Fetal Development Study of DAY101 by Oral (Gavage) in Rats, the percent food consumption from GD 7 to 21 of the 75 mg/kg group was 24.5% (not 25.4%). In the Reproductive and Development Toxicity-Fertility and Early Embryonic Development to Implantation study, females were dosed for 14 days (not 15) prior to cohabitation with untreated males, and through GD 6. Finally, the date of administration of the first dose of DAY101 to male rats was November 8 (not 7), 2021. These discrepancies have no impact on the interpretation of either study. Tovorafenib given to pregnant rats during organogenesis at doses ≥37.5 mg/kg/day caused embryofetal toxicity in the form of 100% post-implantation loss. The maternal exposure at 37.5 mg/kg/day was approximately 0.8-fold the human exposure at the recommended clinical dose of 380 mg/m^2 once weekly based on AUC.

5.5.5. Other Toxicology Studies

Applicant's Position

No studies were conducted with tovorafenib.

The FDA's Assessment

The FDA agrees that no additional toxicology studies were conducted.

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6. Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment

Major review issues for the Clinical Pharmacology team included the appropriateness of the [redacted] (b) (4) dosage and the determination of the drug-drug interaction (DDI) potential of tovorafenib as a victim and a perpetrator.

The Applicant's proposed dosing regimen is [redacted] (b) (4) mg/m^2 orally QW (not to exceed 600 mg) with or without food in patients 6 months of age and older with relapsed or refractory (R/R) pediatric low-grade glioma (pLGG) harboring a BRAF fusion or rearrangement, or BRAF V600 mutation. Tovorafenib is formulated as tablets (NDA 217700) and powder for oral solution (PFOS, NDA 218033). The tablets and PFOS exhibited similar exposures at the same dosage. [redacted] (b) (4)

[redacted] (b) (4) the FDA recommends a dosage of 380 mg/m^2 orally QW (not to exceed 600 mg), with or without food, based on the following review considerations:

- Efficacy: There were no clinically significant differences in exposure-response (E-R) relationships for overall response rate (ORR) observed over the actual dose range of 290 to 476 mg/m^2 evaluated in Arm 1 of FIREFLY-1.
- Safety: The average exposure achieved with 420 mg/m^2 QW in pediatric patients is approximately 33% greater than that of the adult maximum tolerated dose (600 mg QW). Positive trends of E-R relationships were observed for Grade ≥2 adverse events (AEs) and Grade ≥3 AEs.
- Dosing variability: [redacted] (b) (4) dose bands showed heterogeneous variability across the BSA subgroups. This led to dosing variability in FIREFLY-1 such that the FDA's recommended dose of 380 mg/m^2 is within the dose range evaluated in FIREFLY-1. Therefore, data from FIREFLY-1 was sufficient to establish efficacy and safety at the FDA's recommended dosage.

In addition, the current submission inadequately addressed tovorafenib's potential for DDIs. There were no clinical DDI studies conducted for tovorafenib. Furthermore, the Applicant's PBPK modeling was insufficient to evaluate tovorafenib as a victim or a perpetrator. Therefore, three PMRs and one PMC were issued, to evaluate tovorafenib with (1) a strong inhibitor of CYP2C8, (2) a strong or moderate inducer of CYP2C8, (3) substrates of CYP3A4, CYP2C8, CYP1A2, CYP2B6, CYP2C9, and CYP2C19, and (4) a substrate of BCRP.

6.1.1. Recommendations

The Office of Clinical Pharmacology has reviewed the information submitted in NDA 217700 and NDA 218033 and recommends approval pending satisfactory review by other disciplines and provided the Applicant and the FDA reach agreement regarding the labeling language. Table 10 summarizes the key review issues and recommendations.

Table 10. Key Clinical Pharmacology Issues and Recommendations

Review Issue	Recommendations and Comments
Pivotal and supportive evidence of effectiveness	The primary evidence of effectiveness is the ORR observed in Arm 1 of FIREFLY-1 (See Section 8).
General dosing instructions	(b) (4) FDA's recommended dosage is 380 mg/m^2 orally QW (not to exceed 600 mg), with or without food, based on the following review considerations. Efficacy: There were no clinically significant differences in E-R relationships for ORR observed over the actual dose range of 290 to 476 mg/m^2 evaluated in Arm 1 of FIREFLY-1. Safety: The average exposure achieved with the 420 mg/m^2 QW dosage in pediatrics is approximately 33% greater than that of the adult maximum tolerated dose (MTD, 600 mg QW). Positive trends of E-R relationships were observed for Grade ≥2 AEs and Grade ≥3 AEs. Dosing variability: (b) (4) dose bands showed heterogeneous variability across the BSA subgroups. This led to dosing variability in FIREFLY-1 such that FDA's recommended dose of 380 mg/m^2 is within the dose range evaluated in FIREFLY-1. Therefore, data from FIREFLY-1 was sufficient to establish efficacy and safety at FDA's recommended dose.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Hepatic impairment: No dosage adjustment is recommended in patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1x to 1.5x ULN and any AST). The recommended dosage in patients with moderate-or-severe hepatic impairment has not been established (bilirubin > 1.5x to 3x ULN and any AST; bilirubin > 3x ULN and any AST, respectively). Renal impairment: No dosage adjustment is recommended in patients with mild-or-moderate renal impairment (eGFR ≥ 60

Review Issue	Recommendations and Comments
	mL/min/1.73 m^2; eGFR ≥ 30 to 59 mL/min/1.73 m^2, respectively). The recommended dosage in patients with severe renal impairment has not been established (eGFR 15 to 30 mL/min/1.73 m^2). Age: No clinically meaningful differences in tovorafenib's PK were detected based on age (1 to 94 years). The Applicant's proposed age cutoff was 6 months of age and older in the current indication. However, there was limited clinical and PK data in patients 6 months of age to 1 year of age. Considering a combined approach, based on the totality of the clinical and clinical pharmacology data reviewed by FDA, the recommended dosage of 380 mg/m^2 orally QW (not to exceed 600 mg), with or without food, is recommended in patients 6 months of age and older and is supported as follows: Unmet medical need in the proposed patient population extending down to patients 6 months of age and older (Section 8). Mitigation of potential safety concerns by close safety monitoring within the age group of 6 months of age to 1 year of age (Section 8). Adequate PK data from patients aged 1 year and older to allow estimation of the proposed dosage in patients 6 months of age to 1 year of age by using body size allometry in the popPK model, which accounted for PK differences across the evaluable age and BSA-based dosing. Consideration of supportive ontogeny knowledge for the main enzymes responsible for tovorafenib's metabolism (CYP2C8 and aldehyde oxidase (AO)). Supportive data show that CYP2C8-mediated metabolism is expected to be fully mature, although there is very limited information on the ontogeny of AO. Information on AO suggests that AO's activity may be reduced by 61% to 82% of the activity level in adults in patients 6 months of age and 12 months of age, respectively. Sex and race: No dosage adjustment is recommended based on sex or race (White, Black, and Asian). Genetic subpopulations: Responses were observed across BRAF alterations in FIREFLY-1 in patients with at least one measurable lesion at baseline based on RAPNO criteria (N=76). The proposed indication across these BRAF alterations seems appropriate based on the data.
Drug-drug interactions	Tovorafenib as a victim: Avoid coadministration with strong and moderate CYP2C8 inhibitors.

Review Issue	Recommendations and Comments
	Avoid coadministration with strong and moderate CYP2C8 inducers. <u>Tovorafenib as a perpetrator:</u> Avoid coadministration with CYP3A substrates, where minimal concentration changes may lead to serious therapeutic failures, and hormonal contraceptives. <u>Outstanding issues:</u> Tovorafenib is metabolized by CYP2C8 in vitro. A clinical drug-interaction study with a strong inhibitor of CYP2C8 will be conducted as a PMR. Tovorafenib is metabolized by CYP2C8 in vitro. A clinical drug-interaction study with a strong or moderate CYP2C8 inducer will be conducted as a PMC. In vitro, tovorafenib inhibits CYP2C8, CYP2C9, CYP3A4 and CYP2C19, induces CYP3A4, CYP2C8, CYP2B6 and CYP1A2, and has the potential to induce CYP2C9 and CYP2C19. Tovorafenib has the potential to cause drug interactions with substrates of these enzymes. A clinical drug-interaction study with substrates of these enzymes will be conducted as a PMR. Tovorafenib inhibits BCRP in vitro and has the potential to cause drug interactions with BCRP substrates. A clinical drug-interaction study with a BCRP substrate will be conducted as a PMR.
QTc assessment	At the recommended tovorafenib dosage of 380 mg/m^2 orally QW (not to exceed 600 mg), a mean increase in the QT interval > 20 milliseconds (ms) was not observed.
Bridge between the to-be-marketed and clinical trial formulations	Not applicable since FIREFLY-1 administered the to-be-marketed tablets and PFOS formulations.
Labeling	Overall, the proposed labeling recommendations are acceptable.

Source: Reviewer-generated table.

6.1.2. Post-Marketing Requirements and Commitments

The rationale and descriptions of PMRs and PMC are summarized in Table 11. Post-marketing studies are issued to address DDIs.

Table 11. Post-Marketing Requirements and Post-Marking Commitments Pertinent to Clinical Pharmacology

PMR/PMC	Rationale	Description
PMR	Tovorafenib is metabolized by CYP2C8 in vitro. Concomitant use of strong or moderate inhibitors of CYP2C8 may increase systemic concentrations of tovorafenib, leading to increased toxicity from tovorafenib.	Conduct a clinical pharmacokinetic trial of tovorafenib with a strong CYP2C8 inhibitor.
PMC	Tovorafenib is metabolized by CYP2C8 in vitro. Concomitant use of strong and moderate inducers of CYP2C8 may decrease plasma concentrations of tovorafenib, leading to decreased systemic exposures of tovorafenib.	Conduct a clinical pharmacokinetic trial of tovorafenib with a strong or moderate CYP2C8 inducer.
PMR	Tovorafenib inhibits CYP2C8, CYP2C9, CYP3A4, and CYP2C19 in vitro. Furthermore, tovorafenib induces CYP3A4, CYP2C8, CYP1A2, and CYP2B6 in vitro. Tovorafenib also has the potential to induce CYP2C9 and CYP2C19, due to the common induction mechanisms. The potential inhibition of tovorafenib may increase the systemic concentrations of substrate drugs, which may increase the potential toxicity of these substrate drugs. The potential induction effects of tovorafenib may decrease systemic concentrations of substrate drugs that are used in this patient population, which may reduce the efficacy of substrate drugs.	Conduct a clinical pharmacokinetic trial of tovorafenib on sensitive substrates of CYP3A4, CYP2C8, CYP1A2, CYP2B6, CYP2C9, and CYP2C19.
PMR	Tovorafenib inhibits BCRP in vitro. The potential inhibition of tovorafenib may increase the systemic concentrations of BCRP substrates, which may increase the potential toxicity of BCRP substrate drugs.	Conduct a clinical pharmacokinetic trial of tovorafenib with substrates of BCRP.

Source: Reviewer-generated table.

Abbreviations: PMC = post-marketing commitment; PMR = post-marketing requirement.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Applicant's Position

Comprehensive clinical pharmacology assessments of tovorafenib have been performed. These assessments included *in vitro* human biomaterial data, PK characteristics of tablet and powder for reconstitution (PfR) suspension formulations in humans (healthy participants, adult patients with cancer, and pediatric patients with cancer), relative bioavailability assessments of the tablet and PfR suspension formulations, intrinsic and extrinsic factors that may impact tovorafenib PK, drug interaction risk, QTc interval prolongation risk, and exposure-response (E-R) relationships. Taken together, overall clinical pharmacology assessments support the

appropriateness of tovorafenib [redacted] for the intended patient population.

The FDA's Assessment

The FDA generally agrees with the Applicant's position that the clinical pharmacology program supports the use of tovorafenib for the treatment of the currently recommended indication. [redacted] based on the FDA's clinical pharmacology and pharmacometrics reviews, [redacted] the FDA recommends 380 mg/m^2 orally QW (not to exceed 600 mg) as the optimized dosage, with or without food. For details on the recommended dosage, refer to Section 6.3.2.2 and Section 19.4.2.

The clinical pharmacology program for the current submission is supported by clinical studies with tovorafenib. These studies are summarized below:

- Study FIREFLY-1: The pivotal study that administered tovorafenib in patients with pLGG aged between 1 year to 25 years in Arm 1 and Arm 2.
- Study C28001: First-in-human, dose-escalation and expansion study of tovorafenib given QW or Q2D as monotherapy in adult patients.
- Study C28002: Dose-escalation and expansion study of tovorafenib given QW or Q2D as combination therapy in adult patients.
- Study [redacted] 205140: Relative bioavailability and food effect study in healthy adults that compared 3 groups: (1) the to-be-marketed tablets in fasted state, (2) the to-be-marketed PFOS in fasted state, and (3) to-be-marketed tablets in fed state.
- Study DAY101-103: Mass balance study in healthy adults that administered a single oral dose of 100 mg containing approximately 200 µCi of [^{14}C]-tovorafenib in the fasted state.
- Study PNOC014: A phase 1, dose-escalation study in patients aged 1 to <25 years. This was an investigator-led study and there was limited data from this study provided in the NDA.

A summary of tovorafenib's pharmacokinetic characteristics, based on the reviewer's assessment of the studies listed above, is as follows:

- Tovorafenib steady state maximum concentration (C_{max}) is 6.9 mcg/mL (CV 23%) and the area under the time concentration curve (AUC) is 508 mcg*h/mL (CV 31%) in pediatrics. Tovorafenib increases in a dose-proportional manner in adults. No clinically significant tovorafenib accumulation occurs in adults.
- Absorption: Tovorafenib median (minimum, maximum) time to achieve T_{max} is 3 hours (1.5 to 4 hours), following a single dose with tablets or for oral suspension, under fasted conditions in adults.

- Effect of Food: No clinically significant differences in tovorafenib C_{max} and AUC were observed following administration of tablets with a high-fat meal (approximately 859 total calories, 54% fat), but the T_{max} was delayed to 6.5 hours in adults.
- Distribution: Tovorafenib apparent volume of distribution is 60 L/m^2 (CV 23%) in pediatrics. Tovorafenib is 97.5% bound to human plasma proteins in vitro. The blood-to-plasma ratio was 2.73.
- Elimination: Tovorafenib terminal half-life is approximately 56 hours (CV 33%) and the apparent clearance is 0.73 L/h/m^2 (CV 31%) in pediatrics.
- Metabolism: Tovorafenib is primarily metabolized by aldehyde oxidase and CYP2C8 in vitro. CYP2C9, CYP2C19, and CYP3A metabolize tovorafenib to a minor extent in vitro. Following a single oral dose of radiolabeled tovorafenib, unchanged tovorafenib was the most abundant circulating component in plasma. Plasma metabolites were minor (<10% of total plasma radioactivity exposure). Of the plasma metabolites, the most abundant were oxidated DAY101 metabolites (M3 and M26) and the glucuronide conjugate of oxy-DAY101 glucuronide (M16). Metabolism of tovorafenib was mediated primarily by oxidation and, to a lesser extent, by amide hydrolysis.
- Excretion: Following a single oral dose of radiolabeled tovorafenib, 65% of the total radiolabeled dose was recovered in the feces (8.6% unchanged) and 27% of the dose was recovered in the urine (0.2% unchanged) in adults.

For details on tovorafenib's clinical pharmacology characteristics, refer to Section 6.3.1.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

(b) (4)

(b) (4)

The FDA's Assessment

(b) (4) The recommended alternative dosage of 380 mg/m^2 orally QW (not to exceed 600 mg) is supported by the clinical pharmacology and pharmacometrics reviews that concludes an improved benefit-to-risk profile over the 420 mg/m^2 dose. This included assessment of E-R relationships for efficacy and safety over the actual dose range evaluated in FIREFLY-1 and an analysis of the dosing variability in FIREFLY-1 (b) (4), as summarized here:

- Efficacy: There were no clinically significant differences in E-R relationships for ORR observed over the actual dose range of 290 to 476 mg/m^2 in Arm 1 of FIREFLY-1.
- Safety: The average exposure achieved with the 420 mg/m^2 QW dosage in pediatrics is approximately 33% greater than that of the adult MTD (600 mg QW). Positive trends of E-R relationships were observed for Grade ≥2 AEs and Grade ≥3 AEs, where the exposure mostly fell in the near-linear range of the E-R curves. This suggests that a small decrease in dose from 420 mg/m^2 to 380 mg/m^2 would improve the benefit-to-risk profile.
- Dosing Variability: (b) (4) dose bands showed heterogeneous variability across the BSA subgroups. This led to dosing variability in FIREFLY-1 such that FDA's recommended dose of 380 mg/m^2 is within the dose range evaluated in FIREFLY-1. Therefore, data from FIREFLY-1 was sufficient to establish efficacy and safety at the FDA's recommended dose.
- Pharmacological Activity: Similar pharmacological activity is anticipated between the 380 mg/m^2 and 420 mg/m^2 doses, based on the large margin of C_{avg} over in vivo EC_{50} (in vivo EC_{50} was derived using in vitro EC_{50}, unbound fraction, and brain-to-plasma ratio). For details on the dosage, refer to Section 6.3.2.2 and Section 19.4.2.
- Food Effect: Based on the clinical pharmacology review, the FDA agrees with the Applicant on administration of tovorafenib without regard to food. There was no clinically relevant effect of food on tovorafenib's exposures when tablets were taken with a standard high-fat meal versus the fasted condition. The to-be-marketed tablets and PFOS formulation were administered without regard to food in FIREFLY-1. For details, refer to Section 6.3.2.4.

6.2.2.2. Therapeutic Individualization

Applicant's Position

Based on population PK analyses, no therapeutic individualization is needed for the proposed indication based on demographic factors (age, gender, race, and ethnicity) or in specific populations (mild hepatic impairment or patients with renal impairment). No patients with severe renal impairment or severe hepatic impairment have been enrolled in clinical studies of tovorafenib.

In vitro data suggest that tovorafenib is a substrate of CYP2C8. It is recommended to avoid coadministration of tovorafenib with strong or moderate CYP2C8 inhibitors (b) (4) . Coadministration of tovorafenib with a moderate CYP2C8 inducer is predicted to decrease the exposure of tovorafenib and may decrease tovorafenib efficacy. Therefore, it is recommended to avoid coadministration of tovorafenib with strong or moderate CYP2C8 inducers. For more information, see Section 6.3.2.

The FDA's Assessment

Specific Populations

- The FDA agrees that no clinically relevant changes in tovorafenib's PK were detected based on age (1 to 94 years), sex, race (White, Black, and Asian), mild hepatic impairment, and mild-or-moderate renal impairment. The effects of moderate-or-severe hepatic impairment and severe renal impairment on tovorafenib's PK is unknown. PMRs to evaluate the effect of organ impairment on the PK of tovorafenib will not be issued, given that the recommended patient population is not expected to include subpopulations of patients with moderate-or-severe hepatic impairment or severe renal impairment.

Concomitant Medication Instructions (tovorafenib as a victim)

- The FDA agrees that tovorafenib is a substrate of CYP2C8 in vitro and recommends the avoidance of coadministration of strong or moderate CYP2C8 inhibitors and inducers. However, the Applicant's PBPK modeling of tovorafenib as a victim of CYP2C8 was inadequate. For details, refer to the PBPK assessment in Section 19.4.3. Therefore, post-marketing studies will be required to evaluate tovorafenib with a strong CYP2C8 inhibitor and a strong or moderate CYP2C8 inducer.

Concomitant Medication Instructions (tovorafenib as a perpetrator)

- The FDA recommends avoidance of certain substrates of CYP3A, as tovorafenib induces CYP3A. However, the magnitude of CYP3A induction could not be adequately characterized by the Applicant's PBPK modeling and simulation. Therefore, FDA recommends avoiding coadministration of tovorafenib with certain CYP3A substrates where minimal

concentration changes may lead to serious therapeutic failures, including hormonal contraceptives.

- In addition, tovorafenib's effects on other CYPs were uncertain. More specifically, tovorafenib inhibits CYP2C8, CYP2C9, CYP3A4, and CYP2C19 in vitro. Furthermore, tovorafenib induces CYP3A4, CYP2C8, CYP2B6, and CYP1A2 in vitro. Tovorafenib also has the potential to induce CYP2C9 and CYP2C19, due to the common induction mechanisms. The Applicant's PBPK modeling inadequately evaluated tovorafenib as a perpetrator of CYP3A4, CYP2C8, CYP1A2, CYP2B6, and CYP2C9. For details, refer to the PBPK assessment in Section 19.4.3. Therefore, post-marketing studies are issued to evaluate tovorafenib as a perpetrator of CYP3A4, CYP2C8, CYP1A2, CYP2B6, CYP2C9, and CYP2C19.
- Tovorafenib inhibits BCRP in vitro. The Applicant's PBPK modeling of tovorafenib's effects on BCRP was inadequate. For details, refer to the PBPK assessment in Section 19.4.3. Therefore, a PMR to evaluate tovorafenib as a perpetrator of BCRP will be issued.

6.2.2.3. Outstanding Issues

Applicant's Position

No outstanding issues are identified from a clinical pharmacology perspective.

The FDA's Assessment

There were outstanding issues on the DDI assessment. Three PMRs and one PMC were issued, to evaluate tovorafenib with (1) a strong inhibitor of CYP2C8, (2) a strong or moderate inducer of CYP2C8, (3) substrates of CYP3A4, CYP2C8, CYP1A2, CYP2B6, CYP2C9, and CYP2C19, and (4) a substrate of BCRP. These post-marketing studies are discussed in Section 6.1.2.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Applicant's Position

Single-dose PK has been characterized in healthy adult participants and single- and multiple-dose PK have been characterized in adult and pediatric patients with cancer. The following is a summary of PK and absorption, distribution, metabolism, and excretion (ADME) characteristics of tovorafenib.

Pharmacokinetics

- After oral administration of weekly doses of 600 mg tovorafenib in adult patients with cancer, tovorafenib was characterized by a median time to maximum plasma concentration (T_{max}) of 3 hours and C_{max} of 5650 ng/mL.

- Steady-state tovorafenib AUC increased in an approximately dose-proportional manner over the dose ranges of 20 mg to 280 mg Q2D and 400 mg to 800 mg QW in adult patients with cancer.
- Administration of tovorafenib orally Q2D resulted in approximately 2.5-fold mean accumulation in area under the concentration-time curve from time 0 to 48 hours (AUC_{0-48}) at steady state. Minimal to no apparent accumulation was observed with the QW dose regimens in adult patients with cancer.
- The ratio of total radioactivity in whole blood to total radioactivity in plasma (as assessed by area under the concentration-time curve from time 0 to time infinity (AUC_{0-inf}) and area under the concentration-time curve from time 0 to the last measured concentration (AUC_{0-last}) was 0.687 and 0.660, respectively.
- The apparent volume of distribution was estimated to be 115 L using noncompartmental analysis in healthy adult participants from absorption/ metabolism/excretion Study DAY101-103.

Metabolism and Elimination

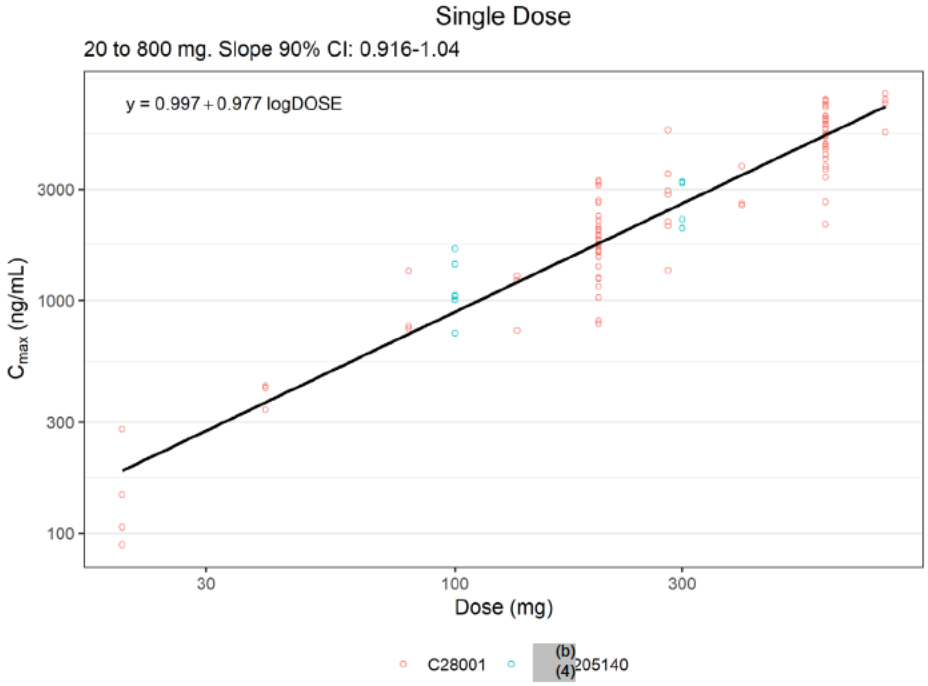
- The majority of radioactivity in urine and feces was identified as metabolites, indicating extensive metabolism of tovorafenib.
  - CYP2C8 and AO are the primary metabolizing enzymes of tovorafenib.
  - Parent tovorafenib was the most abundant circulating component in plasma after oral administration of ^{14}C-tovorafenib. No major metabolites were observed.
- Greater than 60% of the total radioactivity dose was excreted in the feces, suggesting that the major route of elimination is hepatic metabolism and biliary excretion.
- Renal elimination is a minor route of elimination of tovorafenib (urinary excretion of unchanged tovorafenib was 0.147% of the total radioactive dose).
- After oral administration of 100 mg [^{14}C]-tovorafenib in healthy adults, the mean $t_{1/2}$ was estimated to be approximately 48 hours. The mean terminal $t_{1/2}$ in patients ranged from approximately 52 to 71 hours after QW dosing of 400 to 800 mg.

The FDA's Assessment

The FDA generally agrees, with a clarifying remark on the dose proportionality. Tovorafenib's AUC and C_{max} exhibit dose proportionality from 20 mg to 800 mg, which covers the clinically relevant therapeutic exposure range. Dose proportionality was evaluated using PK data from studies C28001 and (b) (4) 205140, which conducted intensive PK sampling. Linearity of C_{max} was evaluated using single-dose PK. Linearity of $AUC_{0-tau,ss}$ was assessed using Q2D and QW frequencies. Note that these two dosing frequencies had to be pooled to evaluate the full linearity range, in order to support the clinical relevance of the dosages tested in the mass balance study (100 mg) and Study (b) (4) 205140. Dose proportionality was evaluated using a power model. The calculated critical region was 0.94, 1.06 with α=0.1, Θ_L=0.80, and Θ_H=1.25.

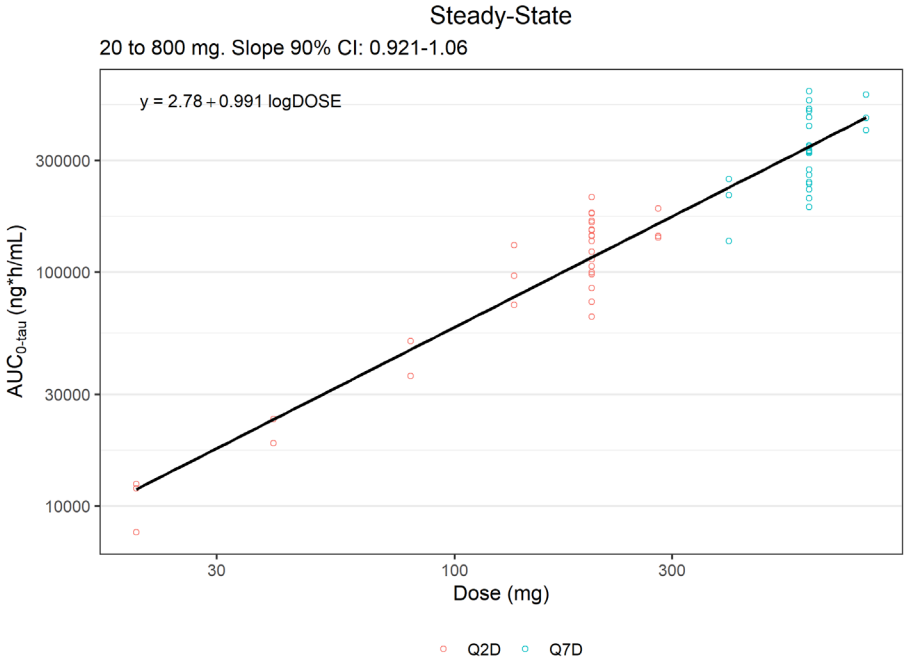
The estimated slope from the power model analysis for C_{max} was 0.98 (90% CI: 0.92, 1.04) (Figure 5). The estimated slope for $AUC_{0\text{-}tau,ss}$ was 0.99 (90% CI: 0.92, 1.06) (Figure 6). The 90% CI of the C_{max} and $AUC_{0\text{-}tau,ss}$ from the power models were reasonably contained within the critical region (0.94, 1.06).

Figure 5. PK Linearity Assessment with C_{max} (single dose)



Source: Applicant's analysis.
Abbreviations: CI = confidence interval; Cmax = maximum plasma concentration; PK = pharmacokinetic.

Figure 6. PK Linearity Assessment of $AUC_{0\text{-}tau}$ at Steady State



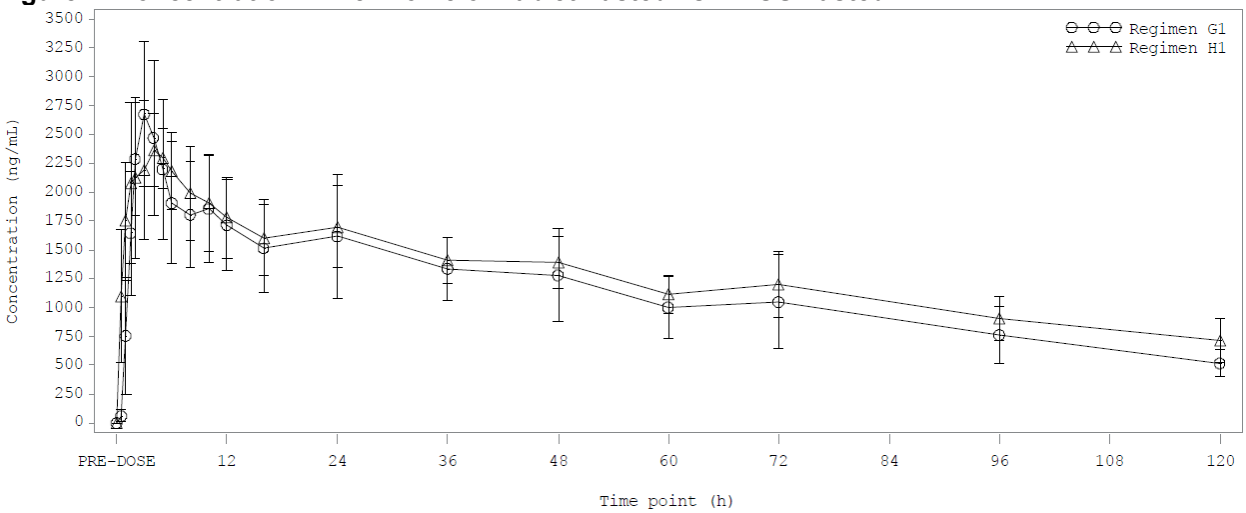
Source: Applicant's Analysis

Abbreviations: AUC = area under the curve; CI = confidence interval; PK = pharmacokinetic.

Regarding the labeling instructions for re-dosing after vomiting, (b) (4) . FDA (b) (4) recommended re-dosing only if vomiting occurs immediately after administration of tablets and PFOS, based on the following considerations:

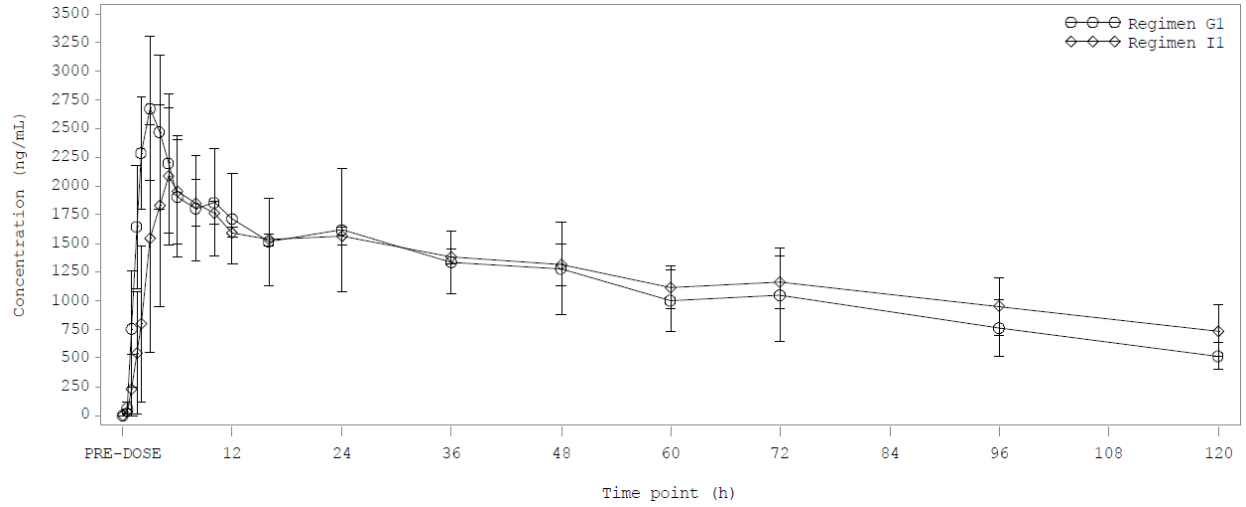
- There was uncertainty in exposures at timepoints up to and including 30 minutes after administration of tablets and PFOS, as shown in Figure 7 and Figure 8. For example, concentrations were variable at the earliest PK timepoint of 30 minutes, with tovorafenib plasma concentrations of 61 ng/mL (CV 79.9%) and 1,100 ng/mL (CV 52.7%) for tablets and PFOS, respectively, under fasted conditions. Re-dosing when vomiting occurs (b) (4) could increase safety risks, given the uncertainty in absorption at early time points after the initial dose and the positive E-R relationships for safety. This is further complicated by the uncertainty in the time course and the rate of absorption of PFOS due to its suspended state.
- Since exposure reaches steady state at approximately 12 days, missing one dose due to vomiting is unlikely to decrease exposure enough to adversely affect the efficacy of tovorafenib, which will likely be administered long-term.

Figure 7. Concentration-Time Profile of Tablet Fasted vs. PFOS Fasted



Source: Applicant's graph. Regimen G1 is the tablet, fasted group. Regimen H1 is the PFOS, fasted group.
Abbreviations: h = hours; PFOS = powder for oral suspension.

Figure 8. Concentration-Time Profile of Tablet Fasted vs. Tablet Fed



Source: Applicant's graph. Regimen G1 is the tablet, fasted group. Regimen I1 is the tablet, fed group.
Abbreviations: h = hours.

For details on the other clinical pharmacology characteristics, refer to Section 6.3.2.4.

For information on the bioanalytical method validation, refer to Section 19.4.4.

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the Clinical Pharmacology Program Provide Supportive Evidence of Effectiveness?

Applicant's Position

Evidence of positive benefit-risk is based on the efficacy, safety, and tolerability findings from Study FIREFLY-1. (b) (4)

The FDA's Assessment

The FDA agrees that FIREFLY-1 provides the primary source of efficacy, which is discussed in Section 8. (b) (4)

FDA recommends 380 mg/m^2 orally QW (not to exceed 600 mg), with or without food. For details on the recommended dosage, refer to Section 6.3.2.2 and Section 19.4.2.

6.3.2.2. Is the Proposed Dosing Regimen Appropriate for the General Patient Population for Which the Indication is Being Sought?

(b) (4)

(b) (4)

The FDA's Assessment

(b) (4) FDA recommends a dosage of 380 mg/m^2 QW (not to exceed 600 mg), with or without food. Furthermore, FDA has modified the dosing table to reduce heterogeneous variability across the BSA subgroups.

The rationale in support of the recommended dosage of 380 mg/m^2 QW (not to exceed 600 mg) is as follows:

- (b) (4) the dose bands show heterogeneous variability across the BSA subgroups, and the dose in mg/m^2 decreases as BSA exceeds 1.4 m^2 due to the maximum dose of 600 mg (Figure 9). Therefore, dosing variability was observed in FIREFLY-1 (b) (4) The FDA's recommended dose of 380 mg/ m^2 is within the dose range evaluated to support efficacy and safety in FIREFLY-1.
- (b) (4) 56 out of 138 patients (41%) in the FIREFLY-1 study (data cutoff date of Dec 22, 2022), and 28 out of 76 patients (37%) in the RAPNO-LGG evaluable analysis set. The average dose intensity for the first cycle and over the treatment duration were 390 mg/m^2 and 375 mg/m^2, respectively (Table 12), both of which are similar to the FDA's recommended dose of 380 mg/m^2.
- (b) (4) When grouped by the dose banding of the first dose, the ORR in the 370-399 mg/m^2 and 330-369 mg/m^2 groups is similar to that of the 400-440 mg/m^2 group as defined by RAPNO-LGG, RANO-LGG, and RANO-HGG criteria (Table 13). The patients who received doses lower than 400 mg/m^2 were predominantly in three age groups: 2 to <6 years, 12-<16 years, and 16-<25 years (Figure 10), and these age groups exhibited an ORR comparable to that of the overall

population based on RAPNO-LGG criteria (Table 14). Conversely, most patients in the 6-<12 years age group received doses at [redacted] (b) (4), (b) (4) and exhibited the lowest ORR amongst patients treated for over one year. [redacted]

- There were no clinically significant differences in E-R relationships for ORR, based on RAPNO-LGG, RANO-LGG, and RANO-HGG criteria, observed over the dose range of 290 to 476 mg/m^2 in FIREFLY-1 (Figure 11). The median exposure of the 380 mg/m^2 dose is expected to align with the median exposure of pediatrics receiving 600 mg QW (Figure 12). In contrast, positive trends of E-R relationships were observed for Grade ≥2 AEs and Grade ≥3 AEs, where the exposure mostly falls in the near-linear range of the E-R curves (Figure 12). For several AEs, including Grade ≥2 rash, Grade ≥2 CPK abnormality, Grade ≥2 ALT abnormality, and Grade ≥1 eye event, with incidence rates positively correlated with exposure, steeper curves were observed in pediatric subgroups compared to adults (Figure 13). These data suggest that a modest dose reduction would improve the benefit-to-risk ratio in pediatric patients.
- A reduction in height-for-age z-score was observed in the majority of pediatric patients in FIREFLY-1, although this rarely necessitated dose interruptions, reductions, or treatment discontinuation. However, it is anticipated that the growth delay in pediatric patients at the 420 mg/m^2 dose may prolong the time needed to reach the BSA for the maximum dose (600 mg), which would expose patients to concentrations that have shown a substantial and sustained impact on growth during treatment. According to predictions made with the Applicant's z-score PK/PD model (Figure 14), a single dose reduction may partially restore growth, potentially offering a more effective strategy in mitigating the impact on growth compared to dose modifications triggered by significant adverse reactions (see Section 19.4.2.5 for additional details).
- The following considerations provide additional support for the 380 mg/m^2 QW dosage [redacted] (b) (4)
  - The average exposure achieved with 420 mg/m^2 QW dose in pediatrics is approximately 33% greater than that of the adult maximum tolerated dose (600 mg QW);
  - Clinical experience in PNCO014 showed that 2 patients treated with 280 mg/m^2 QW demonstrated rapid and substantial tumor shrinkage;
  - Similar pharmacological activity is expected between the 380 and 420 mg/m^2 doses given a large efficacy margin of steady state C_{avg} over *in vivo* EC_{50} (derived using *in vitro* EC_{50}, unbound fraction, and brain-to-plasma ratio).

Based on the above, the clinical pharmacology review team concludes that the current data from FIREFLY-1 are sufficient to recommend 380 mg/m^2 QW (not to exceed 600 mg) for the intended patient population without additional studies. The results from the pharmacometrics

reviewer's analysis support a better benefit-to-risk ratio for the recommended dosage of 380 mg/m^2 QW compared to the 420 mg/m^2 QW dosage, with a maximum dose of 600 mg.

Table 12. Dose Intensity in Patients From FIREFLY-1

FIREFLY-1	Arm 1	Arm 2	Arm 3	Overall
All patients	N=77	N=60	N=3	N=140
First cycle dose intensity	391 (63)	389 (54)	403 (28)	390 (58)
First cycle relative dose intensity	93% (15%)	93% (13%)	96% (67%)	93% (14%)
Dose intensity	377 (59)	373 (63)	362 (20)	375 (60)
Relative dose intensity	90% (14%)	89% (15%)	86% (4.7%)	89% (14%)
Patients treated for ≥6 months	N=68	N=54	--	N=122
Dose intensity	384 (56)	382 (56)	--	383 (56)
Relative dose intensity	91% (13%)	91% (13%)	--	91% (13%)
Patients treated for ≥12 months	N=61	N=14	--	N=75
Dose intensity	389 (54)	407 (42)	--	392 (52)
Relative dose intensity	93% (13%)	97% (10%)	--	93% (12%)

Source: FDA's analysis.

Values are expressed as mean (standard deviation). The relative dose intensity was calculated using a denominator of 420 mg/m^2. First cycle: 1-28 days since the beginning of the treatment. Arm 1, which was the pivotal arm for efficacy, included patients with R/R pLGG with alterations in BRAF between 6 months to 25 years of age. Arm 2 was in patients with R/R pLGG with an activating RAF mutation between 6 months to 25 years old. Arm 3 is in patients with advanced solid tumors and is currently enrolling. In all arms, patients were assigned to receive 420 mg/m^2 orally QW (not to exceed 600 mg).

Table 13. ORR Grouped by Dose Band Based on RAPNO-LGG, RANO-LGG, and RANO-HGG

n/N (%)	First dose (mg/m^2) Overall	>440 (5-19% higher)	400-440 (<±5% of 420 mg/m^2)	370-399 (5-11% lower)	330-369 (12-20% lower)	295-329 (21-29% lower)	265-294 (30-37% lower)
RAPNO-LGG	39/76 (51%)	12/24 (50%)	13/26 (50%)	9 /14 (64%)	5/9 (56%)	0/2 (0%)	0/1 (0%)
RANO-LGG	40/76 (53%)	10/24 (42%)	16/26 (62%)	8 /14 (57%)	4/9 (44%)	2/2 (100%)	0/1 (0%)
RANO-HGG	46/69 (67%)	15/22 (68%)	18/24 (75%)	8 /13 (62%)	4/7 (57%)	1/2 (50%)	0/1 (0%)

Source: FDA's analysis.

Table 14. ORR Based on RAPNO-LGG Grouped by Dose Band for Age Subgroups

n/N (%)	First dose (mg/m^2) Overall	>440 (5-19% higher)	400-440 (<±5% of 420 mg/m^2)	370-399 (5-11% lower)	330-369 (12-20% lower)	295-329 (21-29% lower)	265-294 (30-37% lower)
2-<6 year	11/14 (79%)	3/3 (100%)	2/4 (50%)	4/5 (80%)	2/2 (100%)	NA	NA
6-<12 year	18/40 (45%)	7/17 (41%)	6/14 (43%)	4/7 (57%)	1/2 (50%)	NA	NA
12-<16 year	8/16 (50%)	2/3 (67%)	5/8 (63%)	NA	1/3 (33%)	0/1 (0%)	0/1 (0%)
16-25 year*	2/6 (33%)	0/1 (0%)	NA	1/2 (50%)	1/2 (50%)	0/1 (0%)	NA

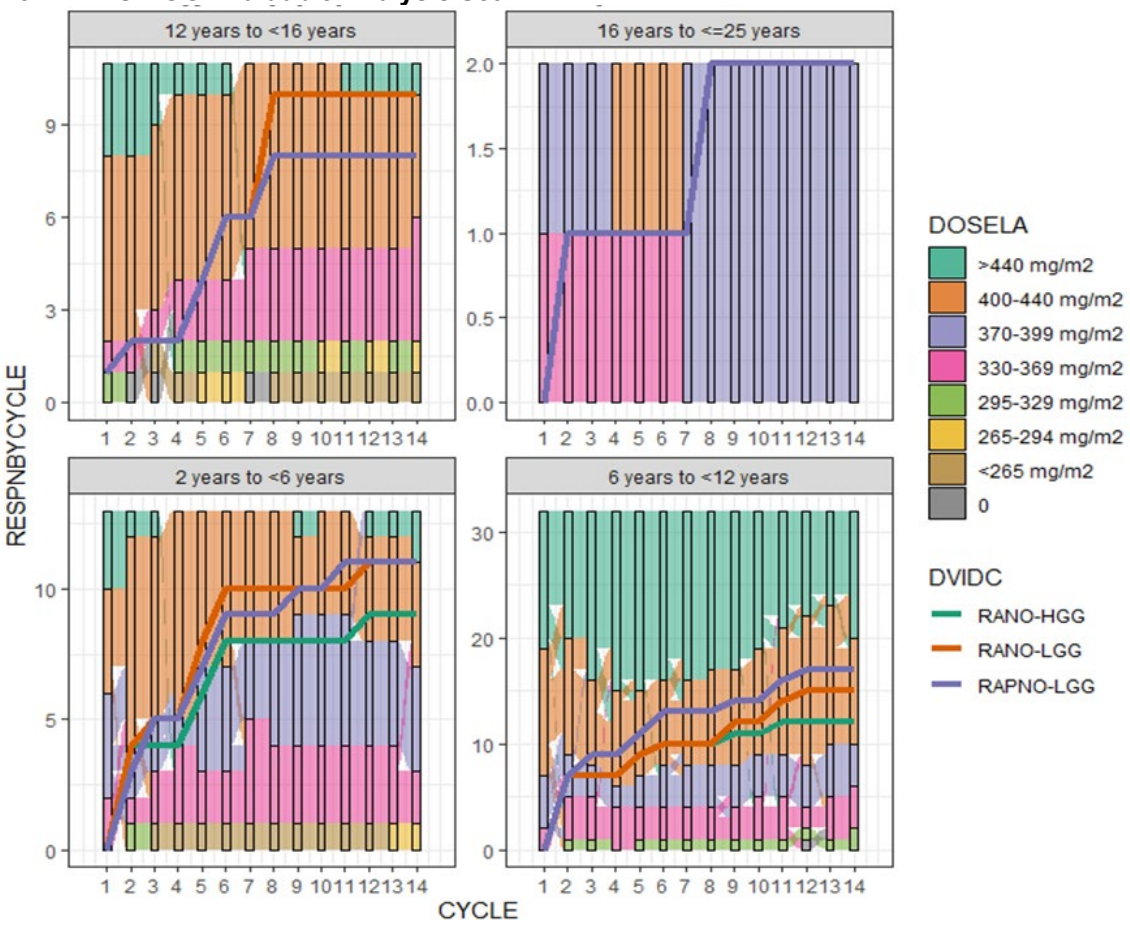
Source: FDA's analysis.

*Patients with a median dosing duration of 245 days compared to >470 days in other age groups. An age of 16 years was used for grouping to align with the cutoff for the functional test with Karnofsky/Lansky performance score.

(b) (4)

Abbreviations: BSA = body surface area; PFOS = powder for oral suspension.

Figure 10. Actual Dose Over Time by Age Group From Patients With Over 1 Year of Treatment in the RAPNO-LGG Evaluable Analysis Set



Source: FDA's analysis.

Each cycle included 28 days of weekly doses. An age of 16 years was used for grouping to align with the cutoff for the functional test with Karnofsky/Lansky performance score.

Figure 11. E-R Relationship for ORR Based on RAPNO-LGG, RANO-LGG, and RANO-HGG for Actual Doses Ranging From 290 to 476 mg/m^2

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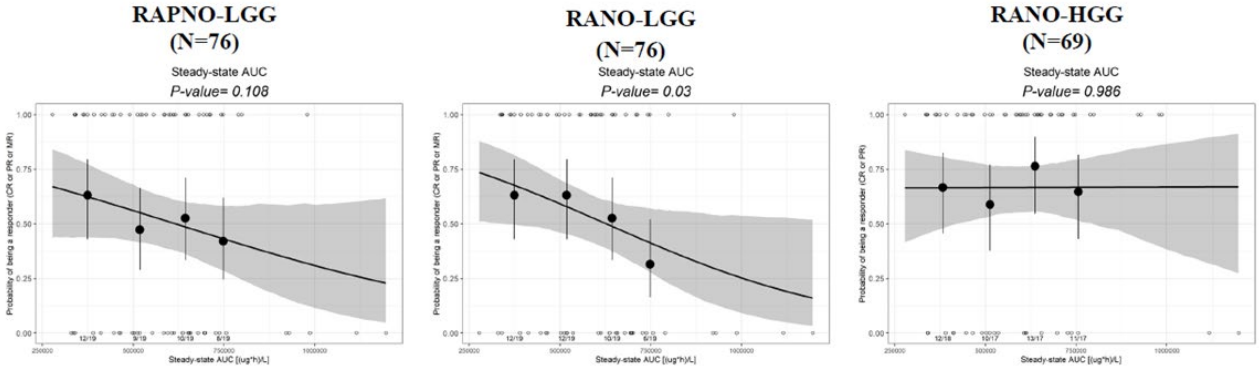
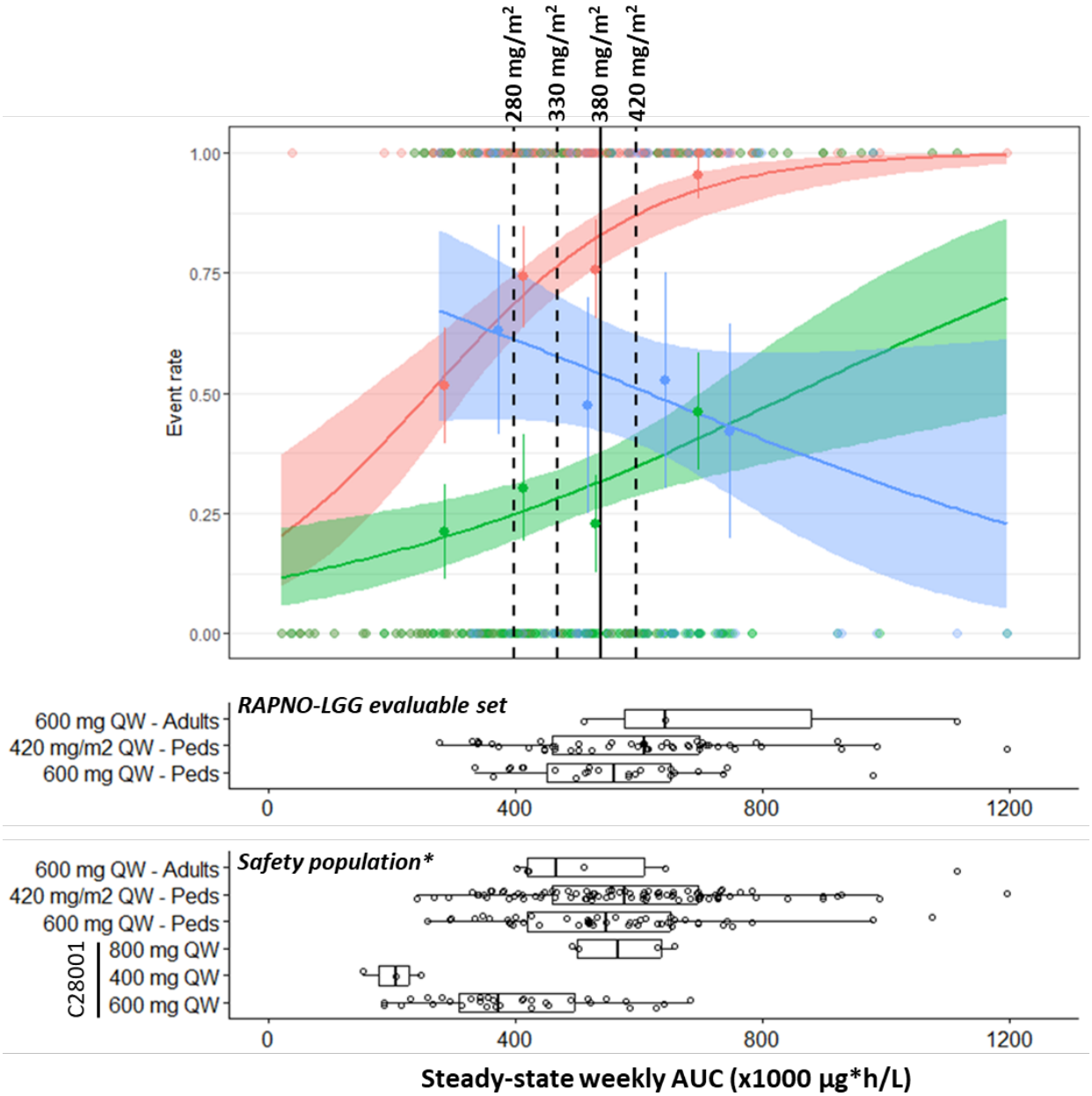


Source: Applicant's analysis.

Abbreviations: AUC = area under the curve; E-R = exposure-response; ORR = overall response rate.

Figure 12. E-R Relationship for ORR Based on RAPNO-LGG, Grade ≥2 or Grade ≥2 AEs for Actual Doses Ranging From 290 to 476 mg/m^2



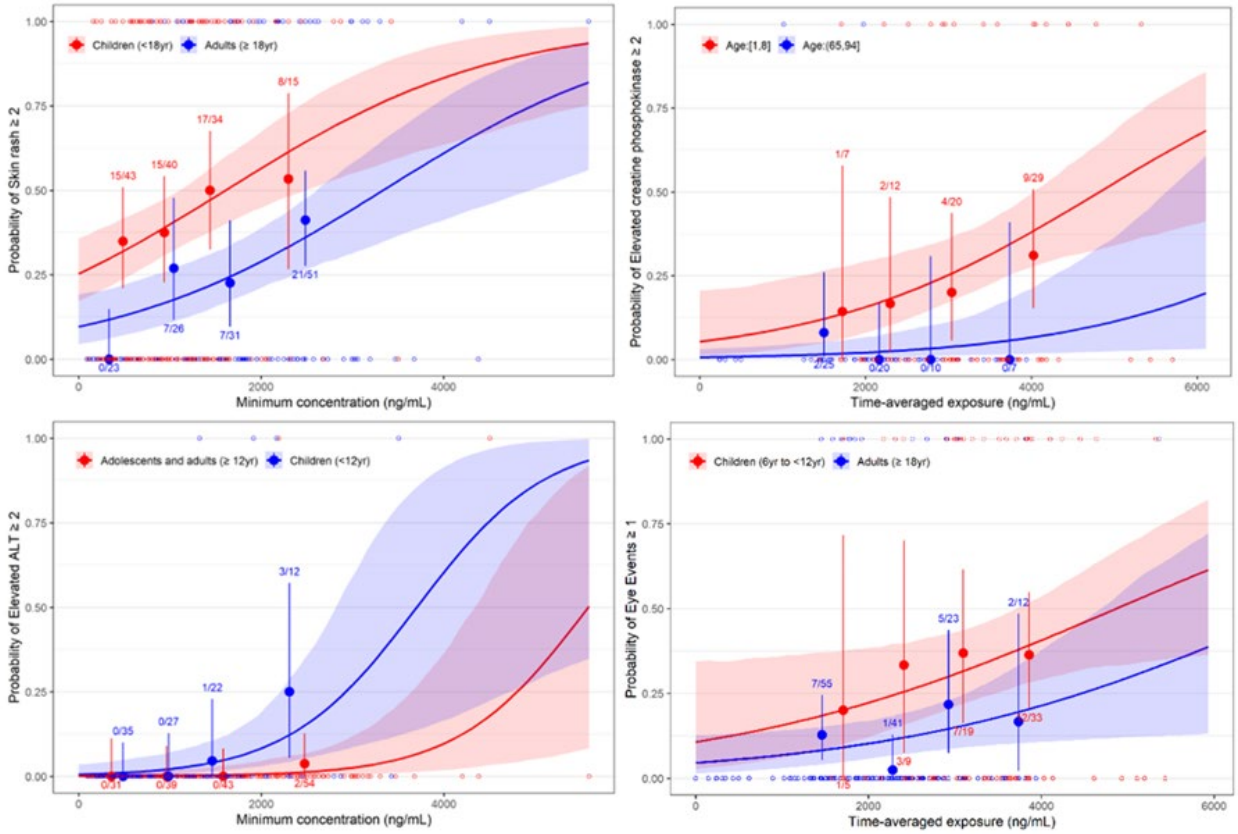
Source: FDA's analysis.

The analysis includes data from Study C28001 (adults) and FIREFLY-1. The red, green, and blue shading indicates Gr≥2 AEs, Gr≥3 AEs, and ORR by RAPNO-LGG, respectively. Median exposures (dotted line) are approximated by the median of individual exposure for a dose range targeting 420 mg/m^2 (intended dose in FIREFLY-1), 380 mg/m^2 (FDA's recommended dose), 330 mg/m^2 (the recommended 1st dose reduction), 280 mg/m^2 (the recommended 2nd dose reduction). Grade ≥2 and Grade ≥3 AEs were a composite of commonly occurring AEs including skin rash, anemia, fatigue, myalgia, nausea and/or vomiting, AST elevation, ALT elevation, bilirubin elevation, and CPK abnormality.

*Safety population included patients who received the Q2D dose, whose exposures were not shown in the bar graph but were included in the E-R curve.

Abbreviations: AE = adverse event; AUC = area under the curve; E-R = exposure-response; ORR = overall response rate; QW = once weekly.

Figure 13. E-R Relationship for AESIs by Age Subgroup

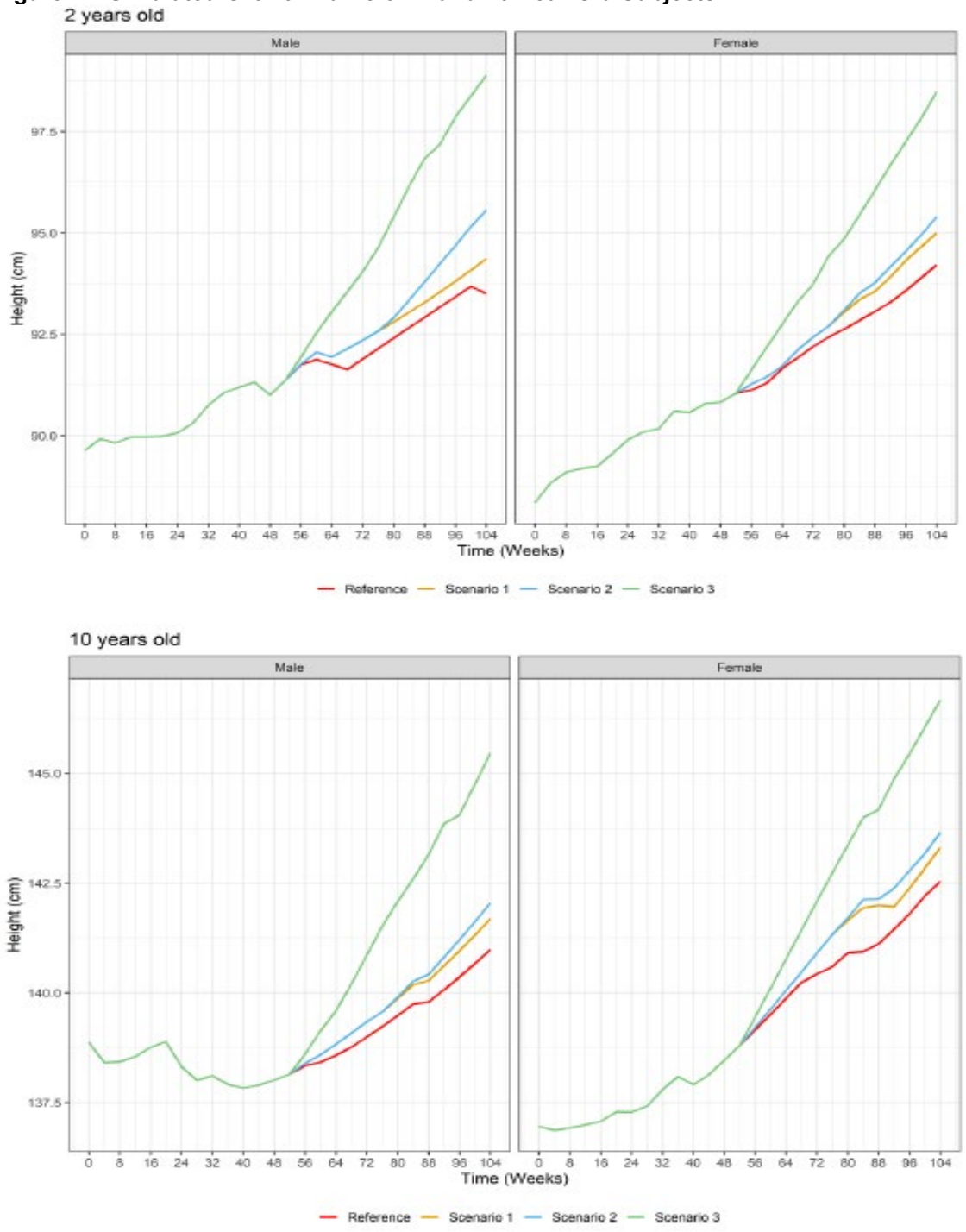


Source: Applicant's analysis.

Eye events definition excluded the following high-level terms: "Lid, lash and lacrimal structural disorders", "Lacrimation disorders", "Lid, lash and lacrimal infections, irritations and inflammations", "Ocular disorders not elsewhere classified".

Abbreviations: AESI = adverse event of special interest; ALT = alanine transaminase; E-R = exposure-response.

Figure 14. Simulated Growth Curve of 2- and 10-Year-Old Subjects



Source: Applicant's analysis.

The reference regimen is 420 mg/m^2 (not to exceed 600 mg) QW for 104 weeks. Scenario 1 is 420 mg/m^2 (not to exceed 600 mg) QW for 52 weeks then drop to first dose reduction for 52 weeks. Scenario 2 is 420 mg/m^2 (not to exceed 600 mg) QW for 52 weeks then drop to first dose reduction for 26 weeks then drop to second dose reduction for 26 weeks. Scenario 3 is 420 mg/m^2 (not to exceed 600 mg) QW for 52 weeks then dose discontinued for 52 weeks.

Abbreviations: QW = once weekly.

6.3.2.3. Is an Alternative Dosing Regimen or Management Strategy Required for Subpopulations Based on Intrinsic Patient Factors (e.g., race, ethnicity, age, performance status, genetic subpopulations, etc.)?

Applicant's Position

No. Based on the assessment of intrinsic factors in population PK analyses, no dose adjustment or change in tovorafenib regimen is required based on demographics or in specific populations (ie, mild hepatic impairment or mild and moderate renal impairment). A summary of the effects of each intrinsic factor on tovorafenib PK is presented below:

Effects of Age on Exposure

With the inclusion of body surface area (BSA) in the population PK model, age (range 1 to 94 years) did not appear to have an additional impact on tovorafenib PK. Age was not identified as a covariate of clearance in the population PK analysis, indicating similar PK profiles between adult and pediatric populations. This is consistent with existing knowledge that tovorafenib is a low-clearance drug and the activity of AO reaches adult level at age of 1 to 2 years.

Effects of Sex on Exposure

In the population PK model, apparent clearance (CL/F) was associated with sex; males were estimated to have a 21.5% higher CL/F than females. Based on univariate analysis, the ratio [95% CI] of AUC, C_{max}, and C_{min} in males relative to females was 0.82 [0.74 – 0.92], 0.93 [0.9 – 0.97], and 0.65 [0.51 – 0.84], respectively.

Effects of Race and Ethnicity on Exposure

Race (White versus non-White) was not identified as a covariate of tovorafenib clearance or volume of distribution in the population PK model and thus not considered to affect tovorafenib PK.

Patients With Renal Impairment

Renal impairment is not expected to impact tovorafenib PK because 0.147% of the administered dose was recovered as unchanged tovorafenib in urine. Moderate (n = 21/341; estimated glomerular filtration rate (eGFR) ≥ 30 to 59 mL/min/1.73 m^2) or mild (n = 108/341; eGFR ≥ 60 to 89 mL/min/1.73 m^2) renal impairment was not identified as a covariate of clearance in population PK analysis. No patients with severe renal impairment (eGFR < 30 ml/min/1.73 m^2) have been enrolled in clinical studies of tovorafenib.

Patients With Hepatic Impairment

Moderate (n = 1/341; bilirubin > 1.5x to 3x upper limit of normal [ULN] and any AST) or mild (n=52/341; bilirubin ≤ ULN and AST > ULN or bilirubin > 1x to 1.5x ULN and any AST) hepatic impairment was not identified as a covariate of clearance in population PK analysis. No patients with severe hepatic impairment (bilirubin > 3 x to 10 x ULN and any AST) have been enrolled in clinical studies of tovorafenib.

The FDA's Assessment

Age 1 Year and Above

No clinically meaningful differences in tovorafenib's PK were detected based on age (1 to 94 years), based on popPK.

Age 6 Months and Above

Since there was limited clinical PK data from patients younger than 1 year of age from FIREFLY-1, the ontogeny of tovorafenib was considered. Tovorafenib appears to be primarily metabolized by aldehyde oxidase and CYP2C8, which appear to reach activity levels found in adults by 1 year of age and by 6 months of age, respectively. However, there is very limited knowledge on the maturation of AO. AO's activity increases from 6 months of age to 1 year of age by approximately 61% to 82% of the AO activity found in adults, respectively, based on published literature data (Tayama Y, 2007, Clin Pharmacol Ther). The clinical relevance of this is uncertain, particularly since the extent of AO's contribution to tovorafenib's metabolism is uncertain. This is further complicated by general uncertainties in age-related changes in hepatic clearance in pediatrics. Available knowledge suggests that infants may have increased hepatic clearance compared to older humans, due to a higher ratio of liver weight to body weight and higher liver blood flow. This is further supported by clinical studies of drugs metabolized in the liver exhibiting an age-dependent increase in plasma clearance in children younger than 10 years of age, compared to adults (Kearns G, 2003, NEJM). Regarding age-related changes in absorption, it is uncertain if tovorafenib's absorption will differ in patients 6 months of age, due to pre-existing uncertainties in how absorption changes in infants aged 6 months (e.g., changes in gastric emptying and intestinal motility). Therefore, the use of tovorafenib in patients from 6 months to 1 year of age is based on the limited ontogeny data described here, the benefit-to-risk ratio, the unmet medical need, and of the anticipated close safety monitoring within the age range of 6 months to 1 year of age (Section 8). Tovorafenib's dosage from 6 months to 1 year of age was estimated using body size allometry in the popPK model, which accounted for PK differences across the evaluable age and BSA-based dosing. For details on the popPK analyses, refer to review Section 19.4.1.

Sex

No clinically meaningful differences in tovorafenib's PK were detected between males and females.

Race

No clinically meaningful differences in tovorafenib's PK were detected between races (White, Black, and Asian), based on popPK analyses.

Hepatic Impairment

The FDA agrees. Hepatic impairment was evaluated using the National Cancer Institute (NCI) criteria. A PMR to evaluate tovorafenib in patients with moderate-or-severe hepatic impairment will not be issued, since the recommended patient population is not expected to include subpopulations of patients with moderate-or-severe hepatic impairment.

Renal Impairment

The FDA agrees and clarifies that tovorafenib has not been evaluated in severe renal impairment (eGFR 15 to 30 ml/min/1.73 m^2). A PMR to evaluate tovorafenib in renal impairment will not be issued, since the recommended patient population is not expected to include a subpopulation of patients with severe renal impairment.

BRAF Alterations and Treatment Efficacy

The FDA explored the efficacy by *BRAF* alterations in Study FIREFLY-1 in patients with at least one measurable lesion at baseline based on RAPNO criteria (N=76). *BRAF* alterations were identified through molecular assays that were routinely performed as part of standard of care diagnostic workup in Clinical Laboratory Improvement Amendments (CLIA) or similarly certified labs. Fusions were identified by Fluorescence in situ Hybridization (FISH) (25%), Next-Generation Sequencing (NGS) (38%), Real-Time Reverse Transcription-Polymerase Chain Reaction (RT-PCR) (27%) or other methods (11%). Mutations were identified by NGS (50%) or other methods (50%). Among the 76 patients, 84% had a *BRAF* fusion (N=64), and 16% had a V600E mutation (N=12). Among patients with a *BRAF* fusion, the *KIAA*1549:*BRAF* fusion was the most common fusion (N=56; 88%). Responses were observed across *BRAF* alterations (Table 15), with ORR=52% for patients with *BRAF* fusions and ORR=50% for patients with a V600E mutation. The results suggested tovorafenib is effective in patients with multiple *BRAF* fusions and the *BRAF* V600E mutation; therefore, the proposed indication across these *BRAF* alterations seems appropriate based on the data.

Table 15. IRC-Assessed Overall Response Rates by BRAF Alterations Based on RAPNO Criteria in Patients With at Least One Measurable Lesion at Baseline in FIREFLY-1 (N=76)

	BRAF Fusion			*BRAF* Mutation	Total
Best Overall Response (ORR)	All *BRAF* Fusion (N/%, N=64)	*KIAA* 1549:*BRAF* (N/%, N=56)	Other *BRAF* Alterations (N/%, N=8)	V600E (N/%, N=12)	
Complete Response	0	0	0	0	0
Partial Response (PR)	24 (38)	21 (38)	3 (38)	4 (33)	28 (37)
Minor Response (MR)	9 (14)	8 (14)	1 (13)	2 (17)	11 (15)
PR + MR	33 (52)	29 (52)	4 (50)	6 (50)	39 (51)
Stable Disease (SD)	20 (31)	17 (30)	3 (38)	3 (25)	13 (17)
Progressive Disease (PD)	10 (16)	9 (2)	1 (13)	3 (25)	23 (30)
Not Evaluable (NE)	1 (2)	1 (2)	0	0	1 (1)

Source: Reviewer's analysis.

Other *BRAF* alterations includes *BRAF* tandem duplication, *BRAF* rearrangement, or other non-*KIAA*1549: *BRAF* fusions. No patients achieved complete response (CR) in this analysis dataset.

Abbreviations: *BRAF* = v-raf murine sarcoma viral oncogene homolog B, IRC = Independent Radiology Review Committee, RAPNO = Response Assessment in Pediatric Neuro-Oncology; N = Number.

6.3.2.4. Are There Clinically Relevant Food-Drug or Drug-Drug Interactions, and What is the Appropriate Management Strategy?

Applicant's Position

Tovorafenib can be taken without regard to food. Following oral administration of 100 mg or 300 mg tovorafenib to healthy participants with a high-fat meal, the median T_{max} was delayed by approximately 2 hours, AUC was unchanged, and C_{max} decreased by approximately 20%. These changes are not expected to meaningfully impact tovorafenib PK based on E-R efficacy and safety analyses.

No clinical drug-drug interaction studies have been conducted with tovorafenib. However, a mechanistic physiological-based PK modeling and simulation model was developed using available *in vitro* and *in vivo* data to assess the drug-drug interaction potential of tovorafenib. Results are summarized below:

- Victim Potential
  - Coadministration of tovorafenib with strong CYP2C8 inhibitor gemfibrozil is predicted to increase tovorafenib C_{max} and area under the concentration-time curve from time 0 to 168 hours (AUC_{0-168}) by 40% and 100%, respectively.
  - Coadministration of tovorafenib with CYP2C8 inducer rifampin is predicted to decrease tovorafenib C_{max} and AUC_{0-168} by 24% and 59%, respectively.

- Perpetrator Potential
  - Coadministration of tovorafenib with breast cancer resistance protein (BCRP) substrate rosuvastatin is predicted to increase the C_{max} and $AUC_{0\text{-}inf}$ of rosuvastatin by 96% and 16%, respectively.
  - Coadministration of tovorafenib with CYP3A4 substrate midazolam is predicted to reduce the C_{max} and $AUC_{0\text{-}inf}$ of midazolam by 58.9% and 61%, respectively.

It is recommended to avoid coadministration of tovorafenib with strong or moderate CYP2C8 inhibitors (b) (4) . Strong or moderate CYP2C8 inducers should be avoided.

(b) (4) Coadministration of tovorafenib with sensitive CYP3A4 substrates is predicted to decrease exposure and may result in loss of efficacy for these substrates. Coadministration of tovorafenib with hormonal contraceptives (CYP3A4 substrates) can render hormonal contraceptives ineffective.

The FDA's Assessment

Food-Drug Interaction; Relative Bioavailability Between Tablets and PFOS

Both formulations (tablets and PFOS) can be administered without regard to food, since the to-be-marketed versions of both formulations were given without regard to food in FIREFLY-1. No apparent differences in tovorafenib exposures (AUC or C_{max}) were seen between these two formulations. Moreover, no apparent trends in PFOS' exposures (AUC or C_{max}) were seen across different BSAs, when BSA was analyzed as (1) quartiles, (2) in 0.1 m^2 increments, (3) binary categories of BSA <0.6 m^2 vs. BSA >0.7 m^2, or (4) BSA <0.8 m^2 vs. BSA >0.9 m^2. A summary of the food effect and relative bioavailability assessment is shown in Table 16.

Table 16. Summary of Food Effect and Relative Bioavailability Assessments

Topic	Supporting Data	Assessment
Relative bioavailability between tablets and PFOS	In FIREFLY-1, similar exposures between formulations were seen, when they were given without regard to food. Study (b) (4) 205140 compared the formulations in the fasted state in a small number of patients. See Table 18 for 90% CI for GMRs.	No apparent differences in exposure between formulations.
Tablets, food effect	In FIREFLY-1, the tablets were given without regard to food. Study (b) (4) 205140 evaluated food effect in a small number of patients. See Table 18 for 90% CI for GMRs.	Tablets can be given without regard to food.
PFOS, food effect	In FIREFLY-1, PFOS was given without regard to food.	PFOS can be given without regard to food.

The to-be-marketed tablets and PFOS formulations were administered in FIREFLY-1 and study (b) (4) 205140.
Abbreviations: CI = confidence interval; GMR = geometric mean ratio; PFOS = powder for oral suspension.

The effect of food on the to-be-marketed tablet formulation (i.e., the T2 formulation) was evaluated in Study (b) (4) 205140. However, the effect of food on the to-be-marketed PFOS formulation was not directly evaluated. The Applicant's rationale was to bridge the food effect results from the tablets to the PFOS. However, FDA had concerns about the design of Study (b) (4) 205140 which are addressed in the reviewer's additional analyses below.

Study (b) (4) 205140 was a two-part study that evaluated the relative bioavailability of the formulations, food effect, and palatability. Part 1, which evaluated palatability, will not be discussed further in this section. In Part 2, bioavailability was evaluated using a 3-way crossover study in healthy adults (Table 17). Participants were randomly assigned to one of three regimen sequences (GHI, HIG, IGH), with 12 participants assigned to each regimen sequence. The Applicant did not justify the sample size, as they considered this study to be exploratory. All participants received a one-time dosage of 300 mg in Period 1. However, the dosage was reduced to 100 mg in Period 2 for all groups, due to musculoskeletal adverse events. The washout period of 14 days between doses was acceptable.

Table 17. Study Design of Study (b) (4) 205140 Part 2 (relative bioavailability and food effect)

Treatment	Regimen	Dose Period 1	Dose Period 2
Tablets, fasted	G	300 mg (Regimen G1)	100 mg (Regimen G2)
PFOS, fasted	H	300 mg (Regimen H1)	100 mg (Regimen H2)
Tablets, fed	I	300 mg (Regimen I1)	100 mg (Regimen I2)

Abbreviations: PFOS = powder for oral suspension.

In all periods, PK sampling occurred at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 60, 72, 96, and 120 hours post-dose. The PK sampling collection interval was too short, at less than 3 elimination half-lives, given tovorafenib's elimination half-life of approximately 56 hours. The fed group received a high-fat meal (859 calories, with 54% of calories from fat), which was acceptable.

To verify the bioavailability results, the reviewer created a linear mixed effects model from the 300 mg dose administered using the to-be-marketed formulations. Data from the 100 mg dose level was not included in the analysis, because data from 300 mg dose level were available, which is a more clinically relevant dosage. The linear mixed effects model incorporated a fixed effect (trtp) and a random effect (subject) to evaluate PK parameters (C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$). The 90% CI of the GMRs are shown in Table 18.

Table 18. PK Analysis of Bioavailability Results from Study (b) (4) 205140

Test vs. Reference*	PK Parameter	GMR (90% CI)*
PFOS, fasted vs. tablets, fasted	C_{max}	94 (71, 125)
PFOS, fasted vs. tablets, fasted	$AUC_{0\text{-}last}$	113 (87, 148)
PFOS, fasted vs. tablets, fasted	$AUC_{0\text{-}inf}$	129 (88, 190)
Tablet, fed vs. tablets, fasted	C_{max}	83 (63, 110)
Tablet, fed vs. tablets, fasted	$AUC_{0\text{-}last}$	107 (82, 140)
Tablet, fed vs. tablets, fasted	$AUC_{0\text{-}inf}$	136 (92, 200)
Tablets, fasted	T_{max}	3 hours (3 to 3 hours)
Tablets, fed	T_{max}	6.5 hours (4 to 24 hours)
PFOS, fasted	T_{max}	3 hours (1.5 to 4 hours)

Source: Reviewer's analysis.

Only the 300 mg dosage was used for comparisons. N=4 in each group.

* T_{max} values are reported for each group in terms of median and range.

Abbreviations: AUC = area under the curve; CI = confidence interval; Cmax = maximum plasma concentration; GMR = geometric mean ratio; PK = pharmacokinetic; Tmax = time to maximum concentration.

The $AUC_{0\text{-}inf}$ 90% CI GMR falling outside 80 to 125 across different comparisons was likely due to the PK sampling collection interval being too short relative to tovorafenib's elimination half-life, leading to inadequate characterization of $AUC_{0\text{-}inf}$. Therefore, C_{max} and $AUC_{0\text{-}last}$ are more reliable values for assessing bioavailability. The C_{max} and $AUC_{0\text{-}last}$ had GMRs that were within 80 to 125 across comparisons. However, the 90% CI for these GMR were outside 80 to 125. The wide CIs are likely due to the small sample sizes. Nevertheless, the tablets' C_{max} decreased approximately 20% in the fed state, compared to the fasted state. The tablets also exhibited a delayed T_{max} in the fed state, compared to the fasted state. These differences in bioavailability do not appear to be clinically meaningful.

Data from FIREFLY-1 were examined to further evaluate (1) bioavailability between tablets and PFOS and (2) food effect. In FIREFLY-1, the to-be-marketed tablets and PFOS formulations were

administered without regard to food. There were no apparent differences in exposures (AUC_{tau} or C_{max}) between formulations (Table 19). Furthermore, there were no apparent trends in PFOS' exposures (AUC_{tau} or C_{max}) across different BSAs, when BSA was analyzed as (1) quartiles, (2) in 0.1 m^2 increments, (3) binary categories of BSA $\leq$0.6 m^2 vs. BSA $\geq$0.7 m^2, or (4) BSA $\leq$0.8 m^2 vs. BSA $\geq$0.9 m^2.

Table 19. Model-Predicted Exposures by Formulation From FIREFLY-1

Parameter	Tablets N=107	PFOS N=32
$AUC_{0\text{-}tau,ss}$ (ng*h/mL)		
Geometric mean (CV%)	568,000 (31%)	496,000 (37%)
Median [Min, Max]	591,000 [259000, 1200000]	499,000 [257000, 942000]
$C_{max,ss}$ (ng/mL)		
Geometric mean (CV%)	7,580 (27%)	7,180 (20 %)
Median [Min, Max]	7,750 [2960, 12600]	7,740 [4480, 10400]

Source: Applicant's analysis. Patients were grouped by formulation based on the formulation administered at the first dose. Exposures were predicted for 420 mg/m^2.

Abbreviations: AUC = area under the curve; Cmax.ss = maximum plasma concentration at steady state; CV = coefficient of variation; PFOS = powder for oral suspension.

Drug-Drug Interaction

The FDA disagrees with several components of the Applicant's DDI assessment. For details, refer to the PBPK team's assessment in Section 19.4.3. Tovorafenib's DDI potential is summarized in Table 20.

Table 20. Summary of DDI Results for Tovorafenib

In Vitro Data	PBPK Modeling Conducted by Applicant	FDA's Assessment
Victim of CYPs		
The contributions of each enzyme are shown in parentheses. • AO (64.8%) • CYP2C8 (22.6%) • CYP2C9 (5.3%) • CYP2C19 (4.3%) • CYP3A4/5 (2.9%)	The contributions of each enzyme were re-estimated. • (b) (4) PBPK modeling with CYP2C8 was conducted.	Tovorafenib is primarily metabolized by CYP2C8 and AO. However, the contributions of CYP2C8 and AO are uncertain. The PBPK modeling was inadequate. For details on the PBPK assessment, refer to Section 19.4.3. A PMR and PMC is issued to evaluate tovorafenib as a victim of CYP2C8.

In Vitro Data	PBPK Modeling Conducted by Applicant	FDA's Assessment
Perpetrator of CYPs		
Reversible inhibition (R_1 > 1.02): • CYP2C8 (IC_{50} = 7.8 µM) • CYP2C9 (46.5 µM) • CYP3A4-testosterone (40.5 µM), CYP3A4-midazolam (>100 µM) • CYP2C19 (82.8 µM) No reversible inhibition: • CYP1A2 (>100 µM) • CYP2B6 (>100 µM) • CYP2D6 (>100 µM) Tovorafenib exhibited little-to-no inhibition of CYP2E1 in vitro. The clinical relevance of CYP2E1 is uncertain. Time-dependent inhibition: Not seen in any of the major 7 CYPs.	PBPK modeling of tovorafenib as a perpetrator of CYP3A4, CYP2C8, CYP1A2, CYP2B6, and CYP2C9 was conducted. PBPK modeling of CYP2C19 was not conducted.	Tovorafenib's effects on substrates of CYP3A4, CYP2C8, CYP1A2, CYP2B6, CYP2C9, and CYP2C19 are uncertain. The PBPK modeling was inadequate. For details on the PBPK assessment, refer to Section 19.4.3. A PMR is issued to further evaluate tovorafenib's effect on substrates of CYP3A4, CYP2C8, CYP1A2, CYP2B6, CYP2C9, and CYP2C19. This PMR includes substrates of CYP2C9 and CYP2C19, due to the co-induction mechanism between CYP3A and CYP2Cs.
Induction (R_3 > 0.8): • CYP3A4 • CYP1A2 • CYP2B6 • CYP2C8 Some induction#: • CYP2C9 • CYP2C19		
Victim of Transporters		
Not a substrate: • BCRP • P-gp • OATP1B1 • OATP1B3	No PBPK modeling was submitted.	In vitro data will be stated in the label.

In Vitro Data	PBPK Modeling Conducted by Applicant	FDA's Assessment
Perpetrator of Transporters		
Inhibition: • BCRP[a] No inhibition: • P-gp[b] • OATP1B1[a] • OATP1B3[a] • OAT1[a] • OAT3[a*] • OCT1[b] • OCT2[b] • MATE1[a*] • MATE2-K[b]	PBPK modeling of tovorafenib as a perpetrator of BCRP, OAT1B1, OAT1B3, and MATE1 was submitted.	Tovorafenib's effect on BCRP substrates is uncertain. The PBPK modeling was inadequate. For details on the PBPK assessment, refer to Section 19.4.3. A PMR is issued to evaluate tovorafenib's effect on BCRP substrates.

Source: Reviewer-generated table.

[#] Enzymes whose mRNA expression increased <2-fold relative to vehicle control but increased >20% of the response of the positive control.

[*] These transporters crossing the threshold depended on rounding.

[a] Based on the regulatory threshold of potential inhibition in vivo.

[b] Based on IC50 values not reached in vitro

X X

Primary Reviewer — Sarah Kim

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7. Sources of Clinical Data

7.1. Table of Clinical Studies

Applicant's Position

Table 21 presents a summary of clinical studies included in this submission. The efficacy of tovorafenib in the treatment of pediatric patients with RAF-altered, relapsed or refractory low-grade glioma (b) (4) is supported by the primary results of the pivotal Study FIREFLY-1. Pediatric patients were enrolled in FIREFLY-1 and Study PNOC014.

The FDA's Assessment

The FDA agrees with the Applicant's description of the clinical studies included in this submission as outlined in Table 21. For these NDAs, the primary clinical data for the FDA's analysis of efficacy were based on data from 76 patients with relapsed or refractory pediatric LGG with BRAF fusion or rearrangement, or BRAF V600 mutation who had measurable disease at baseline according to RAPNO-LGG and were enrolled in Arm 1 of FIREFLY-1. The primary clinical data for the FDA's analysis of safety includes data from all 140 patients treated in FIREFLY-1 and 32 adult patients with advanced solid tumors treated in Study C28001. These 172 patients represent the integrated safety set as this population was treated with tovorafenib at the recommended Phase 2 dosage of 420 mg/m^2 or a maximum dose of 600 mg once weekly as determined in Study PNOC014. Note, Table 21 cites a sample size of 139 patients for FIREFLY-1 based on a data cutoff (DCO) of December 22, 2022; however, the updated data package submitted to these NDAs has a DCO of June 5, 2023, and includes 140 patients with the additional patient enrolled to Arm 2.

Table 21. Listing of Clinical Studies Relevant to Application

Trial Identity NCT no.	Trial Design	Regimen/ Schedule/Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers/ Countries
Primary Efficacy Study							
DAY101-001/ PNOC026 (FIREFLY-1) NCT04775485	Phase 2, non-randomized, open-label; uncontrolled	Tovorafenib 420 mg/m^2 QW (not to exceed 600 mg QW), on a 28-day cycle Oral	• **Arm 1** **Primary**: IRC-assessed ORR by RANO criteria[a] **Secondary**: Safety and tolerability; PK; QTcF prolongation and ECG; Investigator-assessed ORR by RANO criteria[a] IRC-assessed ORR by RAPNO criteria[b]; PFS, DOR, TTR, and CBR by RANO[a] and RAPNO[b] criteria; changes in BCVA; concordance of local and central BRAF molecular profiling • **Arm 2** **Primary**: Safety and tolerability **Secondary**: ORR by RANO[a] and RAPNO[b] criteria; PFS, DOR, TTR, and CBR by RANO[a] and RAPNO[b] criteria; PK; QTcF prolongation and ECG • **Arm 3** **Primary**: IRC-assessed ORR by RECIST v1.1 **Secondary:** Safety and tolerability; PK; QTcF prolongation and ECG; Investigator-assessed ORR by RECIST v1.1; PFS, DOR, TTR, and CBR by RECIST v1.1; concordance of local and central RAF molecular profiling	Up to 26 cycles Number of treated cycles, median (min, max)[c]: Arm 1: 12 (1, 22) Arm 2: 5 (2, 9) Arm 3: 2 (1, 3)	Planned: 140 Treated: 139[c] Arm 1; N = 77 Arm 2; N = 59 Arm 3; N = 3	Patients 6 months to 25 years of age (inclusive) Arm 1; BRAF-altered, relapsed or refractory pLGG Arm 2; RAF-altered, relapsed or refractory pLGG extension arm Arm 3; advanced solid tumors harboring an activating RAF fusion	36/11 United States Australia Canada Denmark Germany Israel Republic of Korea Nether-lands Singapore Switzer-land United Kingdom
Studies to Support Safety and Efficacy							
C28001 NCT01425008	Phase 1, non-randomized, open-label, dose escalation + dose expansion;	Tovorafenib • Q2D Dose Escalation: 20, 40, 80, 135, 200, and	**Primary**: • Safety and tolerability • Determine the MTD	Number of treated cycles, median (min, max):	Planned: 198 Treated: 149	Adult patients ≥ 18 years of age with relapsed or refractory solid tumors (Dose-	16/2 United States United

Trial Identity NCT no.	Trial Design	Regimen/ Schedule/Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers/ Countries
	uncontrolled	280 mg Q2D on a 22-day cycle; and 200 mg Q2D on a 28-day cycle • Q2D Dose Expansion: 200 mg Q2D on a 28-day cycle • QW Dose Escalation: 400, 600, and 800 mg QW on a 28-day cycle • QW Dose Expansion: 600 mg QW on a 28-day cycle Oral	• Determine the RP2D **Secondary**: • Preliminary efficacy per RECIST v1.1 • PK • PD markers in paired tumor biopsies	Q2D Dose Escalation; 2.0 (1, 38) Q2D Dose Expansion; 2.0 (1, 49) QW Dose Escalation; 1.0 (1, 10) QW Dose Expansion; 2.0 (1, 8)	• Q2D Dose Escalation; N = 30 • Q2D Dose Expansion; N = 80 • QW Dose Escalation; N = 20 • QW Dose Expansion; N = 19	escalation phase) or locally advanced, metastatic, and/or unresectable melanoma (Dose-expansion phase)	Kingdom
Other Studies Pertinent to the Review of Efficacy or Safety							
PNOC014 *(Investigator-sponsored trial)* NCT03429803	**Part A**: Non-randomized, open-label, dose escalation; Uncontrolled **Part B:** (BSA subgroups ≤ 1.5 m^2, > 1.5 m^2): Non-randomized, open-label, dose escalation; Uncontrolled	Tovorafenib Starting dose of 280 mg/m^2 with 2 de-escalation dose levels and 3 dose escalation levels (dosing not capped at 600 mg QW) Followed by doses of 420 mg/m^2 QW (no dose cap) and 530 mg/m^2 QW (no dose cap) in 2 BSA subgroups (≤ 1.5 m^2 and > 1.5 m^2) Oral	**Primary:** • Determine the MTD or RP2D for each study part **Secondary:** • Safety and tolerability • PK profile • Preliminary antitumor activity	Up to 24 cycles planned Number of treated cycles, min, max:[d] 1, 24	Planned: • Part A; N = 9-36 • Part B; N = 4-30 Treated: 44[d] • Part A; N = 9 • Part B; N = 35	Patients 1 to < 25 years of age with pLGG and other RAS/RAF/ MEK/ERK pathway activating tumors	15/1 United States

Trial Identity NCT no.	Trial Design	Regimen/ Schedule/Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers/ Countries
(b) (4) 205140 NCT no.: NA	**Part 1**: Randomized, open-label, single-period 6-way cross-over; Uncontrolled **Part 2**: Randomized, open-label, 3-period cross-over; Uncontrolled	Tovorafenib Part 1: • 125 mg PfR sip and spit (fasted); 6 flavoring/ sweetness tastings Part 2: • Reference tablet (fasted); 300 mg (Period 1) then 100 mg (Periods 2, 3) • PfR (fasted); 300 mg (Period 1) then 100 mg (Periods 2, 3) • Test tablet (fed); 300 mg (Period 1) then 100 mg (Periods 2, 3) Oral	**Primary, Part 1**: • Evaluate palatability and overall acceptability of PfR suspension formulations **Primary, Part 2:** • Determine rBA of PfR compared to tablet • Evaluate PK profiles of tablet and PfR • Assess effect of food on the single dose PK profiles for the tablet **Secondary, Part 2:** • Safety and tolerability	**Part 1**: 6 tastings, 1 hour apart **Part 2**: 1 single dose per period, 3 periods ≥ 14 days apart	Planned: 24 Treated: 24 • Part 1; N = 12 • Part 2; N = 12	Healthy adults 18 to 55 years of age	1/1 United States
DAY101-103 NCT no.: NA	Phase 1, non-randomized, open-label; Uncontrolled	Tovorafenib 100 mg containing approximately 200 µCi of [^{14}C]tovorafenib, fasted Oral	**Primary:** • Routes, elimination rates, and mass balance of total radioactivity • Characterize PK and total radioactivity **Secondary:** • Metabolite profiles in plasma, urine, and feces • Safety and tolerability	Single dose	Planned: 8 Treated: 7	Healthy male adults 18 to 55 years of age	1/1 Unites States
C28002[e] (combination therapy) NCT02327169	Phase 1b, non-randomized, open-label, dose escalation + dose expansion; Uncontrolled	Tovorafenib Dose Escalation: • Tovorafenib Q2D + MLN0128 • Tovorafenib Q2D + alisertib	**Primary:** • Safety • MTD and/or RP2D of each combination regimen **Secondary:** • Plasma PK	Up to 12 cycles planned Number of treated cycles,	Planned: 137 Treated: 81 • Dose Escalation; N = 71	Adult patients with advanced non-hematologic solid tumors	14/4 United States France

Trial Identity NCT no.	Trial Design	Regimen/ Schedule/Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers/ Countries
		• Tovorafenib Q2D + paclitaxel • Tovorafenib QW + paclitaxel • Tovorafenib QW + cetuximab • Tovorafenib QW + irinotecan Dose Expansion: • Tovorafenib QW + paclitaxel Oral	• Preliminary efficacy per RECIST v1.1	median (min, max): Dose Escalation; 2.0 (1, 19) Dose Expansion; 3.5 (1, 15)	• Dose Expansion; N = 10		Spain United Kingdom

Source: Applicant-provided table.

[a] RANO-high-grade glioma criteria is referred as RANO criteria.

[b] RAPNO-LGG criteria is referred as RAPNO criteria.

[c] As of the data cutoff date for FIREFLY-1: 22 December 2022

[d] As of the data cutoff date for PNOC014: 13 October 2022

[e] (b) (4) and no patients completed the maximum number of cycles per protocol.

Abbreviations: BCVA = best-corrected visual acuity; BSA = body surface area; CBR = clinical benefit rate; DOR = duration of response; ECG = electrocardiogram; ERK = extracellular signal-related kinase; IRC = Independent Radiology Review Committee; LGG = low-grade glioma; max = maximum; min = minimum; MEK = mitogen-activated protein kinase kinase; MLN0128 = investigational inhibitor of mechanistic target of rapamycin complexes 1 and 2; MTD = maximum tolerated dose; NCT = National Clinical Trial; ORR = overall response rate; PD = pharmacodynamics; PfR = powder for reconstitution; PFS = progression-free survival; PK = pharmacokinetics; pLGG = pediatric low-grade glioma; Q2D = every other day; QTcF = QT corrected by Fridericia's formula; QW = once weekly; RAF = rapidly accelerated fibrosarcoma; RANO = Response Assessment in Neuro-Oncology; RAPNO = Response Assessment in Pediatric Neuro-Oncology; RAS = rat sarcomavirus; rBA = relative bioavailability; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; TTR = time to response.

8. Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. FIREFLY-1

Applicant's Position

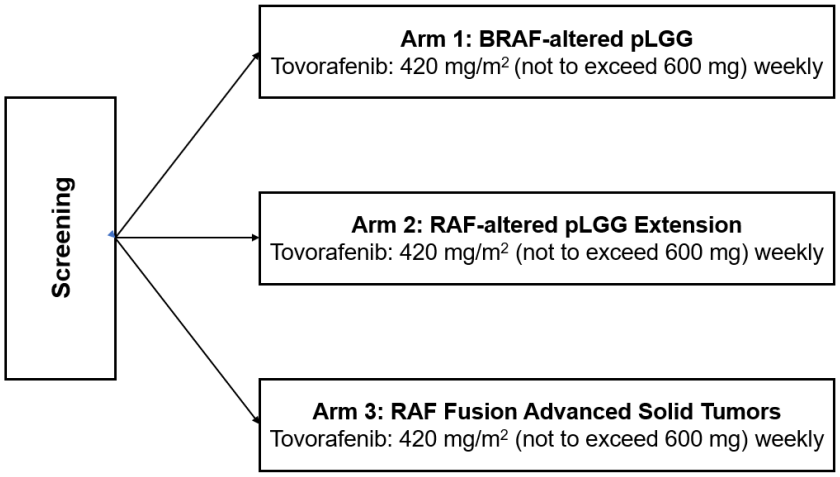
This application is largely based on data from 1 clinical study of tovorafenib in the treatment of patients with RAF-altered pediatric low-grade gliomas, referred to here as Study FIREFLY-1 (also known as DAY101-001 and PNOC026). Efficacy data is based on data from patients in Arm 1 of the study. Safety data is based on data from patients in Arm 1 and Arm 2.

Study FIREFLY-1 is ongoing. Data presented in the body of the application was based on a primary data cut-off date of 22 December 2022, when all treated patients in Arm 1 had either completed 9 months of treatment or discontinued earlier. An update CSR, reflecting data from a 05 June 2023 cutoff, was submitted to complete the application and is summarized in this assessment aid document, with reference to the primary data cut where appropriate.

8.1.1.1. Trial Design

FIREFLY-1 is an ongoing Phase 2, multicenter, multi-arm, open-label study evaluating tovorafenib in patients with pediatric low-grade gliomas and advanced solid tumors. The 3 arms in the study are shown in Figure 15. Arm 3 patients (N=3) are included in the datasets and listings for completeness but are not further considered in this application, due to the difference in disease indication and the small number of patients.

Figure 15. Study Design Schema



Source: Applicant-provided figure.
Abbreviations: BRAF=v-raf murine sarcoma viral oncogene homolog B; pLGG=pediatric low-grade glioma.

Study FIREFLY-1 was conducted in 11 countries (listed in Table 21) with a total of 32 study sites. The countries with the highest percentage of enrolled patients were the US (36.5%) and Australia (19.0%). The study consisted of a screening period, a treatment period, an End-of-Treatment (EOT) visit, a safety follow-up visit, and long-term follow-up assessments. Ongoing safety, disease stability/progression, survival, and subsequent anticancer therapies were assessed in the long-term follow-up period.

8.1.1.2. Study Drug Administration

Tovorafenib was administered at a dose of 420 mg/m^2 (not to exceed 600 mg) by mouth once per week (Days 1, 8, 15, and 22 of a 28-day cycle). Treatment cycles were repeated every 28 days until radiographic evidence of disease progression as determined by the treating investigator, unacceptable toxicity, decision to enter a “drug holiday” period, patient withdrawal of consent, or death. Treatment compliance was monitored via a tovorafenib administration diary completed by the patient or the patient’s parent or legal guardian and reviewed at each clinic visit by the investigator or study nurse.

Patients were to be treated with tovorafenib for a period of 26 cycles (approximately 24 months), after which they could continue on tovorafenib or, at any point, opt to enter a “drug holiday” discontinuation period. Two patients have reached this point and entered a drug holiday within approximately 1 month prior to the data cutoff date of 05 June 2023.

8.1.1.3. Administrative Structure

Safety and efficacy data across the entire tovorafenib program were monitored by an independent Data Safety Monitoring Board (DSMB), which met approximately every three months to review the data. In addition, Arm 2 of FIREFLY-1 was opened based on the recommendation of the DSMB to enroll additional patients prior to approval of tovorafenib and access to commercial drug.

Determination of response by all 3 imaging criteria: RANO-HGG, RAPNO, and RANO-LGG, were based on blinded independent central review of all radiographic scans. In the case of discrepant results, adjudication was performed by a third reader.

The FDA's Assessment

The FDA's primary review of efficacy for this application is based on 76 patients with measurable disease at baseline per RAPNO-LGG criteria, who were enrolled in Arm 1 of the FIREFLY-1 study, with a data cut-off date of June 5, 2023.

8.1.1.4. Eligibility Criteria

Applicant's Position

This study enrolled patients (6 months to 25 years old, inclusive) with RAF-altered, relapsed or progressive low-grade glioma and advanced solid tumors.

The key inclusion criteria were:

- Arm 1 (pivotal, low-grade glioma): Relapsed or progressive low-grade glioma with a documented known activating BRAF alteration as identified through molecular assays as routinely performed at Clinical Laboratory Improvement Amendments (CLIA) or other similarly certified laboratories.
- Arm 2 (expansion cohort, low-grade glioma): Relapsed or progressive low-grade glioma with a documented known or expected to be activating BRAF mutation or RAF fusion, as identified through molecular assays as routinely performed at CLIA-certified or other similarly certified laboratories.
- Arm 3 (advanced solid tumor): Locally advanced or metastatic solid tumor with a documented known or expected to be activating RAF fusion, as identified through molecular assays as routinely performed at CLIA-certified or other similarly certified laboratories, that has relapsed or progressed or was nonresponsive to available therapies and for which no standard or available systemic curative therapy exists.

Patients must have had histopathologic verification of malignancy at either original diagnosis or relapse, must have received at least one line of prior systemic therapy, and must have had documented evidence of radiographic progression. Patients were required to have evaluable and/or measurable disease (imaging had to be performed within 28 days of the initiation of treatment) by criteria defined by the study protocol (RANO-HGG criteria for Arms 1 and 2, and Response Evaluation Criteria in Solid Tumours [RECIST] v1.1 for Arm 3). All patients in Arm 1 were required to have measurable disease at baseline.

The key exclusion criteria were:

- Additional previously known or expected to be activating molecular alteration(s), eg, histone mutation, IDH1/2 mutations, FGFR mutations or fusions, MYBL alterations, NF1 somatic or germline mutations
- Known or suspected diagnosis of neurofibromatosis type 1
- History or current evidence of central serous retinopathy, retinal vein occlusion, or ophthalmopathy present at baseline that would be considered a risk factor for central serous retinopathy or retinal vein occlusion
- Clinically significant history of or active cardiovascular disease
- Active systemic bacterial, viral, or fungal infection
- History of any drug reaction with eosinophilia and systemic symptoms syndrome or Stevens-Johnsons syndrome

The FDA's Assessment

The FDA agrees with the Applicant's presentation of eligibility criteria for FIREFLY-1 and emphasizes that patients were enrolled into non-randomized cohorts labeled as "Arms 1, 2 and 3". Additionally, patients in Arm 1 were required to have at least one measurable lesion as defined by RANO criteria, while patients enrolled in Arm 2 were required to have evaluable and/or measurable disease as defined by RANO criteria. For the purposes of this review, Arm 1 provided the primary data to assess efficacy of tovorafenib in patients with pediatric LGG. Efficacy results from Arm 2 were not submitted or reviewed for this application as the data were immature.

Other relevant eligibility criteria are listed below:

- Patients in Arm 1 must have an archival tumor tissue sample available to participate in the study.
- Radiation therapy to measurable lesion(s) must be completed at least six months prior to the administration of tovorafenib. Patients who have documented radiographic progression less than six months from one or more measurable lesions are eligible.

Regarding the detection of an activating BRAF alteration to confirm eligibility for FIREFLY-1, the methods of molecular testing used for identification were based on institutional preference/availability at the time of diagnosis, and as such, a range of testing methods (e.g., fluorescence in-situ hybridization [FISH], immunohistochemistry [IHC], next-generation sequencing [NGS], polymerase chain reaction [PCR], etc.) were used to support study enrollment.

8.1.1.5. Study Endpoints

Applicant's Position

Objectives and endpoints for Arm 1 of Study FIREFLY-1 are provided in Table 22, as only Arm 1 was analyzed for efficacy in this application.

Table 22. FIREFLY-1 Arm 1 (pivotal, low-grade glioma) Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of tovorafenib as measured by the ORR as determined by an IRC following treatment with tovorafenib in pediatric patients aged 6 months to 25 years, inclusive, with a relapsed or progressive low-grade glioma harboring a known activating BRAF alteration	• ORR, defined as the proportion of patients with best overall confirmed response of CR or PR as determined by the RANO criteria
Secondary	
• To assess the safety and tolerability of tovorafenib	• Type, frequency, and severity of AEs and laboratory abnormalities
• To determine the ORR based on the treating investigator's response assessment using RANO criteria	• Measured by the proportion of patients with best overall confirmed response of CR or PR by RANO criteria
• To determine the ORR based on RAPNO criteria as determined by an IRC	• Measured by the proportion of patients with best overall confirmed response of CR, PR, or MR by RAPNO criteria
• To evaluate the duration of PFS based on RANO and RAPNO criteria following initiation of tovorafenib as determined by 1) an IRC and 2) the treating investigator (RANO only)	• Measured by the time following initiation of tovorafenib to progression or death in patients treated with tovorafenib
• To evaluate DOR in patients with best overall response of CR or PR or MR (RAPNO only) based on RANO and RAPNO criteria as determined by 1) an IRC and 2) the treating investigator (RANO only)	• Measured by the length of response in patients with best overall confirmed response of CR or PR or MR (RAPNO only) by RANO and RAPNO criteria, as applicable

Objectives	Endpoints
• To evaluate TTR (CR or PR or MR [RAPNO only] based on RANO and RAPNO criteria) following initiation of tovorafenib as determined by 1) an IRC and 2) the treating investigator (RANO only)	• Measured by the time to first response following initiation of tovorafenib in patients with best overall confirmed response of CR or PR by RANO and CR, PR, or MR by RAPNO criteria
• To evaluate the clinical benefit rate based on the proportion of patients with best overall response of CR, PR, MR (RAPNO only) or stable disease, based on RANO and RAPNO criteria, lasting 12 months or more following initiation of tovorafenib, as determined by 1) an IRC and 2) the treating investigator (RANO only)	• Measured by the proportion of patients with best overall response of CR, PR, MR (RAPNO only) or stable disease lasting 12 months or more following initiation of tovorafenib
• To evaluate the duration of OS following initiation of tovorafenib	• Measured by the time following initiation of tovorafenib to death of any cause in patients treated with tovorafenib
• To evaluate changes in BCVA outcomes	• Measured by change from baseline in BCVA (converted as logMAR) for each eye
Other Relevant Endpoints	
• To evaluate time to initiation of next treatment following discontinuation of tovorafenib	• Measured by the proportion of patients who discontinue tovorafenib therapy and time to next therapy initiation
• To determine the ORR based on RANO-LGG as determined by an IRC	• Measured by the proportion of patients with best overall confirmed response of CR or PR or MR by RANO-LGG criteria
• To evaluate the duration of PFS based on RANO-LGG criteria following initiation of tovorafenib as determined by an IRC	• Measured by the time following initiation of tovorafenib to progression by RANO-LGG criteria or death in patients treated with tovorafenib
• To evaluate DOR in patients with best overall response of CR or PR or MR based on RANO-LGG criteria as determined by an IRC	• Measured by the length of response in patients with best overall confirmed response of CR or PR or MR by RANO-LGG criteria
• To evaluate TTR (CR or PR or MR based on RANO-LGG criteria) following initiation of tovorafenib as determined by an IRC	• Measured by the time to first response following initiation of tovorafenib in patients with best overall confirmed response of CR or PR or MR by RANO-LGG criteria
• To evaluate the clinical benefit rate based on the proportion of patients with best overall response of CR, PR, MR or stable disease lasting 12 months or more following initiation of tovorafenib based on RANO-LGG criteria, as determined by an IRC	• Measured by the proportion of patients with best overall response of CR, PR, MR or stable disease lasting 12 months or more following initiation of tovorafenib by RANO-LGG criteria

Source: Applicant-provided table.

Note: "RANO" in this table refers to RANO-HGG (Wen 2010), and "RAPNO" refers to RAPNO-LGG (Fangusaro 2020).

Abbreviations: AE = adverse event; BCVA = best corrected visual acuity; BRAF = v-raf murine sarcoma viral oncogene homolog B; CR = complete response; DOR = duration of response; HGG = high-grade glioma; IRC = Independent Radiology Review Committee; LGG = low-grade glioma; MR = minor response; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RANO = Response Assessment in Neuro-Oncology; RAPNO = Response Assessment in Pediatric Neuro-Oncology; TTR = time to response.

The FDA's Assessment

Due to the radiographically distinct nature of pediatric LGG, which shows minimal contrast enhancement on imaging unlike high-grade glioma, the FDA considers response criteria that rely upon percent change in the T2/FLAIR signal rather than contrast enhancement to be more appropriate for evaluation of efficacy in the target patient population. Therefore, although the primary endpoint for Arm 1 in FIREFLY-1 was ORR assessed by BICR per RANO-HGG criteria, the FDA's analysis of efficacy is primarily based upon tumor assessments by BICR according to RAPNO-LGG criteria, which was notably a secondary endpoint in this study.

In contrast to the RANO-HGG criteria which classify responses as only complete response and partial response based upon measurement of 2D contrast enhancement and T2/FLAIR, the RANO-LGG criteria incorporate a third response category of "minor response" (MR) (i.e., 25% to <50% decrease in a target lesion based upon T2/FLAIR measurement) and RAPNO-LGG criteria incorporate MR as well as a fourth category of "major responses" (i.e., ≥75% reduction in a target lesion based upon T2/FLAIR measurement but less than a complete response). The FDA's review of efficacy data in FIREFLY-1 is based on occurrence of minor response, partial response and complete response in study patients.

The FDA considers the endpoint of "clinical benefit rate" to be exploratory in nature. Additionally, in a single arm trial, FDA does not consider time-to-event endpoints to be interpretable, and hence the corresponding analyses were considered descriptive and were not confirmed by the FDA review.

8.1.1.6. Statistical Analysis Plan

Applicant's Position

Efficacy analyses were performed for Arm 1 only, using a data cutoff date of 05 June 2023, which is approximately 15 months after the last patient was enrolled into Arm 1.

Description of Analysis Sets

Full Analysis Set: All patients enrolled into Arm 1 who received at least one dose of study treatment and had measurable disease at baseline per RANO-HGG criteria per the IRC.

RANO-LGG Analysis Set: All patients enrolled into Arm 1 who received at least one dose of study treatment and had measurable disease at baseline per RANO-LGG criteria per the IRC.

RAPNO Analysis Set: All patients enrolled into Arm 1 who received at least one dose of study treatment and had measurable disease at baseline per RAPNO criteria per the IRC.

Safety Analysis Set: All patients enrolled in the study who received at least one dose of study treatment.

Per-protocol Analysis Set: All patients in the Full Analysis Set without any major protocol deviations as defined by the process below.

Protocol deviations were reviewed, assessed, and classified within a data review meeting before database lock. The Per-protocol Analysis Set was used to conduct sensitivity analyses for primary efficacy endpoints ORR and for Arm 1 PFS. Upon database release, protocol deviations were sent to the Sponsor for review. Decisions regarding the exclusion of patients and/or patient data from the Per-protocol Analysis Set were made prior to database lock.

Pharmacokinetic Analysis Set: Patients in the Full Analysis Set who had at least one measurable PK concentration.

Primary Efficacy Analysis: IRC-assessed ORR using RANO-HGG Criteria

The primary efficacy endpoint ORR was calculated by the number of patients with best overall confirmed response of CR or PR as determined by an IRC using RANO-HGG criteria (Wen 2010) for the Arm 1 Full Analysis Set. An exact binomial test was used to compare the observed response rate to the hypothesized null ORR of 21%, and a 95% confidence interval (CI) was calculated using the Clopper-Pearson method.

A response was considered a confirmed response when a response assessment of CR or PR was confirmed by a second scan ≥ 28 days after the initial response. If a CR with confirmation scan showed PR or if a PR with confirmation scan showed CR, PR was assigned.

Patients with initial CR or PR after the start of subsequent anticancer therapy were not included as responders in the ORR calculation.

Sensitivity analyses for Arm 1 ORR was performed based on the Per-protocol Analysis Set.

The uniformity of the treatment effects for the primary efficacy analysis was performed for Arm 1 in the following subgroups, based on the Full Analysis Set: BRAF alteration (BRAF fusion versus BRAF mutation), number of prior lines of therapies, prior mitogen-activated protein kinase (MAPK) inhibitor therapy, prior BRAF inhibitor therapy, sex, age group, and race. The same methodology as the ORR primary analysis was performed in each subgroup.

Secondary Efficacy Analyses

The number and percentage of patients with best overall confirmed response (CR, PR, or MR) using RAPNO criteria (Fangusaro 2020) were calculated for Arm 1 based on IRC assessment in the same manner described above for RANO-HGG. Best overall response was defined as the best response (CR, PR, MR, stable disease, PD, and NE) recorded from the start of the treatment until disease progression/recurrence or death (taking the smallest measurements recorded since the treatment started as a reference for PD). Patients with confirmed MR by RAPNO were considered as responders. If a CR/PR with confirmation scan showed MR or if an MR with confirmation scan showed CR/PR, MR was assigned.

A swimmer plot was provided for confirmed CR/PR, MR (RAPNO only), stable disease, PD, and NE based on different response assessment criteria by IRC.

Progression-free survival were summarized in the efficacy analysis populations of Arm 1 and graphically displayed by the Kaplan-Meier method. The number (%) of patients with PFS events due to disease progression or death, and categories of PFS censoring reason were summarized. Kaplan-Meier curves, estimates 25th, 50th (median), and 75th percentiles along with their corresponding 2-sided 95% CIs for PFS were presented. The percentage of patients with PFS and 95% CI at timepoints 3, 6, 12, 18, and 24 months were provided. Arm 1 PFS by IRC/investigator were repeated for the Per-protocol Analysis Set.

Duration of response (DOR) was analyzed using the same methodology as for the analysis of PFS. The analysis was performed in the efficacy analysis populations who had a best overall confirmed response of CR, PR, or MR (RAPNO only).

Statistical summaries for time to response were provided based on the efficacy analyses populations. The clinical benefit rate was analyzed using the same method as ORR. Descriptive summaries were provided for OS data.

Other Relevant Endpoints

IRC-assessed ORR, PFS, DOR, TTR, and clinical benefit rate based on RANO-LGG criteria (van den Bent 2011) were analyzed in the same manner as described above for RANO-HGG. These analyses were performed in the RANO-LGG Evaluable Analysis Set. In keeping with recommendations from the RANO-LGG group and its publication (van den Bent 2011), and consistent with clinical practice for this disease, patients with confirmed MR by RANO-LGG were considered responders along with confirmed CR or PR. If a CR/PR with confirmation scan showed MR or if an MR with confirmation scan showed CR/PR, MR was assigned. Patients with initial CR, PR or MR (RANO-LGG) after the start of subsequent anticancer therapy were not included as responders in the ORR analysis.

The Arm 1 ORR and time to response based on RANO-HGG, RANO-LGG, and RAPNO criteria by IRC were summarized by the number of prior lines of therapies. The ORR by the number of prior lines of therapies was calculated with the corresponding 95% CI using the Clopper-Pearson method for each subgroup of the number of prior lines of therapies if there were

sufficient data in each subgroup. Time to response by the number of prior lines of therapies were summarized.

The sum of products of the perpendicular diameters (SPPD) and tumor volume original values, changes from baseline at each scheduled visit and the best change from baseline were summarized. Waterfall plots with each patient's best percentage change in SPPD/tumor volume ordered from the largest increase to the largest decrease was provided. Spider plots for the SPPD/tumor volume change from baseline over time were also provided.

Analyses for PFS by best overall response were performed in the RANO-LGG Evaluable Analysis Set and the RAPNO Evaluable Analysis Set in the same manner described above for RANO-HGG in the Full Analysis Set.

Handling of Missing Data

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

All analyses and descriptive summaries were based on the observed data. Unless otherwise specified, missing data were not imputed. The number and percentage of patients with missing data were summarized by major reasons.

A revision history for the Statistical Analysis Plan for Study FIREFLY-1 is provided in Table 23.

Table 23. Study FIREFLY-1 Statistical Analysis Plan Revision History

Version No.	Effective Date	Summary of Changes
1.0	March 18, 2022	NA
1.1	May 9, 2022	Section 3.3.1 – modified full analysis set definition to include patients treated with DAY101 irrespective of their post baseline data availability. Section 4.2.2 – updated drug exposure summary based on the study CRF design and data entry guideline Other section – editorial changes and clarification
2.0	August 5, 2022	Section 4.2.4.1.2 – added AESI summary. Section 4.2.4.4 – removed the languages handling the cases that individual QTc ≥ 500 but the mean QTc < 500; clarified the portion of ECG analyses to be included in the cardiac safety modeling report; removed summary of morphological ECG changes. Other section – editorial changes.
3.0	October 25, 2022	Section 4.2.4.1.2 – revised the scope of Rhabdomyolysis and Intra-tumoral hemorrhage AESIs in accordance with clinical relevance. Other section – editorial changes.
4.0	February 3, 2023	Section 3.4.3.6 – added ORR, BOR, PFS, DOR, TTR and CBR based on RANO-LGG by IRC for Arm 1 as exploratory endpoints. Section 4.2.3.3.5 – added analyses methodology for ORR, BOR, PFS, DOR, TTR and CBR based on RANO-LGG by IRC. Section 4.2.4.4 – removed the summary of ECG clinical significance assessment based on data collected from clinical database. Other sections – editorial changes.
5.0	June 5, 2023	Section 3.3.1 and 4.1.1– added analysis population set for efficacy endpoints based on RANO-LGG/ RAPNO-LGG Section 3.4.3.7, 3.4.3.8 and 4.2.3.3.6 – added exploratory analyses of PFS by BOR based on RANO-LGG/RAPNO-LGG Section 4.2.3.3.7 – added Analysis of Ongoing Treatment by IRC-assessed Best Overall Response (RANO-HGG) Other section – editorial changes.

Source: Applicant-provided table.

The FDA's Assessment

In general, the FDA agrees with the description provided by the Applicant. The study had originally planned to enroll 60 patients each in Arm 1 and Arm 2, respectively, and an additional 20 patients in Arm 3. In Arm 1, per the statistical analysis plan (SAP), assuming a null hypothesis of ORR of 21% and an alternative hypothesis of ORR of 40% with two-sided type I error rate of 0.05, a sample size of 60 will provide 88% power. FDA does not consider inferential procedures

in the evaluation of single arm study results. Instead, the efficacy evaluation is based on the magnitude of response rate and durability of response.

The FDA's analysis is based on a data cut-off date of June 5, 2023. At that time, 77 patients were enrolled in Arm 1 (of which 76 patients had measurable disease at baseline per RAPNO-LGG criteria), 60 patients were enrolled in Arm 2, and 3 patients were enrolled in Arm 3.

8.1.1.7. Protocol Amendments

Applicant's Position

The original protocol (Version 1.0), dated 28 July 2020, was amended twice. Important changes in the conduct of the study are described below in Table 24.

Table 24. Protocol Amendments

Number (date of internal approval)	Description of Change	Brief Rationale
Version 2.0 (global) (23 October 2020)	The RP2D for tovorafenib was changed from 530 mg/m^2 to 420 mg/m^2. [redacted]	Based on feedback from FDA and available data from Study PNOC014, it was determined that [redacted] the safety of the RP2D of 420 mg/m^2 had been established. Subsequently in study PNOC014, 6 DLTs were observed in the 22 patients treated at the 530 mg/m^2 dose (3 in > 1.5 m^2 and 3 in ≤ 1.5 m^2 BSA subgroups). Per the study investigator and statistician, [redacted] and the good tolerability, high response rate, and longer duration of dosing achieved at 420 mg/m^2 in the interim analysis for the FIREFLY-1 study confirmed the RP2D of 420 mg/m^2.
	The upper age limit for patient inclusion was increased from 18 years to 25 years, inclusive.	To increase enrollment rate and enable the evaluation of tovorafenib in this expanded age range.
	The maximum dose of tovorafenib was decreased from 800 to 600 mg, once weekly.	Based on feedback from FDA. The 600-mg dose was established as safe in the adult Phase 2 study (C28001).
	The planned number of cycles was changed from 27 to 26 cycles. Patients could still continue on study treatment beyond this if criteria were met.	Dosing was intended to continue for approximately 24 months (equivalent to 26 cycles).
	[redacted] was deleted.	Based on feedback from FDA.
	Patients with a history of drug reaction with eosinophilia and systemic symptoms syndrome and Stevens Johnsons syndrome were now excluded.	Added based on similar class effects given the limited experience with tovorafenib in the target population.
	The Vineland-3 Motor Skills questionnaire was only to be administered to patients with baseline motor function deficits	To allow consistent assessments by trained personnel and because this questionnaire was not widely used outside the US.

Number (date of internal approval)	Description of Change	Brief Rationale
	enrolled in the US, and only by third-party (trained and centralized) personnel. A time point at Cycle 39 was added.	
Version 2.1 (UK only) (09 November 2020) This amendment was an update of Version 1.0	The RP2D for tovorafenib was changed from 530 mg/m^2 to 420 mg/m^2. (b) (4)	Based on feedback from Medicines and Healthcare products Regulatory Agency (MHRA) and available data from Study PNOC014. (b) (4) The safety of the recommended Phase 2 dose of 420 mg/m^2 has been established in Study PNOC014.
Version 2.4 (Germany only) (12 February 2021)	In addition to the changes listed above for Version 2.0, the following changes were made: • The lower age limit was changed from (b) (4) to 6 years. • The benefit/risk assessment was revised to include a summary of risks from nonclinical studies and the Phase 1 clinical study, dosing considerations, drug metabolism, considerations for required study procedures for the pediatric population, the safety monitoring and risk management plan, and a summary of potential benefits.	Based on feedback from Federal Institute for Drugs and Medical Devices (BfArM).
Version 2.5 (Germany only) (19 March 2021)	The definition for end of study was updated to the date when the last visit occurs for the last patient enrolled.	Based on feedback from Federal Institute for Drugs and Medical Devices (BfArM).

Number (date of internal approval)	Description of Change	Brief Rationale
Version 3.0 (global) (21 October 2021) Version 2.0 (global)	Two new arms were added to the protocol. Arm 2 is an expansion cohort to enroll patients with a low-grade glioma harboring an activating RAF alteration (eg, BRAF or CRAF/RAF1 fusion or BRAF V600 mutations) and was added to provide treatment options to patients following the closure of Arm 1 and prior to commercial availability of tovorafenib. Arm 3 was added to enroll patients with advanced solid tumors harboring activating RAF fusions (eg, BRAF or CRAF/RAF1 fusions). The background, rationale, objectives, design, eligibility criteria, assessments, and statistical analyses sections were revised to incorporate these new arms. The number of study sites was changed from 35 to 40. The efficacy analyses section was updated.	Based on data obtained from other tovorafenib studies and feedback from health authority. The number of study sites was increased to enable enrollment of pediatric patients with advanced solid tumors. The planned efficacy analysis description was updated for the newly added Arms 2 and 3.
	A powder for reconstitution formulation of tovorafenib was added. The investigational product description and general dosing instructions were revised to include details specific to this formulation. Inclusion Criterion 18 was revised to allow patients who are able to swallow liquid or are willing to comply with feeding tube administration to be eligible for the study.	To enable use of a liquid formulation of tovorafenib for patients unable to swallow tablets.
	The requirements for specific visual acuity testing procedures were revised to allow age-appropriate assessments.	To allow for regional differences and age-appropriate testing procedures across sites and countries.
	The definition for end of study was updated to the date when the last visit occurs for the last patient enrolled.	Based on feedback from Federal Institute for Drugs and Medical Devices (BfArM).
	Inclusion Criterion 8 was clarified to add criteria for patients with ongoing retinopathy from prior anticancer therapy.	To minimize the risk of significant ocular toxicities in patients with pre-existing retinopathy.
	The eligibility requirement for patients to have an international normalized ratio < 2.0 was removed from Inclusion Criterion 12.	Administrative clarification.

Number (date of internal approval)	Description of Change	Brief Rationale
	The DLT section was consolidated with dose modifications and management of treatment-related events (sections 5.2.2 and 5.2.3). TEAEs previously considered DLTs for patients enrolled in the safety run-in were incorporated into Table 9 requiring dose interruption.	Terminology changes, (b) (4) was no longer being conducted (previously removed in Protocol Version 2.0).
	The restriction with regard to intake of food was removed; patients could now be fed or fasted.	Based on the lack of significant effect of food on PK parameters demonstrated in Study (b) (4) 205140.
	Medications that are substrates of BCRP were added as prohibited concomitant medications and a table of BCRP substrates was added.	Based on feedback from Ministry of Food and Drug Safety (MFDS).
	Clarification was added that on-treatment ophthalmology examinations and visual acuity assessments were only required for patients with optic pathway glioma or patients with underlying visual deficits related to the primary malignancy. For all other patients, examinations were only required at screening, and symptom-directed examinations could be completed at subsequent visits. Clarification was added that visual acuity assessment could be performed based on local standard practice.	For consistency with standard clinical practice.
	Added assessments of pubertal development according to the Tanner Stages.	Based on feedback from FDA.
	Phosphorous was added as part of the serum chemistry panel. International normalized ratio, cholesterol, and direct bilirubin were removed from the chemistry assessments.	To follow as part of regular safety monitoring, and to reduce unnecessary analyte collection.
	TSH was added as part of the thyroid function tests.	To ensure comprehensive monitoring of thyroid function.
	Clarified that blood sample collections for tovorafenib PK after Cycle 4 were to be collected every subsequent third cycle through Cycle 13, rather than until Cycle 27.	To reduce patient sampling burden after adequate characterization of tovorafenib PK through approximately 1 year after the initiation of therapy.
	The definitions for assessing relationship to study treatment were modified.	Based on feedback from Federal Institute for Drugs and Medical Devices (BfArM).

Source: Applicant-generated table.

FDA's Assessment

The FDA agrees with the Applicant's summary of changes made in the two amendments to the global protocol for FIREFLY-1 that was implemented in the US. The FDA is unable to verify the Applicant's description of revisions made in foreign versions of the protocol (e.g., the version used for study conduct in Germany).

8.1.2. Study Results

8.1.2.1. Compliance With Good Clinical Practices

Applicant's Position

This study was conducted in accordance with the protocol and consensus ethical principles derived from international guidelines including the Declaration of Helsinki, Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable International Council for Harmonisation (ICH) GCP Guidelines, and other applicable laws and regulations.

The protocol, protocol amendments, informed consent form (ICF), pediatric assent form, Investigator Brochure, and other relevant documents (eg, advertisements) were submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) at the study sites and reviewed and approved by the IRB/IEC before the study was initiated.

Patients and/or their legally authorized representative were informed that their participation was voluntary. Patients or their legally authorized representative were required to sign a statement of informed consent that met the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

The FDA's Assessment

The FDA acknowledges the Applicant's statement of compliance with Good Clinical Practice (GCP) guidelines and other applicable laws and regulations. Additionally, in Module 2.5 (*Clinical Overview*), the applications include a statement that all clinical trials were appropriately conducted, including study at foreign sites.

8.1.2.2. Financial Disclosure

Applicant's Position

Financial disclosure information is available in Appendix 19.2.

The FDA's Assessment

The FDA agrees that financial disclosures were provided by the Applicant. Refer to Section 19.2 for details. In the FDA's assessment, the steps taken to minimize any potential investigator bias of the clinical trial results were sufficient.

8.1.2.3. Patient Disposition

Applicant's Position

This multicenter study was conducted at 32 study sites that enrolled patients in 11 countries. As of the data cutoff date (05 June 2023), 77 patients were enrolled and treated in Arm 1 and 60 patients were enrolled and treated in Arm 2 (Table 25). In Arm 1, 26 (33.8%) patients discontinued tovorafenib, most commonly due to progressive disease (10.4%). Seven patients discontinued the study (3 patients were withdrawn by the parent or guardian, 2 patients died, and 2 patients withdrew). In Arm 2, 9 (15.0%) patients discontinued tovorafenib, most commonly due to progressive disease (5.0%) or AE (5.0%). One patient in Arm 2 discontinued the study due to death.

The median duration on study was 13.9 months for the Safety Analysis Set and 16.7 months for the Full Analysis Set, with most patients in Arms 1 and 2 still on treatment as of the data cutoff date (74.5% in the Safety Analysis Set and 66.7% in the Full Analysis Set). The median duration of tovorafenib exposure was 362.0 days, with a median of 13 treatment cycles (see Section 8.2.2.1).

Table 25. Patient Disposition

	Safety Analysis Set			Full Analysis Set
Characteristic	Arm 1 (LGG) N=77	Arm 2 (LGG) N=60	Arm 1 + Arm 2 (LGG) N=137	Arm 1 (LGG) N=69
Patients received study treatment, n (%)	77 (100)	60 (100)	137 (100)	69 (100)
Patients who discontinued study treatment, n (%)	26 (33.8)	9 (15.0)	35 (25.5)	23 (33.3)
Primary reason for treatment discontinuation				
Progressive disease	8 (10.4)	3 (5.0)	11 (8.0)	6 (8.7)
Adverse event	7 (9.1)	3 (5.0)	10[a] (7.3)	7 (10.1)
Withdrawal by parent or guardian	5 (6.5)	1 (1.7)	6 (4.4)	4 (5.8)
Other	3[b] (3.9)	2[c] (3.3)	5 (3.6)	3 (4.3)
Withdrawal by subject	2 (2.6)	0	2 (1.5)	2 (2.9)
Death	1 (1.3)	0	1 (0.7)	1 (1.4)
Patients who discontinued study early, n (%)	7 (9.1)	1 (1.7)	8 (5.8)	6 (8.7)
Primary reason for early study discontinuation				
Withdrawal by parent or guardian	3 (3.9)	0	3 (2.2)	2 (2.9)
Death	2[d] (2.6)	1[e] (1.7)	3 (2.2)	2 (2.9)
Withdrawal by subject	2 (2.6)	0	2 (1.5)	2 (2.9)
Death	2 (2.6)	1 (1.7)	3 (2.2)	2 (2.9)
Death within 30 days after the end of treatment	1 (1.3)	1 (1.7)	2 (1.5)	1 (1.4)
Death >30 days after the end of treatment	1 (1.3)	0	1 (0.7)	1 (1.4)
Study duration (months)				
Mean (SD)	17.46 (4.310)	10.05 (1.734)	14.22 (5.030)	17.47 (4.049)
Median	17.00	10.00	13.90	16.70
Min, Max	1.1, 25.5	4.3, 13.3	1.1, 25.5	1.1, 25.0

Source: FIREFLY-1 Update CSR Table 14.1.1.1, Table 14.1.1.1.a, Table 14.1.1.9, Table 14.1.1.9.1.

[a] Includes adverse events that occurred > 30 days post last dose of study treatment.

[b] "Other" reason for discontinuing tovorafenib was entering drug holiday for 2 patients and clinical progression for 1 patient.

[c] "Other" reason for discontinuing tovorafenib was clinical progression for both patients.

[d] One patient had Grade 5 neurological decompensation considered attributable to the patient's underlying disease, not related to tovorafenib. The second patient had Grade 5 hydrocephalus considered not related to tovorafenib.

[e] One patient had Grade 5 tumor hemorrhage considered not related to tovorafenib.

Note: Study duration is defined as (end of study date – first dose date +1)/30.4375. For ongoing patients, data cutoff date is used for end of study date.

Data Cutoff Date:05 June 2023.

Abbreviations: LGG = low-grade glioma; SD = standard deviation.

The FDA's Assessment

The following table presents the FDA's review of treatment history based on 76 patients with measurable disease at baseline per RAPNO-LGG criteria, who were enrolled in Arm 1 of the FIREFLY-1 study, with a data cut-off date of June 5, 2023.

Table 26. Treatment History

Characteristic	Efficacy Population N=76
Treatment discontinuation	
Patients still on study treatment, n (%)	51 (67)
Patients who discontinued study treatment, n (%)	25 (33)
Primary reason for treatment discontinuation	
Progressive disease	7 (9)
Withdrawal by parent or guardian	5 (7)
Adverse event	7 (9)
Withdrawal by subject	2 (2.6)
Death	1 (1.3)
Other	3 (3.9)
Study discontinuation	
Patients still on the study, n (%)	69 (91)
Patients who discontinued study early, n (%)	7 (9)
Primary reason for early study discontinuation	
Withdrawal by parent or guardian	3 (3.9)
Withdrawal by subject	2 (2.6)
Death	2 (2.6)

Source: Sponsor-provided ADaM dataset adsl.xpt

8.1.2.4. Protocol Violations/Deviations

Applicant's Position

Major protocol deviations were defined as those deviations from the protocol likely to have an impact on the patient's rights, safety, well-being, and/or on the validity of the data for analysis.

Thirty-seven (27.0%) patients had major protocol deviations, most involving informed consent (most commonly failure to reconsent to revised versions of the informed consent form). These major protocol deviations did not impact patient safety or data quality, and none of the patients with major protocol deviations were excluded from Per-protocol Analysis Set.

The FDA's Assessment

The FDA generally agrees with the Applicant's description of major protocol deviations that occurred in 37 patients. Most protocol deviations (28 of the 37 patients affected in total) were related to informed consent procedure, followed by erroneous investigational product administration/study treatment in which 7 patients were administered the wrong dose of tovorafenib, delay in adverse event/serious adverse event reporting (3 patients), administration of prohibited medications (pantoprazole and cimetidine) in 3 patients, and violation of eligibility criteria in 2 patients (1 related to imaging obtained at screening and the other due to a missing laboratory result prior to enrollment), and 1 patient without required MRI at a follow-up visit. The protocol deviations described above are not expected to affect interpretability of study results.

8.1.2.5. Table of Demographic Characteristics

Applicant's Position

As of the data cutoff date (05 June 2023), the median age for all patients in the Safety Analysis Set in Arms 1 and 2 was 9.0 years (range: 1.0 to 24.0 years) (Table 27). A total of 47.4% of patients were 6 to < 12 years of age. Approximately 60% of patients were white, and 71.5% were not Hispanic or Latino. Approximately half (53.3%) of the patients were male. Median height and weight percentiles at baseline were 43.1% and 66.3%, respectively.

Table 27. Demographics and Baseline Characteristics (safety analysis set; arms 1 and 2)

Characteristic	Arm 1 (LGG) N=77	Arm 2 (LGG) N=60	Arm 1 + Arm 2 (LGG) N=137
Age at baseline (years)			
Mean (SD)	9.169 (3.9947)	9.328 (5.3108)	9.238 (4.6000)
Median (min, max)	8.000 (2.00, 21.00)	9.500 (1.00, 24.00)	9.000 (1.00, 24.00)
Age group, n (%)			
6 months to <2 years	0	3 (5.0)	3 (2.2)
2 years to <6 years	14 (18.2)	13 (21.7)	27 (19.7)
6 years to <12 years	41 (53.2)	24 (40.0)	65 (47.4)
12 years to <16 years	16 (20.8)	11 (18.3)	27 (19.7)
16 years to ≤25 years	6 (7.8)	9 (15.0)	15 (10.9)
Sex, n (%)			
Male	40 (51.9)	33 (55.0)	73 (53.3)
Female	37 (48.1)	27 (45.0)	64 (46.7)
Race, n (%)			
Black or African American	2 (2.6)	1 (1.7)	3 (2.2)
Asian	5 (6.5)	5 (8.3)	10 (7.3)
White	41 (53.2)	38 (63.3)	79 (57.7)
Multiple	3 (3.9)	0	3 (2.2)
Other	6 (7.8)	2 (3.3)	8 (5.8)

Characteristic	Arm 1 (LGG) N=77	Arm 2 (LGG) N=60	Arm 1 + Arm 2 (LGG) N=137
Not reported	20 (26.0)	14 (23.3)	34 (24.8)
Ethnicity, n (%)			
Hispanic or Latino	3 (3.9)	1 (1.7)	4 (2.9)
Not Hispanic or Latino	51 (66.2)	47 (78.3)	98 (71.5)
Not Stated	21 (27.3)	12 (20.0)	33 (24.1)
Missing	2 (2.6)	0	2 (1.5)
Height percentile at baseline[a] (%)			
N	76	58	134
Mean (SD)	46.568 (29.8176)	47.416 (31.8899)	46.935 (30.6168)
Median (min, max)	41.840 (0.04, 99.84)	47.730 (0.00, 99.99)	43.075 (0.00, 99.99)
Weight percentile at baseline[a] (%)			
N	76	58	134
Mean (SD)	59.913 (34.9596)	58.862 (33.3762)	59.458 (34.1597)
Median (min, max)	65.650 (0.23, 99.75)	66.315 (0.03, 99.99)	66.315 (0.03, 99.99)
BSA at baseline, (m^2)			
N	77	60	137
Mean (SD)	1.154 (0.3376)	1.183 (0.4471)	1.166 (0.3881)
Median (min, max)	1.070 (0.63, 2.07)	1.165 (0.44, 2.19)	1.110 (0.44, 2.19)

Source: FIREFLY-1 Update CSR Table 14.1.1.4.

Abbreviations: BSA = body surface area; LGG = low-grade glioma; Max = maximum; Min = minimum; SD = standard deviation

[a] Only patients with height and weight percentile available per Centers for Disease Control and Prevention standard growth chart are included in the summary.

Note: Baseline is defined as the last available assessments prior to the start of tovorafenib on Cycle 1 Day 1.

Data Cutoff Date: 05 June 2023

Abbreviations: BSA = body surface area; LGG = low-grade glioma; Max = maximum; Min = minimum; SD = standard deviation.

The FDA's Assessment

The FDA's analysis of demographics and disease characteristics based on the efficacy population which includes 76 patients with measurable disease at baseline per RAPNO-LGG criteria, based on a cutoff date of June 5, 2023, is provided in the following table.

Table 28. Demographics and Baseline Characteristics

	Efficacy Population N=76
Age at baseline (years)	
Mean (SD)	9.2 (4.0)
Median (min, max)	8.5 (2, 21)
Sex, n (%)	
Male	40 (53)
Female	36(47)
Race, n (%)	

	Efficacy Population N=76
White	40 (53)
Asian	5 (7)
Black or African American	2 (2.6)
Multiple	3 (3.9)
Other	6 (8)
Not reported	20 (26)
Ethnicity, n (%)	
Hispanic or Latino	3 (3.9)
Not Hispanic or Latino	50 (66)
Not reported or unknown	23 (30)
Country, n (%)	
USA	25 (33)
ex-USA	51 (67)
KPS/LPS scores, n (%)	
Less than 80	5 (7)
Between 80 and 100	71 (93)
Primary tumor location, n (%)	
Optical pathway	39 (51)
Deep midline structures	9 (12)
Cerebral hemisphere	5 (7)
Brain stem	6 (8)
Cerebellum	5 (7)
Other	12 (16)
Histology, n (%)	
Astrocytic	71 (93)
Mixed Glial-neuronal	4 (5)
Other	1 (1.3)
Pre-operative staging, n (%)	
Localized disease	60 (79)
Disseminated/metastatic disease	8 (11)
Leptomeningeal spread	8 (11)
Post-operative staging, n (%)	
Sub-total resection	35 (46)
Biopsy only, not attempted	40 (53)
Gross total resection	1 (1.3)
BRAF alteration, n (%)	
KIAA1549:BRAF fusion	56 (74)
BRAF V600E mutation	12 (16)
Other	8 (11)
Prior MAPK inhibitors[1], n (%)	
Prior MEK inhibitor	42 (55)
Prior BRAF inhibitor	7 (9)
Prior MEK and BRAF inhibitors	4 (5)
Prior lines of therapy	
Median (range)	3 (1, 9)

Source: Sponsor-provided ADaM dataset adsl.xpt
[1] Patients in subcategories overlap
Abbreviations: SD = standard deviation.

Arm 1 of the study enrolled patients 2 to 21 years of age with a median age of 8.5 years old, which is the expected age distribution for patients with pediatric LGG. The majority were 6 to <12 years of age (53% of the study population). Additionally, most patients enrolled were white and non-Hispanic/Latino, which is likely a reflection of the general lack of diversity in clinical trials as BRAF-altered pediatric LGG is observed across all races and ethnicities. Adequate information on race and ethnicity were not available for 26% and 30% of the patient population respectively.

FIREFLY-1 is a global trial, enrolling patients in a total of eleven countries with approximately a third of patients in the US. Importantly, there are no epidemiologic differences anticipated in pediatric LGG by geographic location.

Regarding baseline disease characteristics, nearly all patients had tumor of astrocytic origin, which is expected. The study population is remarkable for primary tumor situated in the optic pathway in approximately half of patients. Although pediatric LGGs can occur in various locations throughout the brain and spinal cord, the cerebellum is generally the most common location (15-25%) with optic pathway gliomas observed at lower rates (Sievert, 2009). It is possible that due to the requirement to have relapsed or refractory disease in FIREFLY-1, patients with optic pathway tumors were enriched due to the lack of feasible surgical options for such tumors. Additionally, for any patients who received prior tumor-directed surgery for treatment of primary disease, the pre-operative staging indicated approximately 22% had disseminated, metastatic or leptomeningeal spread, which is an adverse prognostic feature and indicates more locally aggressive baseline disease.

The molecular characteristics of patient tumors studied in Arm 1 of FIREFLY-1 is consistent with what is expected in the target population with the KIAA1549:BRAF fusion present in the majority (74%) of patients and BRAF V600E mutation observed in 16% of patients. Patients with "other" activating BRAF alterations (11%) included patients with BRAF duplication or rearrangement that was detected on FISH/ISH testing. Of note, the FIREFLY-1 study population was heavily pre-treated with patients receiving a median of 3 prior lines (range: 1 to 9) of systemic treatment, including prior MEK inhibitor in 55% and prior BRAF inhibitor in 9% of patients.

8.1.2.6. Baseline Disease Characteristics

Applicant's Position

In Arms 1 and 2, the optic pathway was the most common primary tumor location (49.6%), and most patients (92.7%) had tumors with astrocytic histology. Most patients (73.7%) had undergone tumor-directed surgery for treatment of their primary disease. Pre-operative staging was most the commonly localized disease (74.5%), and approximately half of patients (46.0%) underwent a subtotal resection.

In Arm 1, median IRC-assessed SPPD of measurable lesion(s) per RANO-HGG criteria was 729.6 mm^2 (range: 104.0 to 6358.0 mm^2). Most (73.7%) patients in Arms 1 and 2 had a KIAA1549:BRAF fusion, while 16.1% of patients had a BRAF V600E mutation. A total of 52.6% of patients had three or more prior lines of systemic therapy. Most patients (89.8%) had a Karnofsky or Lansky performance score between 80 and 100 at baseline.

The FDA's Assessment

Refer to the FDA's review in Section 8.1.2.5 for additional information.

8.1.2.7. Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Applicant's Position

Treatment Compliance

As of the data cutoff date (05 June 2023), the median treatment compliance was 100%.

Concomitant Medications

Overall, the concomitant medications administered were representative of those commonly prescribed for patients with pediatric low-grade glioma and were not considered to have impacted the study results. The most common therapeutic classes of concomitant medications were other analgesics and antipyretics (73.0%; most commonly paracetamol [70.8%]), plain corticosteroids (67.2%; most commonly hydrocortisone [40.9%]), antihistamines for systemic use (56.2%), antiemetics and antinauseants (54.7%; most commonly ondansetron [48.2%]), drugs for constipation (48.9%), non-steroidal anti-inflammatory and antirheumatic products (40.1%; most commonly ibuprofen [34.3%]), emollients and protectives (38.7%), other beta-lactam antibacterials (34.3%), other mineral supplements (33.6%), corticosteroids (plain) for systemic use (32.8%), antibiotics for topical use (32.8%), and beta-lactam antibacterials penicillins (32.1%).

Rescue Medications

Not applicable, rescue medications were not defined in the protocol nor used during the study.

The FDA's Assessment

The FDA agrees with the Applicant's position. Regarding treatment compliance, the median duration of exposure in Arms 1 and 2 of FIREFLY-1 was 362 days (range: 22 to 722 days) with a median of 13 treatment cycles (range: 1 to 26). At the time of the DCO, 86% of patients had received at least 6 months of treatment with tovorafenib, 49% had at least 12 months of treatment, and 14% had at least 18 months of treatment. Additionally, the FDA notes there was variability in the dose of tovorafenib administered in FIREFLY-1. The RP2D was 420 mg/m^2 orally once weekly with a maximum dose of 600 mg. Due to the bands provided in the study protocol's dosing table, there was heterogeneity in the dose administered, resulting in patients receiving 0.76 – 1.25x the approved dosage. Refer to Section 6 (*Clinical Pharmacology*) for additional details regarding dosage of tovorafenib administered in FIREFLY-1 and the FDA's recommendation for an approved dosage of 380 mg/m^2 orally once weekly.

8.1.2.8. Efficacy Results – Primary Endpoint (including sensitivity analyses)

Applicant's Position

IRC-Assessed ORR Based on RANO-HGG Criteria

IRC-assessed ORR (CR or PR) based on RANO-HGG criteria was 66.7% (95% CI: 54.3, 77.6) based on data from the 05 June 2023 data cutoff date (Table 29). The Full Analysis Set consisted of 69 patients in Arm 1 with measurable disease at baseline determined by the IRC based on RANO-HGG criteria. Characteristics of the response observed were as follows and are summarized graphically in Figure 16:

- Among evaluable patients (N=69), 12 (17.4%) patients had a CR and 34 (49.3%) patients had a PR.
- Of 18 (26.1%) patients with stable disease, 8 (11.6%) patients had stable disease lasting ≥12 months (Table 29).
- The type of BRAF alteration did not affect response: ORR was 69.5% (95% CI: 56.1, 80.8) for patients harboring BRAF fusions (n=59); ORR was 50% (95% CI: 18.7, 81.3) for patients harboring BRAF mutations (n= 10) (Table 30).
- Prior therapy with MEK or BRAF inhibitors did not affect response: ORR was 70.7% (95% CI: 54.5, 83.9) for patients with any prior MAPK-targeted therapy (n= 41); ORR was 60.7% (95% CI: 40.6, 78.5) for patients with no prior MAPK-targeted therapy (n= 28) (Table 30).

Table 29. IRC-Assessed Overall Response Rate Based on RANO-HGG Criteria (full analysis set; arm 1)

Characteristic	Arm 1 (Low-Grade Glioma) N=69
Best overall response, n (%)	
Complete Response (CR)	12 (17.4)
Partial Response (PR)	34 (49.3)
Stable Disease	18 (26.1)
Stable Disease ≥12 months	8 (11.6)
Stable Disease <12 months[a]	10 (14.5)
Progressive disease (PD)	4 (5.8)
Not evaluable (NE)	1 (1.4)
Number of patients with confirmed response	46
ORR[b] (95% CI)	66.667 (54.288, 77.563)

Source: FIREFLY-1 Update CSR Table 14.2.1.1.1

[a] Among 10 patients with stable disease < 12 months, 3 were continuing on treatment as of the 05 June 2023 data cutoff date.

[b] The exact 95% CIs are calculated using Clopper-Pearson method.

Data Cutoff Date: 05 June 2023

Abbreviations: CI = confidence interval; IRC = Independent Radiology Review Committee; ORR = overall response rate; RANO-HGG = Response Assessment in Neuro-Oncology for High-grade Glioma

Table 30. IRC-Assessed Overall Response Rate by BRAF Alteration Based on RANO-HGG Criteria (full analysis set; arm 1)

	BRAF Alteration		Prior Therapy	
Characteristic	BRAF Fusion[a] N=59	BRAF Mutation N=10	Prior MAPK Therapy N=41	No Prior MAPK Therapy N=28
Best overall response, n (%)				
Complete response (CR)	10 (16.9)	2 (20.0)	10 (24.4)	2 (7.1)
Partial response (PR)	31 (52.5)	3 (30.0)	19 (46.3)	15 (53.6)
Stable disease (SD)	14 (23.7)	4 (40.0)	8 (19.5)	10 (35.7)
Stable disease ≥12 months	8 (13.6)	0	4 (9.8)	4 (14.3)
Stable disease <12 months	6 (10.2)	4 (40.0)	4 (9.8)	6 (21.4)
Progressive disease (PD)	3 (5.1)	1 (10.0)	3 (7.3)	1 (3.6)
Not evaluable	1 (1.7)	0	1 (2.4)	0
Number of patients with confirmed response	41	5	29	17
Overall response rate[b] (95% CI)	69.492 (56.134, 80.814)	50.000 (18.709, 81.291)	70.732 (54.463, 83.870)	60.714 (40.577, 78.496)

Source: FIREFLY-1 Update CSR Table 14.2.1.1.1.a , Table 14.2.1.1.1.h.

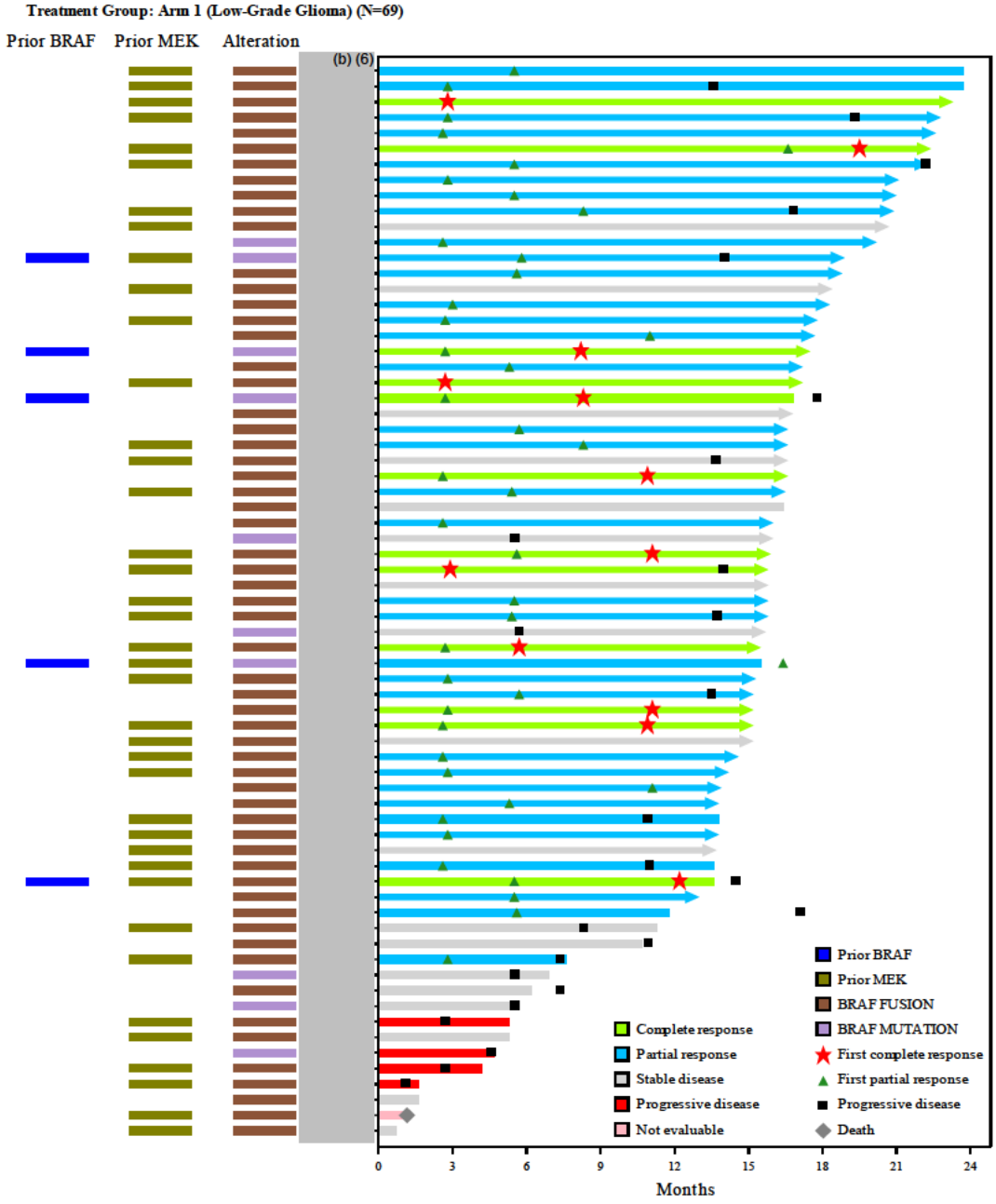
[a] The classification of BRAF fusions includes BRAF tandem duplication, BRAF rearrangement, or other non-KIAA1549:BRAF fusions. These were grouped together along with KIAA1549:BRAF fusions.

[b] The exact 95% CIs are calculated using Clopper-Pearson method.

Data Cutoff Date: 05 June 2023.

Abbreviations: BRAF = v-raf murine sarcoma viral oncogene homolog B; CI = confidence interval, IRC = Independent Radiology Review Committee, MAPK = mitogen-activated protein kinase; RANO-HGG = Response Assessment in Neuro-Oncology for High-Grade Glioma.

Figure 16. Swimmer Plot for IRC-Assessed Overall Response Based on RANO-HGG Criteria (full analysis set; arm 1)



Source: FIREFLY-1 Update CSR Figure 14.2.1.1.1.

Bar color represents best overall response. Bar length represents duration of treatment. Arrow at the end of the bar represents ongoing study treatment.

Data cutoff date: 05 June 2023

Abbreviations: BRAF = v-raf murine sarcoma viral oncogene homolog B; IRC = Independent Radiology Review Committee; MEK = mitogen-activated protein kinase; RANO-HGG = Response Assessment in Neuro-Oncology for High-grade Glioma.

The FDA's Assessment

The efficacy results for the primary endpoint of ORR as assessed by BICR provided by the Applicant is based on the RANO-HGG criteria. The following table provides the results of FDA's primary analysis, which is based on the RAPNO-LGG criteria. The primary efficacy population includes 76 patients with measurable disease at baseline, who were enrolled in Arm 1 of the FIREFLY-1 study, with a data cut-off date of June 5, 2023. The definition of ORR includes minor responses in addition to complete and partial responses. Refer to Section 8.1.1 (*FIREFLY-1*) for the definition of minor response and to Section 8.1.2.15 (*Additional Analyses Conducted on the Individual Trial*) for discussion regarding the clinical relevance of minor responses.

Table 31. Analysis of ORR Assessed by BICR per RAPNO-LGG Criteria

Characteristic	RAPNO-LGG N=76
Overall response rate % (95% CI)	51 (40, 63)
Complete response, n (%)	0
Partial response, n (%)	28 (37)
Minor response, n (%)	11 (14)

Source: Sponsor-provided ADaM datasets adeff.xpt and adrs.xpt

Abbreviations: BICR = blinded independent centralized review; CI = confidence interval; ORR = overall response rate.

8.1.2.9. Data Quality and Integrity

Applicant's Position

No potential issues were identified concerning the submitted data quality or integrity. All data were collected on original source documents, and the investigator maintained detailed records for all study patients. Data security was controlled through appropriate and specific restriction of access to data and systems. The database existed on physically secured servers. Data backups were performed regularly and stored in separate facilities.

Fifteen investigator site audits were conducted. The COVID-19 pandemic had minimal impact on the interpretation of the results of this study.

The FDA's Assessment

The FDA agrees with the Applicant's position. The data submitted were organized and adequate to perform a complete review of the efficacy of tovorafenib in patients with relapsed or refractory pediatric LGG harboring BRAF fusion or rearrangement, or BRAF V600 mutation. The FDA issued information requests during the review cycle to obtain clarification and additional information regarding data included in the NDA and all requests were addressed appropriately.

8.1.2.10. Efficacy Results – Secondary and Other Relevant Endpoints

Applicant's Position

IRC-Assessed ORR Based on RAPNO Criteria

IRC-assessed ORR (CR, PR, or MR) using RAPNO criteria was 51.3% (95% CI: 39.6, 63.0) based on data from the 05 June 2023 data cutoff date (Table 32). The RAPNO evaluable analysis set consisted of 76 patients in Arm 1 with measurable disease at baseline determined by the IRC based on RAPNO criteria. Characteristics of the response observed were as follows and are summarized graphically in Figure 17:

- Among evaluable patients (N=76), no patients had a CR, 28 (36. 8%) patients had a PR, 11 (14.5%) patients had an MR.
- Of 23 (30.0%) patients with stable disease, 4 patients (5.3%) had stable disease lasting ≥ 12 months.
- Thirteen (17.1%) patients had a best overall response of PD at their first scan based on RAPNO criteria. Of these, 6 patients had subsequent reductions in tumor size below baseline following the initial progression: 1 patient experienced subsequent tumor reduction of ≥ 50%, and 4 patients had subsequent tumor reduction of ≥ 25% to < 50%. Seven of these 13 patients remain on treatment as of the data cutoff date.
- The type of BRAF alteration did not affect response: ORR was 51.6% (95% CI: 38.7, 64.3). for patients harboring BRAF fusions (n=64); ORR was 50.0% (95% CI: 21.1, 78.9) for patients harboring BRAF mutations (n= 12).
- Prior therapy with MEK or BRAF inhibitors did not affect response: ORR was 48.9% (95% CI: 33.7, 64.2). for patients with any prior MAPK-targeted therapy (n= 45); ORR was 54.8% (95% CI: 36.0, 72.7) for patients with no prior MAPK-targeted therapy (n= 31).

Table 32. IRC-Assessed Overall Response Rate Based on RAPNO Criteria (RAPNO evaluable analysis set; arm 1)

Characteristic	Arm 1 (Low-Grade Glioma) N=76
Best overall response, n (%)	
Complete response (CR)	0
Partial response (PR)	28 (36.8)
Minor response (MR)	11 (14.5)
Stable disease	23 (30.3)
Stable disease ≥12 months	4 (5.3)
Stable disease <12 months	19 (25.0)
Progressive disease (PD)	13 (17.1)
Not evaluable	1 (1.3)
Number of patients with confirmed response	39
ORR (95% CI)[a]	51.316 (39.569, 62.957)

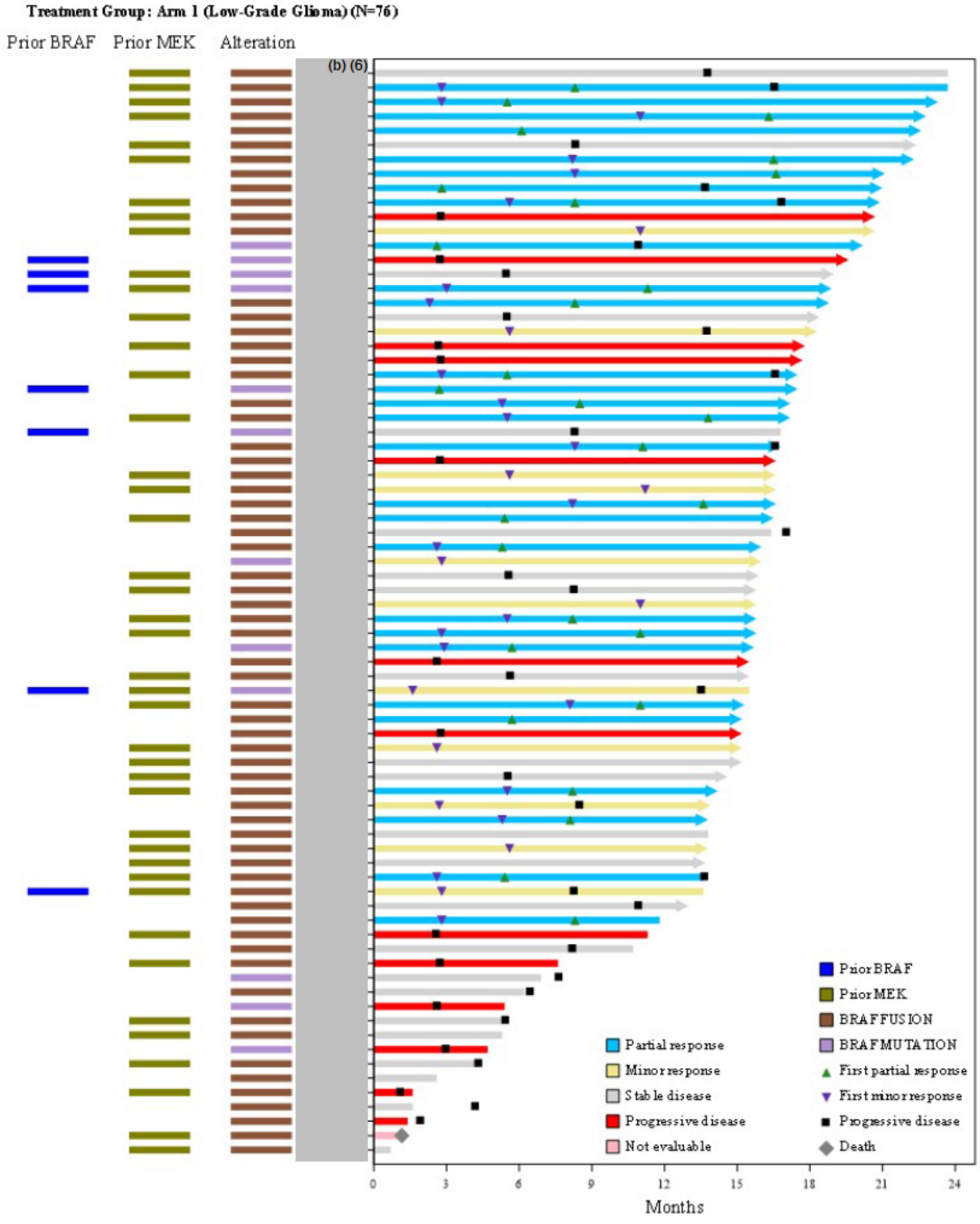
Source: FIREFLY-1 Update CSR Table 14.2.1.2.1.

[a] The exact 95% CIs are calculated using Clopper-Pearson method.

Data Cutoff Date: 05 June 2023.

Abbreviations: CI = confidence interval; IRC = Independent Radiology Review Committee; RAPNO = Response Assessment in Pediatric Neuro-Oncology.

Figure 17. Swimmer Plot for IRC-Assessed Overall Response Based on RAPNO Criteria (RAPNO evaluable analysis set; arm 1)



Source: FIREFLY-1 Update CSR Figure 14.2.1.2.

Bar color represents best overall response. Bar length represents duration of treatment. Arrow at the end of the bar represents ongoing study treatment.

Data Cutoff Date: 05 June 2023.

Abbreviations: BRAF=v-raf murine sarcoma viral oncogene homolog B; IRC=Independent Radiology Review Committee; MEK=mitogen-activated protein kinase; RAPNO=Response Assessment in Pediatric Neuro-Oncology.

IRC-Assessed ORR Based on RANO-LGG Criteria

IRC-assessed ORR (CR, PR, or MR) using RANO-LGG criteria was 52.6% (95% CI: 40.8, 64.2) based on data from the 05 June 2023 data cutoff date (Table 33). The RANO evaluable analysis set consisted of 76 patients in Arm 1 with measurable disease at baseline determined by the IRC based on RANO-LGG criteria. Characteristics of the response observed were as follows and are summarized graphically in Figure 18.

- Among evaluable patients (N=76), no patients had a CR, 20 (26.3%) patients had a PR, 20 (26.3%) patients had an MR.
- Of 23 (30.0%) patients with stable disease, 6 (7.9%) patients had stable disease lasting ≥ 12 months.
- Eleven patients had a best overall response of PD based on RANO-LGG criteria as assessed by an IRC at their first post therapy scan. An analysis of these patients revealed that 5 patients went on to have subsequent reductions in tumor size below baseline following the initial progression. Of those, 2 had subsequent tumor reduction of ≥ 50%, and 2 had subsequent tumor reduction of ≥ 25% to < 50%. Of note, 5 of 11 patients with a best overall response of PD based on RANO-LGG criteria remain on treatment as of the data cutoff date.
- The type of BRAF alteration did not affect response: ORR was 51.6% (95% CI: 38.7, 64.3). for patients harboring BRAF fusions (n=64); ORR was 50.0% (95% CI: 21.1, 78.9) for patients harboring BRAF mutations (n= 12).
- Prior therapy with MEK or BRAF inhibitors did not affect response: ORR was 48.9% (95% CI: 33.7, 64.2). for patients with any prior MAPK-targeted therapy (n= 45); ORR was 54.8% (95% CI: 36.0, 72.7) for patients with no prior MAPK-targeted therapy (n= 31).

Table 33. IRC-Assessed Overall Response Rate Based on RANO-LGG Criteria (RANO evaluable analysis set; arm 1)

Characteristic	Arm 1 (Low-grade Glioma) N=76
Best overall response, n (%)	
Complete response (CR)	0
Partial response (PR)	20 (26.3)
Minor response (MR)	20 (26.3)
Stable disease	23 (30.3)
Stable disease ≥12 months	6 (7.9)
Stable disease <12 months	17 (22.4)
Progressive disease (PD)	11 (14.5)
Not evaluable (NE)	2 (2.6)
Number of patients with confirmed response	40
ORR (95% CI)[a]	52.632 (40.844, 64.208)

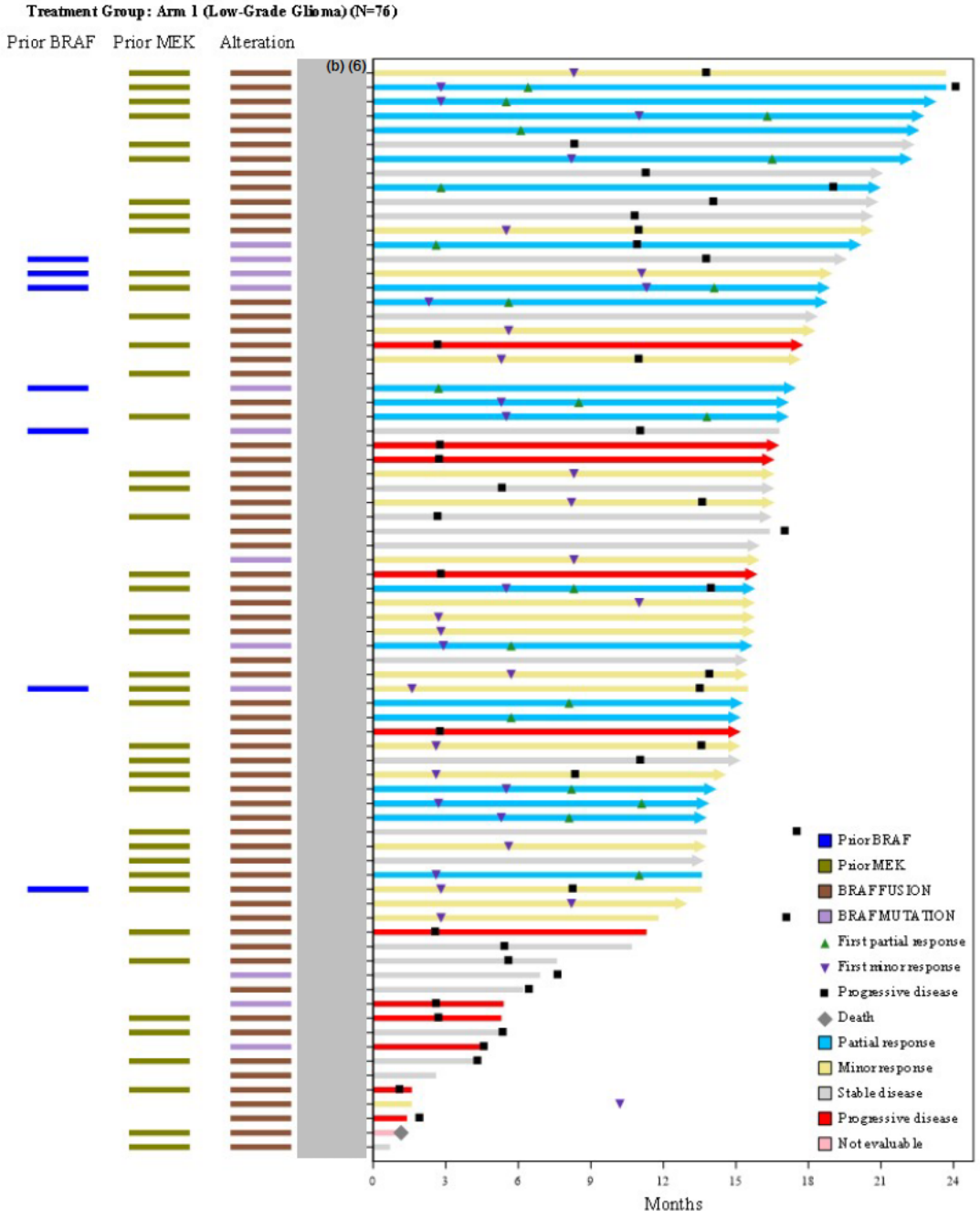
Source: FIREFLY-1 Update CSR Table 14.2.1.5.1.

[a] The exact 95% CIs are calculated using Clopper-Pearson method.

Data Cutoff Date: 05 June 2023.

Abbreviations: CI = confidence interval; IRC = Independent Radiology Review Committee; ORR = overall response rate; RANO-LGG = Response Assessment in Neuro-Oncology for Low-Grade Glioma.

Figure 18. Swimmer Plot for IRC-Assessed Overall Response Based on RANO-LGG Criteria (RANO evaluable analysis set; arm 1)



Source: FIREFLY-1 Update CSR Figure 14.2.1.2.1.

Bar color represents best overall response. Bar length represents duration of treatment. Arrow at the end of the bar represents ongoing study treatment.

Data Cutoff Date: 05 June 2023.

Abbreviations: BRAF=v-raf murine sarcoma viral oncogene homolog B; IRC=Independent Radiology Review Committee; MEK=mitogen-activated protein kinase; RANO-LGG=Response Assessment in Neuro-Oncology for Low-Grade Glioma.

Other Secondary and Exploratory Endpoints

IRC-assessed DOR: The median IRC-assessed DOR was 16.6 months (95% CI: 11.6, NE) based on RANO-HGG criteria, 13.8 months (95% CI: 11.3, NE) based on RAPNO criteria, and 14.4 months (95% CI: 11.0, NE) based on RANO-LGG criteria. The Kaplan-Meier (KM) estimates of the probability of continued response by RANO-HGG, RAPNO, and RANO-LGG criteria were 81.7% (95% CI: 65.3, 90.9), 85.1% (95% CI: 67.7, 93.6), 72.8% (95% CI: 53.8, 85.0) at 9 months, respectively; and 66.9% (95% CI: 47.0, 80.7), 62.6% (95% CI: 37.6, 80.0), and 60.7% (95% CI: 37.4, 77.6) at 12 months, respectively.

IRC-assessed PFS: The median estimated IRC-assessed PFS was 19.4 months (95% CI: 16.9, NE) based on RANO-HGG criteria, 13.8 months (95% CI: 8.3, 16.9) based on RAPNO criteria, and 13.9 months (95% CI: 11.1, 19.1) based on RANO-LGG criteria.

IRC-assessed Time to Response: The median IRC-assessed TTR was 3.0 months to 5.5 months (overall range: 1.6 to 16.6 months) depending on which tumor assessment criteria was used.

Changes in Total Tumor Size: As assessed by an IRC based on RANO-HGG criteria, the median maximum percent change in SPPD from baseline was -91.9% (range: -100.0% to +53.0%). Based on RANO-HGG criteria, 17 of 18 patients with stable disease had tumor shrinkage, with at least 50% reduction from baseline in SPPD for 5 of the 18 patients. Based on RAPNO criteria, 20 of 23 patients with stable disease had tumor shrinkage, with at least 50% reduction from baseline in SPPD for 4 of the 23 patients. Based on RANO-LGG criteria, 22 of 23 patients with stable disease had tumor shrinkage, with at least 50% reduction from baseline in SPPD for 2 of the 23 patients.

Overall Survival: As of the data cutoff date (05 June 2023), with a median study duration of 16.7 months, 2 patients in the Full Analysis Set of Arm 1 have died (one on Day 35 and one on Day 382). The Kaplan-Meier estimate of median OS was not reached. The Kaplan-Meier estimate of OS was 98.6% (95% CI: 90.2, 99.8) at 12 months.

The FDA's Assessment

The following table provides the ORR analysis based on the RANO-LGG criteria, considered supportive to the primary analysis. The ORRs based on RANO-LGG and RAPNO-LGG criteria are similar.

Table 34. Analysis of ORR Assessed by BICR per RANO-LGG Criteria

Characteristic	RANO-LGG N=76
Overall response rate, % (95% CI)	53 (41, 64)
Complete response, n (%)	0
Partial response, n (%)	20 (26)
Minor response, n (%)	20 (26)

Source: Sponsor-provided ADaM datasets adeff.xpt and adrs.xpt

Abbreviations: BICR = blinded independent central review; CI = confidence interval; ORR = overall response rate.

Of note, there were 39 responders by RAPNO-LGG criteria, while 40 patients were considered responders by RANO-LGG criteria. Of these patients, 32 were considered responders by both RAPNO-LGG and RANO-LGG criteria. Seven patients were considered responders by RAPNO-LGG criteria only and 8 patients were considered responders by RANO-LGG criteria only. Thus, there was at least 80% agreement between the RAPNO-LGG and RANO-LGG criteria. Among the 32 patients who were considered responders by both criteria, 22 were considered to have a partial response and 10 a minor response per RAPNO-LGG criteria whereas per RANO-LGG criteria, 19 patients were partial responders and 13 were minor responders.

The following table provides the duration of response (DOR) and time to response (TTR) based on the RAPNO-LGG and RANO-LGG criteria which are numerically similar.

Table 35. Analysis of DOR Assessed by BICR

Characteristic	RAPNO-LGG N=76	RANO-LGG N=76
Number of responders	n=39	n=40
Duration of response		
Median in months (95% CI)	13.8 (11.3, NE)	14.4 (11.0, NE)
DOR ≥6 months[1], n (%)	33 (85)	27 (68)
DOR ≥12 months[1], n (%)	9 (23)	8 (20)
Time to response		
Median in months (range)	5.3 (1.6, 11.2)	5.5 (1.6, 11.3)

Source: Sponsor-provided ADaM datasets adeff.xpt and adtte.xpt

[1] Based on observed duration

Abbreviations: BICR = blinded independent central review; CI = confidence interval; DOR = duration of response; NE = not evaluable.

The FDA considers time-to-event endpoints such as PFS and OS to be not interpretable in a single arm study. Statistical analyses for PFS and OS in FIREFLY-1 were not verified.

The following table provides exploratory subgroup analyses of ORR assessed by BICR per RAPNO-LGG criteria. There are no major differences between subgroups, with overlapping 95% CIs. Importantly, the response rates were similar in patients with the KIAA1549:BRAF fusion and those with the BRAF V600E mutation. Further, prior treatment with a MEK and/or BRAF inhibitor as well as receipt of multiple lines of previous therapy did not preclude patients from demonstrating a response to tovorafenib. Due to the limited subgroup sizes (and unavailability of adequate information on race and ethnicity for a high fraction of the patient population) these results should be interpreted with caution.

Table 36. Exploratory Subgroup Analyses of ORR per RAPNO-LGG Criteria

Characteristics	Responders/n	ORR (95% CI)
Age		
≤6 years	14/21	67 (43, 85)
>6 years, and <12 years	15/33	45 (28, 64)
≥12 years	10/22	45 (24, 68)
Sex		
Female	22/36	61 (43, 77)
Male	17/40	42 (27, 59)
Race		
White	25/40	62 (46, 77)
Black or African American	0/2	-
Asian	3/5	60 (15, 95)
Other/Not Available	8/26	31 (14, 52)
Ethnicity		
Hispanic or Latino	0/3	-
Not Hispanic or Latino	29/50	58 (43, 72)
Not reported or unknown	10/23	43 (23, 66)
Country		
USA	14/25	56 (35, 76)
ex-USA	25/51	49 (35, 63)
BRAF alterations		
KIAA:1549 BRAF fusion	29/56	52 (38, 65)
BRAF V600E mutation	6/12	50 (21, 79)
Other	4/8	50 (16, 84)
Prior types of treatment[1]		
MEK inhibitor	21/42	50 (34, 66)
BRAF inhibitor	4/7	57 (18, 90)
Both	3/4	75 (19, 99)
Prior lines of therapy		
1 to 3	27/53	51 (37, 65)
4 to 6	8/16	50 (25, 75)
≥7	4/7	57 (18, 90)

Source: Sponsor-provided ADaM datasets adsl.xpt and adeff.xpt

[1] Patients in subcategories overlap

Abbreviations: CI = confidence interval; ORR = overall response rate.

The following table provides the exploratory subgroup analyses of ORR assessed by BICR per RANO-LGG criteria. There are no major differences between subgroups based on this criterion, with overlapping 95% CIs. Efficacy findings similar to those cited above as per the RAPNO criteria were also observed as per the RANO-LGG criteria. As previously stated, due to the limited subgroup sizes (and unavailability of adequate information on race and ethnicity for a high fraction of the patient population) these results should be interpreted with caution.

Table 37. Exploratory Subgroup Analyses of ORR per RANO-LGG Criteria

Characteristics	Responders/n	ORR (95% CI)
Age		
≤6 years	13/21	62 (38, 82)
>6 years, and <12 years	14/33	42 (25, 61)
≥12 years	13/22	59 (36, 79)
Sex		
Female	18/36	50 (33, 67)
Male	22/40	55 (38, 71)
Race		
White	24/40	60 (43, 75)
Black or African American	1/2	50 (1, 99)
Asian	2/5	40 (5, 85)
Other/Not Available	11/26	42 (23, 63)
Ethnicity		
Hispanic or Latino	1/3	33 (1, 91)
Not Hispanic or Latino	29/50	58 (43, 72)
Not reported or unknown	10/23	43 (23, 66)
Country		
USA	14/25	56 (35, 76)
ex-USA	26/51	51 (37, 65)
BRAF alterations		
KIAA:1549 BRAF fusion	31/56	55 (41, 69)
BRAF V600E mutation	7/12	58 (28, 85)
Other	2/8	25 (3, 65)
Prior types of treatment[1]		
MEK inhibitor	22/42	52 (36, 68)
BRAF inhibitor	5/7	71 (29, 96)
Both	4/4	100 (40, 100)
Prior lines of therapy		
1 to 3	28/53	53 (39, 67)
4 to 6	10/16	62 (35, 85)
≥7	2/7	29 (4, 71)

Source: Sponsor-provided ADaM datasets adsl.xpt and adeff.xpt

[1] Patients in subcategories overlap

Abbreviations: CI = confidence interval; ORR = overall response rate.

Overall, these exploratory analyses appear to support the primary efficacy analysis. They appear to show a consistent and clinically relevant response rate in the pediatric LGG patient population which is supported by a robust duration of response.

8.1.2.11. Dose/Dose Response

Applicant's Position

Please refer to Section 6 for a discussion of dose.

The FDA's Assessment

Please refer to Section 6.3.2 for additional details regarding the FDA's analysis of dose/dose response.

8.1.2.12. Durability of Response

Applicant's Position

Duration of response is discussed above under Other Secondary and Exploratory Endpoints. As of the data cutoff date (05 June 2023), more than 90% of responders (CR, PR, MR) have been followed for at least 6 months from onset of response across all three tumor assessment criteria. Table 38 outlines the proportion of patients with observed duration of response (DOR) of ≥ 6 and ≥ 12 months across RANO-HGG, RAPNO and RANO-LGG criteria, respectively.

Table 38. Proportion of Patients With Observed DOR of ≥6 and ≥12 Months

Statistic	RANO-HGG [a] N=69 (Wen 2010)	RAPNO N=76 (Fangusaro 2020)	RANO-LGG N=76 (Van den Bent 2011)
Number of confirmed responders	46 [b]	39 [c]	40 [c]
Proportion of responders followed longer than 6 months from onset of response [d]	43/46 (93.5%)	37/39 (94.9%)	39/40 (97.5%)
Observed proportion of patients with DOR of 6 months	39/46 (84.8%)	33/39 (84.6%) [e]	27/40 (67.5%) [f]
Number of patients with DOR censored before 6 months, while ongoing on study	6	4	7
Observed Proportion of patients with DOR of 12 months	14/46 (30.4%)	9/39 (23.1%)	8/40 (20.0%)
Number of patients with DOR censored before 12 months, while ongoing on study	21	21	21

Source: Sponsor Response to FDA's Information Request Regarding Updated FIREFLY-1 Topline Efficacy Data, Table 1

Note: Data cutoff date 05 June 2023.

[a] Full Analysis Set for Arm 1 which includes all patients enrolled who received at least 1 dose of study treatment and have measurable disease per RANO-HGG as determined by the IRC at baseline.

[b] Per RANO-HGG criteria, confirmed responders include patients with confirmed CR or PR.

[c] Per RAPNO or RANO-LGG criteria, confirmed responders include patients with confirmed CR, PR, or MR.

[d] Duration of follow up (month) defined as (clinical cutoff date – first date of response of CR/PR/MR + 1)/30.4375.

When the protocol-specified 7 day visit window is applied, the proportion of patients with confirmed CR/PR/MR and DOR ≥ 6 months is 35/39 (89.7%).

When the protocol-specified 7 day visit window is applied, the proportion of patients with confirmed CR/PR/MR and DOR ≥ 6 months is 29/40 (72.5%).

Abbreviations: CR = complete response; DOR = duration of response; MR = minor response; ORR = Overall Response Rate; PR = partial response; RANO-HGG = Response Assessment in Neuro-Oncology – High grade glioma; RANO-LGG = Response Assessment in Neuro-Oncology – Low grade glioma; RAPNO = Response Assessment in Pediatric Neuro-Oncology.

The FDA's Assessment

Refer to the FDA's review in Section 8.1.2.10 for additional information regarding durability of response.

8.1.2.13. Persistence of Effect

Applicant's Position

As of the data cutoff date (05 June 2023), 2 patients had entered the drug holiday period following 26 cycles of therapy with tovorafenib. As the drug holiday started within

approximately 1 month before the data cutoff date, neither patient had received follow-up imaging assessments yet.

While patients who have discontinued tovorafenib for reasons other than disease progression have been observed to remain in response or with continued stable disease, no formal analyses had been conducted yet.

The recommended duration of treatment is until loss of clinical benefit or unacceptable toxicity.

The FDA's Assessment

The FDA agrees with the Applicant's position. Formal analyses to inform persistence of effect were not conducted by the FDA.

8.1.2.14. Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints

Patient-reported outcomes were not analyzed for this application.

The FDA's Assessment

The FDA agrees with the Applicant's position. Although clinical outcome assessment (COA) data including patient-reported outcome data was collected during the conduct of FIREFLY-1, the Applicant noted that interpretation of these data were limited by the high percentage of missingness. As a result, COA data were not included in the data package.

8.1.2.15. Additional Analyses Conducted on the Individual Trial

Applicant's Position

In an analysis of Kaplan-Meier estimated PFS by best overall response based on RAPNO criteria, a longer PFS was associated with a better best overall response (Table 39 and Figure 19). The 9-month PFS rate among patients who achieved PR or MR was 100% and 81.8%, respectively, which was substantially higher than that in patients who achieved stable disease (30.2%) or PD/NE (0%). By log-rank tests comparing the PFS of patients with a best overall response of MR against other patients, the two-sided nominal p-value comparing MR to stable disease was 0.004, and p-value of MR versus PR was 0.106, suggesting that the best overall responses of PR and MR were associated with comparable PFS, which were substantially longer than the PFS in patients who achieved a best overall response of stable disease or worse.

Table 39. Summary of Kaplan-Meier Estimate of Progression-Free Survival by IRC-Assessed Best Overall Response by RAPNO Criteria (RAPNO evaluable analysis set; arm 1)

	Arm 1 (Low-Grade Glioma) N=76		
Best Overall Response	**6-Month PFS Rate (95% CI)**	**9-Month PFS Rate (95% CI)**	**p-value[a] of Log-rank Test Comparing to MR**
PR	100 (100, 100)	100 (100, 100)	0.106
MR	100 (100, 100)	81.818 (44.743, 95.116)	-
SD	60.317 (36.055, 77.838)	30.159 (12.336, 50.327)	0.004
PD/NE	0.000 (-, -)	0.000 (-, -)	<0.001

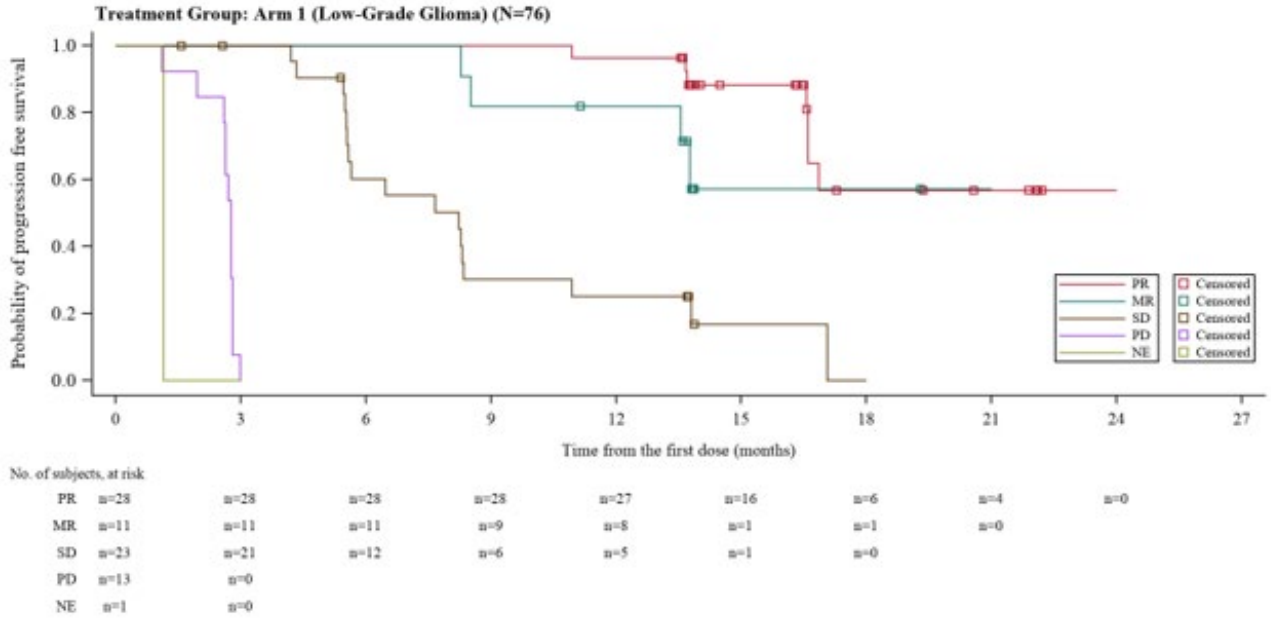
Source: FIREFLY-1 Update CSR Table 14.2.2.2.1.1.

[a] p-values are nominal and not adjusted for multiple comparisons.

Data Cutoff Date: 05 June 2023.

Abbreviations: CI = confidence interval; IRC = Independent Radiology Review Committee; MR = minor response; NE = not evaluable; PD = progressive disease; PFS = progression-free survival; PR = partial response; RAPNO = Response Assessment in Pediatric Neuro-Oncology; SD = stable disease.

Figure 19. Kaplan-Meier Plot of Progression-Free Survival by IRC-Assessed Best Overall Response by RAPNO Criteria (RAPNO evaluable analysis set; arm 1)



Source: FIREFLY-1 Update CSR Figure 14.2.2.1.3.

Data Cutoff Date: 05 June 2023.

Abbreviations: IRC = Independent Radiology Review Committee; MR = minor response; NE = not evaluable; PD = progressive disease; PR = partial response; RAPNO = Response Assessment in Pediatric Neuro-Oncology; SD = stable disease.

The FDA's Assessment

As previously stated, the FDA considers PFS analyses to be exploratory in the context of a single arm trial and did not confirm these analyses.

The FDA also reviewed individual case narratives for all patients enrolled in Arm 1 of FIREFLY-1. These "clinical efficacy narratives" submitted by the Applicant detailed relevant information including the patient's diagnosis; prior treatment history; investigator-reported assessment of the patient's condition at baseline including functional deficits (e.g., visual deficits, hemiparesis, etc.); treatment-emergent adverse events; assessment of tumor response; the patient's response to tovorafenib, including descriptions of changes in symptoms, function, or medical condition as reported by the investigator, parent or guardian; and current treatment status. With the exception of visual acuity assessments, the narratives are not based on data gathered using validated clinical outcome assessment instruments and represent qualitative summaries based on the information described above.

These narratives were particularly important to inform the FDA's understanding of the clinical relevance of the minor response category included in the RAPNO and RANO-LGG criteria. There were 22 patients in the efficacy population who were determined to have a minor response by either tumor assessment criteria. A summary of the narratives for the 15 patients who exhibited clinical improvement and/or improvement in visual acuity is provided in Table 40.

The clinical changes reported while on treatment included improvement in headaches, neurocognitive function, mobility, developmental delays (motor and verbal), and fatigue; better control or resolution of tumor-related medical complications including diabetes insipidus and endocrinopathies; ability to attend school; improvement in scholastic performance; and ability to engage in other activities of daily living typical for patient age. In terms of visual acuity, six patients had documented improvement with a reduction of ≥ 0.2 logMAR in one or both eyes.

The FDA acknowledges that the case narratives have certain limitations (e.g., data was retrospectively collected for review, some patient symptoms may be subjective and were reported by the treating physician, etc.); as such, the information provided was not considered to have been sufficiently rigorously or comprehensively collected to contribute to an assessment of direct clinical benefit. However, review of these narratives provided clinical documentation of preliminary information suggesting that minor responses are clinically meaningful and that patients demonstrating tumor shrinkage, even if not meeting the criteria for a partial or complete response, may potentially derive benefit from treatment. As such, the FDA's evaluation of efficacy in FIREFLY-1 is based upon RAPNO-LGG criteria inclusive of observed minor response, partial response, and complete response rates.

Table 40. Summary of Disease Manifestations and Reported Improvements in Clinical Status in Patients With Minor Response by RAPNO or RANO-LGG Criteria in Arm 1 of FIREFLY-1

Patient ID	Age/Sex	Tumor Diagnosis & Location	Genomic Alteration	Clinical Baseline & Reported Deficits	Response by RAPNO	Response by RANO-LGG	Best Change in SPPD* of Measurable Lesion	Reported Clinical Improvements
(b) (6)	10 yo M	Pilocytic astrocytoma located in the posterior optic apparatus, brainstem & thalamus	BRAF V600E alteration	Visual acuity - Right eye: 1 logMAR; left eye: 0.3 logMAR.	Stable disease	Minor response	-55% by RAPNO, -- 48% by RANO-LGG	Investigator reported: improved headache, dizziness, intermittent blurry vision, and general quality of life. Parent reported: patient is more confident, less anxious, and able to perform most of his activities.
(b) (6)	14 yo F	Piloymyxoid optic pathway glioma	KIAA1549:BRAF fusion	Visual acuity - Right eye: Unable to be assessed due to poor vision; left eye: 0.49 logMAR	Stable disease	Minor response	-8% by RAPNO, -47% by RANO-LGG	Investigator reported: patient's hemiparesis was described as "essentially resolved". Visual acuity was assessed throughout study and right eye was found to have reduction of 0.55 logMAR (2.1 in Cycle 15 to 1.55 in Cycle 26) while the left eye remained stable.

Patient ID	Age/Sex	Tumor Diagnosis & Location	Genomic Alteration	Clinical Baseline & Reported Deficits	Response by RAPNO	Response by RANO-LGG	Best Change in SPPD* of Measurable Lesion	Reported Clinical Improvements
(b) (6)	4 yo F	Astrocytic optic pathway glioma	KIAA1549:BRAF fusion	Visual acuity - Right eye: -0.1 logMAR; left eye 0.1 logMAR	Minor response	Partial response	-53% by RAPNO, -74% by RANO-LGG	Investigator reported: resolution of headache and mood changes, and ability to play at school and at home without interruption secondary to clinical symptoms that had previously disrupted activities of daily living. Visual acuity was assessed throughout the study and right eye acuity had reduction of 0.1 logMAR from baseline and the left eye had reduction of 0.2 logMAR from baseline.

Patient ID	Age/Sex	Tumor Diagnosis & Location	Genomic Alteration	Clinical Baseline & Reported Deficits	Response by RAPNO	Response by RANO-LGG	Best Change in SPPD* of Measurable Lesion	Reported Clinical Improvements
(b) (6)	5 yo M	Astrocytic optic pathway glioma	KIAA1549:BRAF fusion	Clinical baseline: limited visual fields and no light perception in the left eye. Visual acuity – right eye: 0.18 logMAR; left eye – not performed due to blindness. The patient also had insomnia, anorexia, constipation, and gastroesophageal reflux at baseline.	Minor response	Minor response	-41% by RAPNO, -31% by RANO-LGG	Investigator reported: improvements in anorexia, and constipation, gastroesophageal reflux; increased oral intake and weight permitting removal of g-tube. Visual acuity was assessed throughout the study and right eye acuity had reduction of 0.1 logMAR from baseline.
(b) (6)	10 yo M	Pilocytic astrocytoma – optic pathway glioma	KIAA1549:BRAF fusion	Clinical baseline: short term memory loss after prior treatment with chemotherapy. Visual acuity in both eyes was 0 logMAR.	Minor response	Minor response	-33% by RAPNO; -40% by RANO-LGG	Investigator reported: improvement in short term memory during treatment.

Patient ID	Age/Sex	Tumor Diagnosis & Location	Genomic Alteration	Clinical Baseline & Reported Deficits	Response by RAPNO	Response by RANO-LGG	Best Change in SPPD* of Measurable Lesion	Reported Clinical Improvements
(b) (6)	2 yo M	Pilomyxoid astrocytoma of the optic pathway	KIAA:1549 BRAF fusion	Clinical baseline: decreased vision in the right eye, global developmental delay and diabetes insipidus (DI). Visual acuity – right eye: not evaluated due to vision loss, left eye: 0.7 logMAR.	Minor response	Minor response	-43% by RAPNO, -46% by RANO-LGG	Investigator reported: improvement in patient's global development including mobility (able to walk, run, ride a scooter, go up and down stairs after receiving tovorafenib), greater engagement in communication with increased language (able to speak a few words after receiving tovorafenib), more energy, and better control of DI. Parent reported: patient gained energy and strength, improved upon motor delays; he was more expressive, seizure-free with fewer hospitalizations, and able to start school. Visual acuity was assessed throughout the study and right eye had reduction of 0.64 logMAR from baseline.

Patient ID	Age/Sex	Tumor Diagnosis & Location	Genomic Alteration	Clinical Baseline & Reported Deficits	Response by RAPNO	Response by RANO-LGG	Best Change in SPPD* of Measurable Lesion	Reported Clinical Improvements
(b) (6)	5 yo F	Pilocytic astrocytoma of the pathway	KIAA1549:BRAF fusion	Clinical baseline: global development delay, optical atrophy, and right hemiparesis. Vision testing attempted but unable to be performed due to patient's developmental delay.	Stable disease	Minor response	-49% by RAPNO, -65% by RANO-LGG	Investigator reported: improvement in baseline clinical symptom, general behavior and learning abilities; increase in mobility (e.g., can now ride a tricycle and raise her right arm above her head); increase in language (can speak some sentences after treatment with tovorafenib) and desire to communicate; started school. Parent reported: significant improvements in cognition and comprehension, able to spend full day in school with minimal issues, able to focus on activities such as coloring and drawing which she was previously unable to do, learning to read and now capable of speaking in full sentences, and remarkable improvement in functional vision.

Patient ID	Age/Sex	Tumor Diagnosis & Location	Genomic Alteration	Clinical Baseline & Reported Deficits	Response by RAPNO	Response by RANO-LGG	Best Change in SPPD* of Measurable Lesion	Reported Clinical Improvements
(b) (6)	15 yo F	Astrocytic glioma in fourth ventricle	BRAF duplication	Clinical baseline: decrease in balance in the right extremities, slight dysmetria with right finger to nose, slightly unstable rope walk, nystagmus of left eye, neuropathic pain requiring pregabalin and concentration deficit disorder	Partial response	Minor response	-57% by RAPNO, -73% by RANO-LGG	Investigator reported: clinical improvement enabling patient to taper off pregabalin during treatment with tovorafenib.
(b) (6)	8 yo M	Pilomyxoid astrocytoma of the optic pathway with leptomeningeal spread	KIAA1549:BRAF fusion	Clinical baseline: blindness in right eye, and hyperphagia.	Stable disease	Minor response	-6% by RAPNO, -49% by RANO-LGG	Investigator reported: stability in baseline clinical symptoms during treatment; patient's visual fields in the right eye improved; patient sleeping better with fewer waking episodes.
(b) (6)	11 yo F	Astrocytic glioma in the optic pathway	KIAA1549:BRAF fusion	Visual acuity - right eye: not evaluable (no light perception), left eye: 1.1 logMAR	Minor response	Stable disease	-36% by RAPNO, -40% by RANO-LGG	Visual acuity was assessed throughout the study and left eye had reduction of 0.48 logMAR from baseline.

Patient ID	Age/Sex	Tumor Diagnosis & Location	Genomic Alteration	Clinical Baseline & Reported Deficits	Response by RAPNO	Response by RANO-LGG	Best Change in SPPD* of Measurable Lesion	Reported Clinical Improvements
(b) (6)	8 yo F	Pilocytic astrocytoma of the optic pathway	BRAF V600E mutation	Visual acuity - Right eye: unable to assess; left eye: 0.2 logMAR.	Minor response	Minor response	-34% by RAPNO and RANO-LGG	Investigator reported: stable clinical symptoms, improved quality of life with less time in clinic or managing side effect., able to participate in extensive extra-curricular activities such as dancing, able to attend school-full-time without modification to activities (which was required while on prior treatments). Visual acuity was assessed throughout the study and left eye had reduction of 0.15 logMAR from baseline.

Patient ID	Age/Sex	Tumor Diagnosis & Location	Genomic Alteration	Clinical Baseline & Reported Deficits	Response by RAPNO	Response by RANO-LGG	Best Change in SPPD* of Measurable Lesion	Reported Clinical Improvements
(b) (6)	15 yo M	Pilocytic astrocytoma of the optic pathway	KIAA1549:BRAF fusion	Visual acuity – Right eye: unable to assess due to blindness; left eye: 1.7 logMAR.	Stable disease	Minor response	-46% by RANO-LGG and RAPNO	Investigator reported: improved neurocognitive function, patient more involved in self-care and treatment, improved physical performance and improved appetite (discontinued nutritional supplements), engaging in activities such as dancing, music class, football, and attends school full time after starting tovorafenib. Visual acuity was assessed throughout the study and left eye had reduction of 0.2 logMAR from baseline.
(b) (6)	8 yo F	Pilocytic astrocytoma of the optic pathway	KIAA1549:BRAF fusion	Clinical baseline: pituitary insufficiency and precocious puberty.	Minor response	Minor response	-71% per RAPNO, -64% per RANO-LGG	Investigator reported: general clinical improvement, and treatment for precocious puberty was able to be discontinued.

Patient ID	Age/Sex	Tumor Diagnosis & Location	Genomic Alteration	Clinical Baseline & Reported Deficits	Response by RAPNO	Response by RANO-LGG	Best Change in SPPD* of Measurable Lesion	Reported Clinical Improvements
(b) (6)	9 yo F	Pilocytic astrocytoma of the optic pathway	KIAA1549:BRAF fusion	Clinical baseline: visual deficits resulting in vision that was too impaired to perform acuity testing.	Partial response	Minor response	-78% per RAPNO, -40% per RANO-LGG	Investigator reported: improvement in baseline fatigue, attention span and scholastic performance; greater length of motor activity during the day without requiring rest; patient appears happier, more engaged with family; and has greater mental and physical capacity for school and leisure activities such as dancing and skiing.
(b) (6)	7 yo M	Astrocytic glioma in the optic pathway	KIAA1549:BRAF fusion	Clinical baseline: nystagmus, visual deficits.	Minor response	Minor response	-30% per RAPNO, -29% per RANO-LGG	Investigator reported: patient's clinical symptoms remained stable during treatment including visual acuity.
(b) (6)	9 yo F	Pilomyxoid astrocytoma of the optic pathway	KIAA1549:BRAF fusion	Clinical baseline: visual deficits including left homonymous hemianopia and precocious puberty. Visual acuity – right eye: 0.3 logMAR, left eye: 0.4 logMAR.	Partial response	Minor response	-72% by RAPNO, -54% by RANO-LGG	Investigator reported: improved vision and visual fields, patient is more mobile and less clumsy with fewer accidents. Visual acuity was assessed throughout the study and right eye had reduction of 0.2 logMAR from baseline and left eye had reduction of 0. 3 logMAR from baseline.

Patient ID	Age/Sex	Tumor Diagnosis & Location	Genomic Alteration	Clinical Baseline & Reported Deficits	Response by RAPNO	Response by RANO-LGG	Best Change in SPPD* of Measurable Lesion	Reported Clinical Improvements
(b) (6)	16 yo M	Pilocytic astrocytoma in the deep midline structures	KIAA1549:BRAF fusion	Clinical baseline: facial and trigeminal nerve palsies, right ear deafness, double vision, nysagmus, hemiplegia, intermittent headaches	Stable disease	Minor response	-16% per RAPNO, -34% per RANO-LGG	Investigator reported: patient had stable clinical symptoms during tovorafenib treatment.

Source: Reviewer-generated table.

*SPPD: Sum of products of perpendicular diameters

Abbreviations: F = female; M = male; yo = year-old.

8.1.2.16. Integrated Review of Effectiveness (supplements only)

The FDA's Assessment

Not applicable for this application.

8.1.3. Assessment of Efficacy Across Trials

This NDA is based on the results from Arm 1 of the Phase 2, open-label Study FIREFLY-1; therefore, no efficacy comparisons across studies were made.

The FDA's Assessment

The FDA agrees with the Applicant's position with respect to the efficacy data provided for FDA review in this application.

However, the FDA considered data from PNOC014, an investigator sponsored study, as confirmatory evidence supporting substantial evidence of effectiveness. PNOC014 is an investigator-sponsored dose-finding study of tovorafenib in patients 1 to 25 years of age with recurrent or progressive non-hematologic malignancies, including CNS tumors, that harbor a genomic mutation resulting in the activation of the RAS/RAF/MEK/ERK pathway. The study enrolled 34 patients with pediatric LGG with an activating BRAF alteration, of which 29 patients harbored a RAF fusion (24/29 patients had the KIAA1549:BRAF fusion). Of these patients, 31 had measurable disease, were evaluable for response assessment using Response Assessment in Neuro-Oncology (RANO) criteria and had post-baseline imaging. In these 31 patients, 3 had a complete response and 10 had a partial response. The demonstration of responses in a heavily pre-treated patient population constitutes confirmatory evidence of the effectiveness of tovorafenib in the intended population. Limited data was provided from this study in the application, precluding a determination of the acceptability of PNOC014 as a second adequate and well-controlled trial supporting substantial evidence of effectiveness.

8.1.4. Integrated Assessment of Effectiveness

Applicant's Position

Treatment of a molecularly-defined patient population with tovorafenib confers meaningful clinical benefit to pediatric patients with relapsed or refractory pediatric low-grade glioma. The study met its primary endpoint based on the prespecified ORR analysis.
Response to tovorafenib was observed when utilizing either T1-Gd+-based (RANO-HGG) or T2/FLAIR-based (RAPNO-LGG and RANO-LGG) response criteria (Table 41). ORR was similar across all 3 response assessment criteria. Furthermore, graphical presentations show that tumor shrinkage was seen for the majority of treated patients.

Defining the optimal imaging characteristics in low-grade glioma is challenging due to the heterogeneity of pediatric low-grade gliomas and differences between the pediatric and adult manifestations of the disease. Thus the 3 available response assessment criteria were used to analyze efficacy in Study FIREFLY-1: RANO-HGG was identified in the protocol as assessment criteria for the primary endpoint, RAPNO-LGG as a secondary endpoint, and RANO-LGG as an exploratory endpoint. All 3 response assessment criteria provided consistent results that demonstrate the efficacy of treatment with tovorafenib.

Table 41. Overall Response Rate by RANO-HGG, RAPNO-LGG, and RANO-LGG Criteria

Characteristic	ORR by RANO-HGG N=69	ORR by RAPNO-LGG N=76	ORR by RANO-LGG N=76
Best overall response, n (%)			
Complete response (CR)	12 (17.4)	0	0
Partial response (PR)	34 (49.3)	28 (36.8)	20 (26.3)
Minor response (MR)	-	11 (14.5)	20 (26.3)
Stable disease	18 (26.1)	23 (30.3)	23 (30.3)
Stable disease ≥12 months	8 (11.6)	4 (5.3)	6 (7.9)
Stable disease <12 months[a]	10 (14.5)	19 (25.0)	17 (22.4)
Progressive disease (PD)	4 (5.8)	13 (17.1)	11 (14.5)
Not evaluable (NE)	1 (1.4)	1 (1.3)	2 (2.6)
Number of patients with confirmed response	46	39	40
ORR[b] (95% CI)	66.667 (54.288, 77.563)	51.316 (39.569, 62.957)	52.632 (40.844, 64.208)

Source: Applicant-provided table.

Abbreviations: ORR = overall response rate.

Responses following tovorafenib treatment were observed in all subgroups by all 3 response assessment criteria, including in patients with BRAF fusions or V600E mutations, without prior MAPK inhibitor therapy or with prior MAPK-targeted therapy, or following numerous lines of prior therapy. No differences were observed for subgroups of patients by sex, age, or race. Responses to tovorafenib were rapid (median time to response of 3 to 5 months) by all 3 response assessment criteria. The response was durable, with a median duration of response ranging from 13.8 to 16.6 months depending on the response assessment criteria used.
By utilizing both T1-Gd+-based (RANO-HGG) and T2/FLAIR-based (RAPNO-LGG and RANO-LGG) response criteria, this study provided the opportunity to assess the impact of tovorafenib on different aspects of low-grade glioma tumor biology. Despite the unique challenges of ascertaining an optimal, single set of response assessment criteria for this heterogeneous disease, evidence of tumor response to tovorafenib was observed across the three different neuro-oncology response assessment criteria (RANO-HGG, RAPNO-LGG, RANO-LGG). Furthermore, radiographic evidence of tumor response across response criteria was coupled with clinical manifestations of symptomatic improvement (e.g., visual, motor, cognitive, or

behavioral improvement) across all subgroups. Taken together, the available efficacy data provide comprehensive and robust evidence in support of the proposed indication.

The FDA's Assessment

Based on the review of clinical data from Arm 1 of FIREFLY-1 (n=76), the clinical and statistical review teams conclude that the Applicant provided substantial evidence of effectiveness of tovorafenib in pediatric patients 6 months of age and older with relapsed or refractory pediatric LGG harboring a BRAF fusion or rearrangement, or BRAF V600 mutation. The overall response rate of 51%, inclusive of minor, partial and complete responses, and the durability of responses (median: 13.8 months), as determined by BICR according to RAPNO criteria, in FIREFLY-1's heavily pretreated patient population including disseminated disease are considered clinically meaningful and supportive of substantial evidence of effectiveness as these tumors are not expected to regress without intervention. Importantly, similar response rates were observed in patients with BRAF fusions or rearrangements and BRAF V600E mutation, as well as patients previously treated with MEK and/or BRAF inhibitors and patients with multiple prior lines of systemic treatment. Information submitted by the Applicant in individual efficacy narratives provided sufficient evidence of improvement in tumor associated signs or symptoms in patients with minor responses to support inclusion of minor responses in the calculation of response rate. However, the FDA does not consider that this information was sufficiently rigorously collected to constitute robust evidence of direct clinical benefit.

Verification of benefit will be based on results from a randomized trial of tovorafenib compared to standard of care chemotherapy in patients with pediatric LGG with a primary endpoint of ORR and a key secondary endpoint of PFS. The Applicant intends to submit efficacy data from FIREFLY-2, an ongoing, international, open-label, randomized (1:1) controlled trial comparing tovorafenib to standard of care chemotherapy as first line treatment in 400 patients who require systemic therapy for pediatric LGG. The study was initiated in 2023, is accruing patients at a reasonable rate, (b) (4).

8.2. Review of Safety

Applicant's Position

Review of safety following treatment with tovorafenib is based primarily on data from Study FIREFLY-1, with supportive data drawn from 5 other clinical studies (Studies C28001 and C28002 in adult patients with advanced cancer, Studies (b) (4) 205140 and DAY101-103 in healthy participants, and an ongoing investigator-sponsored study PNOC014).

The overall safety profile of tovorafenib is acceptable and manageable in this heavily pre-treated patient population. Toxicities associated with tovorafenib may be effectively managed medically, with dose interruptions and reductions as appropriate. All 137 patients in Arm 1 and Arm 2 of Study FIREFLY-1 experienced at least 1 TEAE. Grade 3 or higher TEAEs occurred in

62.8% of patients, most of which resolved while continuing treatment with tovorafenib, as evidenced by infrequent treatment discontinuation due to AEs. Ten (7.3%) patients discontinued tovorafenib due to toxicity. No deaths occurred that were attributed to treatment with tovorafenib.

The most frequent (>40% incidence) TEAEs were hair color changes, fatigue, vomiting, headache, and rash maculo-papular. Common laboratory abnormalities (>40% incidence) were blood creatine phosphokinase increased, anemia, and hypophosphataemia.

Toxicities typically associated with MAPK targeted therapies were not observed with tovorafenib, including clinically significant cardiomyopathy, ophthalmologic events, hepatotoxicity, or significant immune compromise. With the monitorable, reversible, and manageable safety profile, tovorafenib demonstrates a positive benefit-risk profile for patients with pediatric low-grade glioma.

Detailed review of data from the 5 supportive studies as well as pooled analysis of Study FIREFLY-1 and Study C28001 did not identify new or additional safety concerns beyond those that were observed in Study FIREFLY-1 alone.

The FDA's Assessment

Refer to Sections 8.2.1 and 8.2.2 for the FDA's safety review.

8.2.1. Safety Review Approach

Applicant's Position

Safety analyses summarized in this assessment aid document are based on updated data for Study FIREFLY-1 Arm 1 and Arm 2, comprising 137 patients with pediatric low-grade glioma who received tovorafenib 420 mg/m^2 orally once a week. Comprehensive analyses of the entire safety database, which includes all 3 arms of Study FIREFLY-1 as well as 5 other supportive clinical studies, are presented in the Summary of Clinical Safety.

The original primary data cutoff dates for the ongoing studies in this submission were 22 December 2022 for Study FIREFLY-1 and 13 October 2022 for Study PNOC014. An updated data cutoff date of 05 June 2023, approximately 15 months after the last patient was enrolled into Arm 1, provides an additional 6 months of follow up in Study FIREFLY-1. The updated data from FIREFLY-1 Arms 1 and 2 are the primary focus of the safety review, as these data are most pertinent to the proposed indication and no additional safety concerns were identified from analysis of the 3 patients with other solid tumors enrolled in FIREFLY-1 Arm 3 or other clinical studies in both adults and children.

Across the 6 individual clinical studies, 432 unique individuals had systemic exposure to at least one dose of tovorafenib and were evaluable for safety as summarized in the body of the application with the original primary cutoff date of 22 December 2022. As of the updated cutoff date of 05 June 2023, one additional patient has been enrolled and treated in Arm 2 of Study FIREFLY-1 for a total of 137 patients in Study FIREFLY-1 and 433 unique individuals in the safety database.

Thorough review of the entire safety database alongside focused review of the target patient population is considered sufficient to detect and characterize events that are likely to occur following treatment with tovorafenib in the proposed indication of patients 6 months of age and older with relapsed or refractory pediatric low-grade glioma (LGG).

The FDA's Assessment

The FDA generally agrees with the Applicant's description of the primary and supportive safety datasets included in these NDAs. The FDA's evaluation of safety included analysis of the submitted clinical study reports, datasets, line listings, electronic case report forms and case narratives. Additionally, reports of serious adverse events (SAEs) and adverse events of special interest (AESI) were also reviewed.

The FDA's safety review focused largely on data (DCO of June 5, 2023) from FIREFLY-1, a single-arm clinical trial that enrolled 137 patients (77 patients in Arm 1 and 60 patients in Arm 2) with pediatric LGG harboring a BRAF alteration or RAF fusion and comprised the primary safety population for the proposed indication. The pooled safety population for the FDA's analysis includes all 140 patients in FIREFLY-1 (including the 3 additional patients from Arm 3) and 32 adult patients with advanced solid tumors from Study C28001 who were treated with tovorafenib at the recommended Phase 2 dose of 420 mg/m^2 once weekly (maximum dose of 600 mg) for an integrated safety set (ISS) comprising 172 patients. Study C28001 was a nonrandomized, multicenter, open-label dose escalation and dose expansion study that evaluated the safety, efficacy and pharmacokinetics of tovorafenib in two dosing schedules (every other day and once weekly) in adult patients with advanced solid tumors including melanoma.

Additionally, the FDA reviewed supportive safety data from supportive studies PNOC014, C28002, (b) (4) 205140 and DAY101-103, which are further described in Section 7.1 (*Table of Clinical Studies)*.

8.2.2. Review of the Safety Database

8.2.2.1. Overall Exposure

Applicant's Position

As of 05 June 2023, a total of 137 patients in Arm 1 and Arm 2 of Study FIREFLY-1 had received at least one dose of tovorafenib. The median duration of tovorafenib exposure was 362.0 days (or 11.9 months) (range: 22 to 722 days, or 0.72 to 23.7 months), with a median of 13 treatment cycles (range: 1 to 26 cycles). Of the 137 patients, 118 patients (86.1%) received ≥6 months of tovorafenib treatment, 67 patients (48.9%) received ≥ 12 months of treatment, and 19 patients (13.9%) received ≥18 months of treatment.

Table 42. Duration of Exposure to Tovorafenib (safety analysis set; arms 1 and 2)

Statistic	Arm 1 (LGG) N=77	Arm 2 (LGG) N=60	Arm 1 + Arm 2 (LGG) N=137
Duration of maximum exposure[a] (days)			
Mean (SD)	445.9 (180.97)	277.9 (86.80)	372.3 (169.02)
Median (min, max)	480.0 (22, 722)	296.0 (36, 404)	362.0 (22, 722)
Duration of treatment, n (%)			
≥6 months	66 (85.7)	52 (86.7)	118 (86.1)
≥12 months	59 (76.6)	8 (13.3)	67 (48.9)
≥18 months	19 (24.7)	0	19 (13.9)
Patients who had a drug holiday[b]	0	0	0
Total expected dose (mg)			
Mean (SD)	28119.7 (13143.72)	17433.3 (8072.24)	23439.5 (12374.41)
Median	29200.0	14975.0	23400.0
Min, Max	1300, 58200	3300, 34200	1300, 58200
Total actual dose received (mg)			
Mean (SD)	27907.0 (13056.81)	17290.4 (8085.67)	23257.4 (12311.75)
Median	28000.0	14850.0	23400.0
Min, Max	1300, 58200	3300, 34200	1300, 58200
Number of cycles treated[c]			
Mean (SD)	16.2 (6.43)	10.3 (3.00)	13.6 (5.97)
Median (min, max)	18.0 (1, 26)	11.0 (2, 15)	13.0 (1, 26)
Treatment compliance[d] (%)			
Mean (SD)	99.30 (1.630)	99.05 (2.875)	99.19 (2.255)
Median	100.00	100.00	100.00
Min, Max	92.5, 100.0	82.8, 100.8	82.8, 100.8
Patients with dose interruptions due to an adverse event, n (%)	39 (50.6)	25 (41.7)	64 (46.7)
Duration of interruptions[e] (days)			
Mean (SD)	25.3 (25.27)	17.9 (18.08)	22.4 (22.87)
Median (min, max)	14.0 (7, 119)	14.0 (7, 84)	14.0 (7, 119)
Patients with dose reductions due to an adverse event, n (%)	21 (27.3)	11 (18.3)	32 (23.4)

Source: FIREFLY-1 Update CSR Table 14.3.1, Table 14.3.1.1.

[a] Duration of maximum exposure = date of last dose of study treatment including tovorafenib re-treatment after drug holiday – date of first dose of study treatment + 1.

[b] No patients reached 2 calendar years of treatment at the time of the data cutoff <<For QC: per protocol>>. Two patients completed 26 cycles of treatment and were therefore eligible for a drug holiday. <<For QC: per DOB>>

[c] A cycle is counted if received at least one dose of tovorafenib in a cycle.

[d] Treatment compliance (%) = total actual dose (mg) / total expected dose (mg) ×100%.

[e] Duration of interruptions (days) = number of times dose not administered due to adverse event × 7.

Data Cutoff Date: 05 June 2023.

Abbreviations: LGG = low-grade glioma; Max = maximum; Min = minimum; SD = standard deviation.

The FDA's Assessment

The FDA agrees with the Applicant's summary of drug exposure as presented in Table 42. Patient exposure to tovorafenib in Arms 1 and 2 of FIREFLY-1 permit an adequate assessment of the drug's safety profile in patients who are representative of the intended target population. Given the likely chronic use of tovorafenib in pediatric patients due to the prolonged natural history of pediatric LGG, a post marketing requirement (PMR) will be included in the approval letter to conduct comprehensive safety analyses from clinical studies that further characterize the serious risk of long-term adverse effects of tovorafenib on growth and development, including growth plate abnormalities. The FDA considers evaluation of the safety of long-term administration to be a priority in further development of tovorafenib for this target population.

8.2.2.2. Relevant Characteristics of the Safety Population

Applicant's Position

As of 05 June 2023, the median age of the safety population in Arm 1 and 2 of Study FIREFLY-1 was 9.0 years and ranged from 1 to 24 years. By age group, 3 patients were 6 months to <2 years, 27 patients were 2 to <6 years, 65 patients were 6 to < 12 years, 27 patients were 12 to <16 years, and 15 patients were 16 to ≤25 years of age.

Approximately half of the patients (53.3%) were male, approximately 60% of patients were White, and 71.5% were not Hispanic or Latino.

The optic pathway was the most common primary tumor location (49.6%). More than half of patients (52.6%) had three or more prior lines of systemic therapy.

The FDA's Assessment

The FDA agrees with the overview of relevant demographic and baseline disease characteristics provided for the heavily pre-treated pediatric LGG population enrolled in FIREFLY-1. Additionally, 33% of patients participating in the study were from the US. The overall demographics and disease characteristics of the safety population permit sufficient assessment of safety in the proposed indication. Refer to the FDA's assessment in Section 8.1.2.5 for additional details.

The FDA also evaluated safety findings in the ISS population (n=172) in which the median age was 10 years (range: 1 to 83 years), 52% of patients were male, 65% of patients were White, 73% were not Hispanic or Latino and 44% of patients were from the US.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Applicant's Position

The safety analyses and conclusions in this submission are based primarily on 137 pediatric patients with relapsed or refractory pediatric low-grade glioma in Study FIREFLY-1 Arm 1 and Arm 2, in which patients received (b) (4) 420 mg/m^2 (maximum of 600 mg) once weekly. This assessment aid focuses on updated data from the 05 June 2023 data cutoff, 6 months after the original data cutoff of 22 December 2023 presented in the body of the application. Safety analyses were further supported by data from monotherapy studies C28001 in adult patients with advanced solid tumors and the investigator-sponsored trial PNOC014 in pediatric patients who received a range of treatment dosing regimens (b) (4) . Two studies with healthy participants and a combination therapy study in cancer patients round out the safety database of events following exposure to tovorafenib.

The safety data across these 6 studies are considered adequate to support the proposed NDA for the indication of relapsed refractory pediatric low-grade glioma in patients 6 months of age and older.

The FDA's Assessment

The FDA agrees with the Applicant's description of the safety database and the adequacy of the analyses performed to determine the safety profile of tovorafenib. The 137 patients enrolled in Arms 1 and 2 of FIREFLY-1 are considered representative of the intended patient population with relapsed or refractory pediatric LGG harboring the specified BRAF alterations.

8.2.3.1. Issues Regarding Data Integrity and Submission Quality

Applicant's Position

There are no major concerns about the quality and integrity of the submitted datasets and case narratives that comprise the core safety analysis in Study FIREFLY-1; and data from the submitted clinical study reports was sufficiently complete for a comprehensive analysis of the safety data.

Among the studies that evaluated the safety of tovorafenib in patients (FIREFLY-1, C28001, PNOC014, and C28002), safety data collection and reporting elements were generally similar. Key distinctions among FIREFLY-1, C28001, and C28002 in the collection and reporting of safety data relevant to interpretation of results are the reporting requirements for death due to disease progression and availability of certain clinical laboratory data for chemistry.

For investigator-sponsored Study PNOC014 only, safety information is based on personal communication from the investigator-sponsor DFCI to Day One and the ClinicalTrials.gov posting in addition to ICSRs for SAEs and aggregate unmonitored data as provided from DFCI to Day One. Data from Study PNOC014 are considered supportive and are included in the body of the submission for completeness.

The FDA's Assessment

The FDA agrees with the Applicant's position. No meaningful concerns were identified in the quality and integrity of the submitted clinical study reports, datasets, and individual case narratives. The FDA was able to complete a comprehensive analysis of safety data.
The NDA submission contains all required components of the electronic common technical document (eCTD). See Section 8.1.2.9 "Data Quality and Integrity" for the FDA's assessment of overall data quality and integrity in the NDA. Further, refer to Section 4.1 "Office of Scientific Investigation" for a summary of clinical site inspections.

8.2.3.2. Categorization of Adverse Events

Applicant's Position

The focus of the safety assessment was the evaluation of AEs, specifically treatment-emergent adverse events (TEAEs).

A TEAE was defined as an AE that started on or after the first administration of study treatment and within 30 days post last dose of tovorafenib. Adverse event terms were coded by SOC and PT using MedDRA Version 23.1. The severity of AEs was graded according to NCI CTCAE using Version 5.0. The relationship of AEs to study treatment was assessed by the investigator as related or not related and summarized accordingly.

The overall number of deaths within 30 days after the last dose of study treatment and more than 30 days after last dose of study treatment were summarized.

Adverse Events of Special Interest Plan

The Sponsor has established grouped terms to identify adverse events of special interest (AESIs) for the tovorafenib development program. Adverse events of special interest were selected based on review of early tovorafenib nonclinical and clinical data as well as consideration of similar drug class effects. Chosen events included those having clinical importance to the treatment population or for which closer observation was warranted to determine the significance of clinical impact. The search strategy was as follows:

- Rhabdomyolysis/myopathy (Narrow scope), based on selected terms from the Standardised MedDRA Query (SMQ) "Rhabdomyolysis/myopathy"

- Ventricular arrhythmias, based on the SMQ "Ventricular tachyarrhythmias"
- Intra-tumoral hemorrhage, based on the SMQ "Haemorrhagic central nervous system vascular conditions" and the Medical Dictionary for Regulatory Activities (MedDRA) preferred term "tumour haemorrhage"
- Secondary primary malignancies, based on the SMQ "Non-haematological malignant tumours"
- Ophthalmologic events, based on the MedDRA system organ class (SOC) of Eye Disorders, excluding the high-level group terms of "Congenital eye disorders (excluding glaucoma)", "Ocular neoplasms", and "Ocular neuromuscular disorders"

Events identified by the AESI search algorithm were further reviewed and adjudicated by an experienced senior safety physician for clinical relevance to the categories of events of interest.

The FDA's Assessment

The FDA agrees with the description of the Applicant's strategy for categorization of adverse event data including AESIs and considers the general methods used for the assessment of safety and tolerability of tovorafenib to be acceptable. Of note, the FDA also identified skin toxicity including photosensitivity, reduction in growth velocity, and hepatotoxicity as clinically significant adverse events. The safety analyses for these adverse reactions are further described in Section 8.2.5 (*Analysis of Submission-Specific Safety Issues*).

8.2.3.3. Routine Clinical Tests

Applicant's Position

Laboratory monitoring for Study FIREFLY-1 consisted of routine monitoring of hematology and chemistry laboratory test results at visits specified in the study protocols.

Toxicity grades were assigned to corresponding laboratory values when available using NCI CTCAE Version 5.0. Overall, the frequency and scope of laboratory monitoring was adequate to assess the safety in the proposed indication of patients 6 months or older with relapsed or refractory pediatric low-grade glioma.

Cardiovascular Evaluations

For study FIREFLY-1, echocardiograms and ECGs were collected routinely per the study protocol. Electrocardiograms for FIREFLY-1 were centrally read and analyzed for trends in QTc and other intervals. For echocardiograms, measures of left ventricular ejection fraction (LVEF) and fractional shortening (FS), along with assessment of any clinically significant abnormalities were recorded by the investigator in the study database. Heart rate and blood pressure were

collected at the study visit at the start of each cycle and evaluated against age and gender standards. Overall, the routine collection and analysis of cardiovascular data was sufficient to evaluate the safety of tovorafenib in the proposed treatment population.

The FDA's Assessment

The FDA agrees with the Applicant's summary of routine clinical tests including laboratory monitoring and cardiovascular evaluations conducted in FIREFLY-1. The FDA notes that additional safety assessments stipulated in the study protocol included periodic ophthalmologic examination and visual acuity assessments in patients with an optic pathway glioma (OPG) or an underlying visual deficit related to the primary malignancy, dermatologic examinations, neurologic examinations, and assessments of pubertal status.

8.2.4. Safety Results

8.2.4.1. Deaths

Applicant's Position

As of 05 June 2023, a total of four deaths have occurred in Study FIREFLY-1 all of which were considered not related to tovorafenib. Two deaths occurred on-study in Arm 1 and Arm 2. One death in Arm 1 occurred more than 30 days after the last dose of tovorafenib, and 1 death occurred in Arm 3.

- One 4-year-old male patient in Arm 1 had a Grade 5 (fatal) TEAE of brain death. The patient experienced Grade 1 seizures on Day -6, Day 2, Day 15. On Day 33, a brain CT showed worsening mass effect of the tumor and new hemorrhages plus suspected stroke in the right temporal region and collapse of the ventricles. The patient was diagnosed with Grade 4 neurological decompensation. On Day 35, 5 days after the last dose of tovorafenib, a brain perfusion scan demonstrated no flow, consistent with brain death. The investigator and Sponsor considered brain death as not related to tovorafenib.
- One 18-year-old female patient in Arm 1 with a disseminated spinal and posterior fossa tumor first diagnosed in (b) (6) at the age of 5 years had a Grade 5 (fatal) AE of hydrocephalus. Medical history included acute hydrocephalus requiring revision of left ventriculo-peritoneal (VP) shunt ((b) (6)) and hydrocephalus with VP shunt. On Day 334, the patient discontinued tovorafenib due to Grade 1 tumor hemorrhage which was identified on a per protocol MRI scan. On Day 362, 36 days after the last dose of tovorafenib, the patient had a serious AE of Grade 4 hydrocephalus due to the intra-tumoral bleed which was still ongoing. Several shunt revisions were performed, and a right external ventricle drain (EVD) was inserted (Day 371). On Day 373, the shunt kept blocking and the EVD did not drain. On Day 382, 55 days after the last dose of tovorafenib, supportive care was withdrawn and the patient died due to Grade 5 hydrocephalus. There was no apparent

increase in the size of the tumor bleed or tumor size. Grade 5 hydrocephalus was considered by the investigator and Sponsor as not related to tovorafenib.

- One 14-year-old male patient in Arm 2 with a mixed glial-neuronal tumor with leptomeningeal dissemination had a Grade 5 (fatal) TEAE of tumour hemorrhage in the setting of disease progression. The patient's last dose of study treatment was 7 days prior to the onset of the event. On Day 224, the patient was admitted to the hospital for IV hydration and electrolyte correction after going to the emergency department for abdominal pain. On Day 226, the patient experienced multiple hemorrhages; a full brain MRI was concerning for 2 hemorrhagic lesions in the cerebellum. Over the course of hospitalization, the patient had multiple procedures to control intracranial pressure including placement of an external ventricular drain. On Day 239 the EVD was removed and the patient died, 21 days after the last dose of tovorafenib. The event was considered not related to tovorafenib and was noted by the investigator to be attributable to disease progression.
- One patient in Arm 3, a 13-year-old female with Stage IV metastatic rectal adenocarcinoma, died due to progressive disease 32 days after the last dose of tovorafenib. On Day 51, 850 mL of peritoneal fluid was drained. On Day 54 the patient returned to the clinic and an abdominal CT scan showed the known case of metastatic rectal carcinoma with mixed response. On Day 78 the patient discontinued tovorafenib due to progressive disease. On Day 85 the patient was hospitalized with Grade 3 pulmonary embolism and was treated with enoxaparin along with oral morphine and oral methadone for abdominal pain. On Day 93, the patient showed good symptomatic relief and a chest x-ray showed large bilateral pleural effusions which appeared stable from previous scans. On Day 104, 32 days after the last dose of tovorafenib, the patient died due to disease progression. The investigator and Sponsor considered the SAE of pulmonary embolism as not related to tovorafenib.

In supportive study C28001, 13 adult patients with advanced solid tumors died on-study (including 1 patient whose on-study death was not reported as an AE/SAE in the clinical database) (Table 43). None of these deaths were assessed as treatment related except one fatal SAE of respiratory failure.

Table 43. Adverse Events Leading to Death, Study C28001

	QW Dosing		Q2D Dosing
MedDRA System Organ Class Preferred Term	400 mg/ 600 mg N=35 n (%)	800 mg N=4 n (%)	C28001 N=110 n (%)
Any AE leading to death	2 (5.7)	1 (25.0)	9 (8.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (5.7)	0	4 (3.6)
Metastatic malignant melanoma	0	0	2 (1.8)
Colon cancer	0	0	1 (0.9)
Colon cancer metastatic	1 (2.9)	0	0
Malignant melanoma	0	0	1 (0.9)
Malignant neoplasm progression	1 (2.9)	0	0
Infections and infestations	0	0	2 (1.8)
Pneumonia	0	0	1 (0.9)
Sepsis	0	0	1 (0.9)
Respiratory, thoracic and mediastinal disorders	0	0	2 (1.8)
Respiratory failure	0	0	2 (1.8)
Cardiac disorders	0	1 (25.0)	0
Cardio-respiratory arrest	0	1 (25.0)	0
Gastrointestinal disorders	0	0	1 (0.9)
Small intestinal obstruction	0	0	1 (0.9)

Source: ISS Table 1.4.11

Note: MedDRA version 23.1.

Data cutoff date for FIREFLY-1: 22 December 2022

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; Q2D = every other day; QW = once weekly.

The FDA's Assessment

The FDA examined causes of death for patients receiving tovorafenib in FIREFLY-1 and Study C28001 based on review of death narratives submitted by the Applicant.

Deaths in FIREFLY-1

Although the FDA generally agrees with the brief synopses including relevant medical history and details on the deaths of four patients participating in FIREFLY-1, the FDA does not agree with the Applicant's assessment that a contribution of tovorafenib in all four deaths can reliably be excluded. See below for the FDA's comments regarding attribution of individual study patient deaths in FIREFLY-1.

- Patient (b) (6) was a 14-year-old male with BRAF-altered mixed glial-neuronal tumor with leptomeningeal dissemination enrolled in Arm 2 who died on study day 239 (21 days after receiving last dose of tovorafenib). The reported cause of death was tumor hemorrhage. The patient had received multiple lines of prior systemic therapy including carboplatin, vemurafenib, dabrafenib and trametinib, vinblastine, temozolomide and

bevacizumab. On study day 226 (7 days after last dose of tovorafenib), the patient was hospitalized for a serious adverse event of Grade 4 tumor hemorrhage with concern for hemorrhagic metastasis. He was noted to have multiple hemorrhages in the cerebellum with vasogenic edema and mass effect on the fourth ventricle. He underwent external ventricle drain (EVD) placement and emergent posterior fossa craniectomy for evacuation of hemorrhage and duraplasty; however, he continued to have worsening hemorrhage and mass effect impacting the brainstem. The investigator attributed the patient's death to disease progression. Autopsy revealed acute intracranial hemorrhage with severe mass effect due to tumor overlying ventral brain surface.

Reviewer Comments: Although the severity of the patient's baseline disease with leptomeningeal involvement may be a risk factor for the development of tumor hemorrhage, this patient did not have prior history of intratumoral bleed or other bleeding events and was not receiving any anticoagulants. The potential contribution of tovorafenib to the intratumoral bleed cannot be ruled out. The rapid development of tumor hemorrhage occurred in the absence of definitive disease progression on imaging, although the investigator considered the tumor bleeding to be indicative of hemorrhagic metastasis.

- Patient (b) (6) was a 13-year-old female with stage IV rectal adenocarcinoma enrolled in Arm 3 who died on study day 104 (32 days after receiving last dose of study treatment). The reported cause of death was disease progression. The patient had received prior systemic therapy with irinotecan, 5-fluorouracil, oxaliplatin, and trametinib. On study day 43, she underwent peritoneal catheter insertion for ascites. On study day 49, she developed abdominal pain and was noted to have Grade 2 post-procedural hemorrhage (hemoglobin 65 g/L, platelet count of 566K) requiring blood transfusion. On study day 78, she discontinued tovorafenib due to progressive disease. She subsequently developed Grade 3 pulmonary embolism (PE) in the right main pulmonary artery on Day 85 and was hospitalized for management. She was treated with subcutaneous enoxaparin for the PE and demonstrated symptomatic improvement. On study day 104, she died due to disease progression. The investigator considered the patient's ascites, anemia, abdominal pain, post-procedural hemorrhage and pulmonary embolism as not related to tovorafenib.

  Reviewer Comments: The FDA agrees that the patient's cause of death is likely due to disease progression. Although use of tovorafenib may have contributed to the development of post-procedural hemorrhage, concomitant anticoagulant treatment for PE is a clear confounding factor.

- Patient (b) (6) was an 18-year-old female with BRAF-altered pilocytic astrocytoma of the spine and posterior fossa with leptomeningeal spread enrolled in Arm 1 who died on study day 83 (55 days after the last dose of tovorafenib) when medical care was withdrawn. The reported cause of death was Grade 5 hydrocephalus. The patient had received prior treatment including vincristine and carboplatin, vinblastine, and craniospinal irradiation. Additionally, she had a history of acute hydrocephalus requiring VP shunt-related

procedures. The patient underwent tendon release surgery during cycle 9 of treatment and was treated with post-operative enoxaparin for a total of 43 days from study day 228 through study day 271. On study day 334, the patient was noted to have Grade 1 hemorrhage identified on a routine study MRI. Tovorafenib was discontinued due to the bleed. On study day 362, the patient had Grade 4 acute hydrocephalus in the setting of intratumoral bleed and a blocked shunt (Grade 3 device occlusion) was detected on imaging. Head CT showed hydrocephalus due to obstructing posterior fossa tumor. She underwent shunt revisions and on study day 371, the left ventricular drain was removed and a right EVD was inserted. The patient failed to regain consciousness despite EVD placement. Head MRI showed enlarging brainstem tumor with metastatic disease and dural thickening with no apparent increase in the size of the tumor bleed. Supportive care was withdrawn. The investigator considered the Grade 5 hydrocephalus as not related to tovorafenib and instead attributed it to high CSF protein with possible leptomeningeal spread of disease.

Reviewer Comments: As noted in correspondence with the Applicant during the review of this application, this patient had persistent challenges including unsuccessful attempts to achieve shunt drainage and adequate ventricular decompression via the VP shunt, even prior to the start of study treatment. Based on review of the narrative, the patient's death due to hydrocephalus is likely the result of VP shunt malfunction and not likely related to tovorafenib. Tovorafenib may have contributed to the development of the tumor bleed in the setting of post-operative DVT prophylaxis.

- Patient (b) (6) was a 4-year-old male patient with BRAF-altered astrocytoma involving the cerebellum with leptomeningeal spread enrolled in Arm 1 who died on study day 35 (5 days after last dose of tovorafenib). The reported cause of death was brain death. The patient was previously treated with vincristine and carboplatin, vinblastine and trametinib. Additionally, he had prior history of intralesional hemorrhage. He experienced Grade 1 seizures prior to initiation of tovorafenib and within the first two weeks of study treatment, in the context of mild cerebral edema with poor decompression by VP shunt. On study day 31, the patient was hospitalized for abdominal pain and ascites. Head CT showed concern for intratumoral hemorrhage. The patient was treated for possible sepsis and underwent aspiration of ascites which revealed hemorrhagic inflammation and reactive changes without indication of metastasis. He clinically deteriorated and underwent externalization of the shunt and had an EVD placed. Worsening mass effect of the tumor and new hemorrhages in the tumor periphery resulted in Grade 4 neurological decompensation. On study day 35, a brain perfusion scan demonstrated no flow, consistent with brain death. The investigator considered the patient's death as not related to tovorafenib.

  Reviewer Comments: The patient's clinical picture is consistent with rapid progression of disease in association with tumor bleeding. Tovorafenib may have contributed to the development of intratumoral hemorrhage; however, the patient's severe baseline disease including leptomeningeal spread also represents a risk factor for bleeding as the patient

has a history of intralesional hemorrhage that was documented on prior imaging, as confirmed during correspondence with the Applicant regarding this patient.

Of note, the FDA review team identified intratumoral hemorrhage as a common factor in these patient deaths and as a safety signal warranting description in the USPI based on the finding of hemorrhage in safety analyses of the FIREFLY-1 study population and ISS. These bleeding-related toxicities are further described in Section 8.2.4 and have been included in the USPI for tovorafenib as a warning for prescriber awareness.

Deaths in Study C28001

The FDA agrees with the Applicant's description of treatment-emergent deaths of 13 adult patients with advanced solid tumors in Study C28001. The FDA notes that only two of these deaths (both considered related to progression of the underlying disease upon review of narratives) occurred in the ISS as these patients received the RP2D of tovorafenib while the remaining 11 deaths occurred in patients receiving an alternate regimen (Q2D dosing or 800 mg once weekly) of tovorafenib. The FDA notes that the SAE of respiratory failure described in the applicant section above was likely attributable to progression of pulmonary metastatic disease, based on review of a limited available narrative which described imaging findings.

8.2.4.2. Serious Adverse Events

Applicant's Position

As of 05 June 2023, 61 patients (44.5%) in Arm 1 and Arm 2 of Study FIREFLY-1 had SAEs reported. The most commonly reported SAEs (for >5% patients) were pyrexia, seizure, and vomiting.

Serious adverse events considered by the investigator to be related to tovorafenib treatment were reported for 20 (14.6%) patients in Arm 1 and Arm 2 of Study FIREFLY-1, most commonly tumor hemorrhage (4 patients), decreased appetite (2 patients), hyponatremia (2 patients), and vomiting (2 patients). All other treatment-related SAEs were reported in 1 patient each. Both patients with hyponatremia had medical histories of hyponatremia and disorders of antidiuretic hormone regulation (diabetes insipidus and syndrome of inappropriate antidiuretic hormone secretion)

Table 44. Serious Adverse Events Reported in Three or More Patients, FIREFLY-1 (safety analysis set; arms 1 and 2)

Number of Patients, n (%)	Arm 1 (LGG) N=77 n (%)	Arm 2 (LGG) N=60 n (%)	Arm 1 + Arm 2 N=137 n (%)
Any serious TEAE	32 (41.6)	29 (48.3)	61 (44.5)
Pyrexia	4 (5.2)	3 (5.0)	7 (5.1)
Seizure	2 (2.6)	5 (8.3)	7 (5.1)
Vomiting	4 (5.2)	3 (5.0)	7 (5.1)
Hydrocephalus	5 (6.5)	1 (1.7)	6 (4.4)
Tumour haemorrhage	3 (3.9)	3 (5.0)	6 (4.4)
Headache	4 (5.2)	1 (1.7)	5 (3.6)
Hyponatraemia	2 (2.6)	3 (5.0)	5 (3.6)
Sepsis	4 (5.2)	1 (1.7)	5 (3.6)
Viral infection	3 (3.9)	2 (3.3)	5 (3.6)
Pneumonia	1 (1.3)	3 (5.0)	4 (2.9)
Decreased appetite	2 (2.6)	1 (1.7)	3 (2.2)
Hypernatraemia	0	3 (5.0)	3 (2.2)
Otitis media	2 (2.6)	1 (1.7)	3 (2.2)
Rhinovirus infection	2 (2.6)	1 (1.7)	3 (2.2)

Source: FIREFLY-1 Update CSR Table 14.3.2.6.1.1.
Medical Dictionary for Regulatory Activities (MedDRA) version 23.1
Data cutoff date for FIREFLY-1: 05 June 2023
Abbreviations: LGG = low-grade glioma; TEAE = treatment-emergent adverse event

The FDA's Assessment

The FDA noted generally minor discrepancies in the rates of certain serious adverse events (SAEs) in Arms 1 and 2 of FIREFLY-1 reported by the Applicant that are likely related to use of grouped terms. . In particular, the FDA's analysis yielded the following SAE rates that differed from the Applicant's analysis: 9% for viral infection and 4% for pneumonia.

Based upon review of SAE reports, the FDA considers most of the SAEs observed in FIREFLY-1 to be likely attributable to the underlying disease (e.g., seizure, hydrocephalus, headache, visual impairment) or to common ailments observed in pediatric patients (e.g., infections); however, intracranial hemorrhage including tumor hemorrhage was identified as a highly clinically relevant SAE that may be related to tovorafenib and was also categorized by the Applicant as an AESI. Refer to Section 8.2.5 for dedicated discussion of the FDA's analysis of this safety signal.

Additionally, SAE data for the ISS (n=172) is shown in the table below. The most commonly reported SAEs (for >4% patients) were hemorrhage, pneumonia, seizure, vomiting, pyrexia and rash. As noted previously, the USPI for tovorafenib includes a warning for hemorrhage to advise prescribers of this significant safety signal.

Table 45. Serious Adverse Events Reported in Three or More Patients in the ISS

Serious Adverse Event	Tovorafenib ISS Safety Population N=172 n (%)
Patients with serious AEs	76 (44)
Infections and Infestations	
Pneumonia (GT)	7 (4.1)
Sepsis	5 (2.9)
Viral Infection	5 (2.9)
Otitis Media	3 (1.7)
Rhinovirus Infection	3 (1.7)
Nervous System Disorders	
Seizure	7 (4.1)
Hydrocephalus	6 (3.5)
Headache (GT)	5 (2.9)
Gastrointestinal Disorders	
Vomiting (GT)	7 (4.1)
General Disorders and Administration Site Conditions	
Pyrexia (GT)	7 (4.1)
Vascular Disorders	
Hemorrhage (GT)	11 (6)
Metabolism And Nutrition Disorders	
Hyponatremia	5 (2.9)
Decreased Appetite	3 (1.7)
Hypernatremia	3 (1.7)
Blood And Lymphatic System Disorders	
Anemia	3 (1.7)
Respiratory, Thoracic and Mediastinal Disorders	
Dyspnea (GT)	5 (2.9)
Skin And Subcutaneous Tissue Disorders	
Rash (GT)	7 (4.1)

Source: ADSL (Subject-Level Analysis Dataset) - 2023-10-25, ADAE (Adverse Event Analysis Dataset) - 2023-10-25.

Group Vomiting (GT) includes PT terms VOMITING,

Group Pyrexia (GT) includes PT terms PYREXIA,

Group Hemorrhage (GT) includes PT terms TUMOUR HAEMORRHAGE, POST PROCEDURAL HAEMORRHAGE, SUBDURAL HAEMORRHAGE, GASTROINTESTINAL HAEMORRHAGE, INTRACRANIAL TUMOUR HAEMORRHAGE, UPPER GASTROINTESTINAL HAEMORRHAGE,

Group Headache (GT) includes PT terms HEADACHE,

Group Dyspnea (GT) includes PT terms DYSPNOEA,

Group Pneumonia (GT) includes PT terms PNEUMONIA, PNEUMONIA HAEMOPHILUS, LOWER RESPIRATORY TRACT INFECTION,

Group Rash (GT) includes PT terms RASH MACULO-PAPULAR, RASH PRURITIC, RASH MACULAR, ERYTHEMA MULTIFORME, RASH ERYTHEMATOUS,

Group Acute Kidney Injury (GT) includes PT terms ACUTE KIDNEY INJURY,

Group Growth Retardation (GT) includes PT terms GROWTH RETARDATION,

Group Dizziness (GT) includes PT terms DIZZINESS,

Group Abdominal Pain (GT) includes PT terms ABDOMINAL PAIN,
Group Hypotension (GT) includes PT terms HYPOTENSION,
Group Diarrhea (GT) includes PT terms ENTEROCOLITIS, DIARRHOEA,
Group Visual Impairment (GT) includes PT terms VISUAL IMPAIRMENT, DYSCHROMATOPSIA,
Group Oedema (GT) includes PT terms FACE OEDEMA,
Group Fatigue (GT) includes PT terms ASTHENIA, FATIGUE,
Group Stomatitis (GT) includes PT terms STOMATITIS,
Group Arrhythmia (GT) includes PT terms VENTRICULAR EXTRASYSTOLES,
Variables used: USUBJID, POPIRFL, TRTEMFL, AEDECOD, AETOXGRN, AEACN, AEBODSYS, AESER
Abbreviations: AE = adverse event; ISS = integrated summary of safety.

8.2.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Applicant's Position

As of 05 June 2023, discontinuations in Study FIREFLY-1 due to TEAEs were low. A total of 10/137 patients (7.3%) in Arm 1 and Arm 2 discontinued study treatment due to TEAEs. The most common adverse events resulting in discontinuation were intratumoral hemorrhage (n=3) and growth retardation (n=2). Adverse events resulting in discontinuation of 1 patient each were cerebrospinal fluid circulation disorder, fatigue, ventricular extrasystoles, bone marrow failure, shunt malfunction, hemolysis, and autoimmune hemolytic anemia. Although 9/10 patients had events that were assessed as related to tovorafenib by the investigator, review by the sponsor concluded that the events of tumor hemorrhage, cerebrospinal fluid circulation disorder and hemolysis were more consistent with underlying disease or other etiologies. Thus 4/10 patients discontinued treatment due to events considered by the sponsor to be related to treatment. (FIREFLY-1 Update CSR Listing 16.2.7.3).

The FDA's Assessment

The FDA generally agrees with the Applicant's description of drug discontinuation due to treatment-emergent adverse events (TEAEs) in FIREFLY-1 and the most common AEs leading to withdrawal of tovorafenib. The individual listing of AEs leading to drug discontinuation according to the FDA's analysis is shown in the table below.

Table 46. Drug Discontinuation Due to Adverse Effects in Arms 1 and 2 of FIREFLY-1

Adverse Effect	Tovorafenib N=137 n (%)
Study treatment - drug withdrawn - due to AEs	10 (7)
Hemorrhage (GT)	3 (2.2)
Growth Retardation (GT)	2 (1.5)
Arrhythmia (GT)	1 (0.7)
Autoimmune Hemolytic Anemia	1 (0.7)
Bone Marrow Failure	1 (0.7)
Fatigue	1 (0.7)
Cerebrospinal Fluid Circulation Disorder	1 (0.7)
Hemolysis	1 (0.7)
Shunt Malfunction	1 (0.7)

Source: ADSL (Subject-Level Analysis Dataset) - 2023-08-31, ADAE (Adverse Event Analysis Dataset) - 2023-08-31.

Group Hemorrhage (GT) includes PT terms EPISTAXIS, TUMOUR HAEMORRHAGE, GINGIVAL BLEEDING, INTRACRANIAL TUMOUR HAEMORRHAGE, SUBDURAL HAEMORRHAGE, VAGINAL HAEMORRHAGE, LOWER GASTROINTESTINAL HAEMORRHAGE, GASTROINTESTINAL HAEMORRHAGE,

Group Growth Retardation (GT) includes PT terms GROWTH RETARDATION,

Group Arrhythmia (GT) includes PT terms SINUS TACHYCARDIA, VENTRICULAR EXTRASYSTOLES, ELECTROCARDIOGRAM QT PROLONGED, SINUS BRADYCARDIA, VENTRICULAR ARRHYTHMIA,

Variables used: USUBJID, TRT01A, SAFFL, TRTEMFL, AEDECOD, AETOXGRN, AEACN, AEBODSYS, AESER

Abbreviations: AE = adverse event.

Additionally, the FDA notes that the case of drug discontinuation due to bone marrow failure occurred in a patient with optic pathway glioma who was previously treated with chemotherapy including carboplatin and vincristine, and TPCV (thioguanine, procarbazine, lomustine and vincristine). On Day 73 of study treatment, the patient exhibited myelosuppression (decreased hemoglobin and absolute neutrophil count), and on Day 141 she was diagnosed with Grade 2 bone marrow failure per bone marrow aspiration studies. She was noted to have a hypocellular bone marrow and abnormal clonal evolution that was considered by the investigator to be most likely myelodysplasia secondary to prior alkylating chemotherapy. The FDA agrees that bone marrow failure in this patient was likely related to her previous treatment for pediatric LGG and did not identify any additional cases of bone marrow failure in the safety dataset.

8.2.4.4. Dose Interruption/Reduction Due to Adverse Effects

As of 05 June 2023, 33/137 (24.1%) patients had TEAEs leading to dose reduction. All events were considered related to tovorafenib. The most commonly reported events leading to dose reduction (>2% incidence) were rash maculo-papular (4.4%), decreased appetite (2.9%), fatigue (2.2%), and anemia (2.2%). (FIREFLY-1 Update CSR Table 14.3.2.8)

Seventy-eight (56.9%) patients had a TEAE leading to dose interruption. The most commonly reported events (>5% incidence) leading to dose interruption were rash maculo-papular (10.2%), pyrexia (8.8%), vomiting (8.8%), and fatigue (5.1%). Treatment-related drug-interruptions occurred in 36.5% of patients with the most common (≥ 4%) reasons for interruption being maculopapular rash (9.5%), alanine aminotransferase increased (4.4%), vomiting (4.4%), and fatigue (4.4%). Interruptions not related to study drug were often due to holding doses during hospitalizations or while the patient was recovering from illness. The median duration of interruption was 14 days or 2 doses, and all patients with dose reductions or interruptions were able to continue therapy. (FIREFLY-1 Update CSR Table 14.3.2.9, Table 14.3.2.9.1)

The FDA's Assessment

The FDA generally agrees with the Applicant's summary of dose reduction and dose interruption due to adverse events in FIREFLY-1; however, we note that the FDA's analysis for the most commonly reported adverse events leading to dose reduction of tovorafenib varies from the Applicant's analysis in that decreased appetite and anemia occurred in approximately 1% instead of 2.2%. The FDA does not assign attribution to dose reductions and dose interruptions and considers all modifications as potentially treatment related.

8.2.4.5. Significant Adverse Events

Applicant's Position

Overall, 44.5% of patients in the target safety population of Arm 1 and Arm 2 in Study FIREFLY-1 experienced serious TEAEs (14.6% treatment-related) and 61.3% of patients required dose modification as a result of TEAEs (43% due to treatment-related events) (Table 47). However, most patients were able to continue treatment and only 7.3% had to discontinue tovorafenib because of adverse events. Rash maculo-papular was the most common reason for treatment interruption and reduction, as might be expected for a Type I BRAF inhibitor. Vomiting/decreased appetite and fatigue were also frequent reasons for treatment modification.

Three patients in Arms 1 and 2 had treatment-emergent SAEs with fatal outcomes (2 of whom died within 30 days of last dose). None were treatment related and all occurred in the setting of disease progression.

Table 47. Summary of Serious or Significant Adverse Events (safety analysis set; arms 1 and 2)

Category	Arm 1 (LGG) N=77 n (%)	Arm 2 (LGG) N=60 n (%)	Arm 1 + Arm 2 N=137 n (%)
All TEAEs	77 (100)	60 (100)	137 (100)
Grade ≥3 TEAEs	49 (63.6)	37 (61.7)	86 (62.8)
Serious TEAEs	32 (41.6)	29 (48.3)	61 (44.5)
Treatment-related serious TEAEs	12 (15.6)	8 (13.3)	20 (14.6)
Fatal (Grade 5) TEAEs[a]	1 (1.3)	1 (1.7)	2 (1.5)
TEAEs leading to dose modification	50 (64.9)	34 (56.7)	84 (61.3)
Treatment-related AEs leading to dose modification	36 (46.8)	23 (38.3)	59 (43.1)
TEAEs leading to dose reduction	21 (27.3)	12 (20.0)	33 (24.1)
Treatment-related AEs leading to dose reduction	21 (27.3)	12 (20.0)	33 (24.1)
TEAEs leading to dose interruption	45 (58.4)	33 (55.0)	78 (56.9)
Treatment-related AEs leading to dose interruption	28 (36.4)	22 (36.7)	50 (36.5)
TEAEs leading to study treatment discontinuation	7 (9.1)	3 (5.0)	10 (7.3)
Treatment-related TEAEs leading to study treatment discontinuation	6 (7.8)	3 (5.0)	9 (6.6)

Source: FIREFLY-1 Update CSR Table 14.3.2.1.1, 14.3.2.8.1, 14.3.2.9.1

[a] One patient in Arm 1 had Grade 5 brain death considered attributable to the patient's underlying disease, not related to tovorafenib. One patient in Arm 2 had Grade 5 tumour haemorrhage, considered not related to tovorafenib. A third patient in Arm 1 died 55 days after last dose of tovorafenib after Grade 4 hydrocephalus 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 TEAEs are counted only once under the TEAE with the maximum severity.

Medical Dictionary for Regulatory Activities Version 23.1; Common Terminology Criteria for Adverse Events Version 5.0.

Data Cutoff Date: 05 June 2023.

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

The FDA's Assessment

The FDA agrees with the Applicant's summary of high-grade adverse events and SAEs, as well as the presentation of TEAEs, SAEs, and AEs leading to study treatment modification (dose reduction, interruption and drug discontinuation) in Arms 1 and 2 of FIREFLY-1 as shown in Table 47. Significant treatment-emergent adverse events included Grade 3 or 4 visual impairment (n=2) in patients with optic pathway glioma and decreased visual acuity at baseline and were considered to be related to worsening of underlying disease based on review of narratives. As previously noted, the FDA does not assign attribution to dose reductions and

dose interruptions and considers all drug modifications as potentially related to tovorafenib. For discussion regarding AESIs for tovorafenib, please refer to Section 8.2.5.

8.2.4.6. Treatment Emergent Adverse Events and Adverse Reactions

Applicant's Position

As of 05 June 2023, the most frequent (>40% incidence) TEAEs reported in Arms 1 and 2 of Study FIREFLY-1 were hair color changes, fatigue, vomiting, headache, and rash maculo-papular (Table 48).

Table 48. Treatment-Emergent Adverse Events (excluding laboratory abnormalities) Reported by >20% of Patients, FIREFLY-1 (safety analysis set; arms 1 and 2)

	N=137 n (%)	
Event	**Any Grade**	**Grade ≥3**
Any TEAE	137 (100)	86 (62.8)
Hair colour changes	104 (75.9)	0
Fatigue	76 (55.5)	6 (4.4)
Vomiting	68 (49.6)	6 (4.4)
Headache	61 (44.5)	2 (1.5)
Rash maculo-papular	60 (43.8)	11 (8.0)
Pyrexia	53 (38.7)	5 (3.6)
Dry skin	49 (35.8)	0
Constipation	45 (32.8)	0
Nausea	45 (32.8)	0
Upper respiratory tract infection	43 (31.4)	2 (1.5)
Dermatitis acneiform	42 (30.7)	1 (0.7)
Epistaxis	42 (30.7)	1 (0.7)
Decreased appetite	39 (28.5)	5 (3.6)
Paronychia	36 (26.3)	2 (1.5)
Pruritus	35 (25.5)	1 (0.7)
COVID-19	34 (24.8)	0
Cough	30 (21.9)	1 (0.7)
Weight decreased	30 (21.9)	2 (1.5)
Diarrhoea	29 (21.2)	2 (1.5)

Source: FIREFLY-1 Update CSR Table 14.3.2.2.1.1 and Table 14.3.2.4.1.

Medical Dictionary for Regulatory Activities Version 23.1; Common Terminology Criteria for Adverse Events Version 5.0.

Data Cutoff Date: 05 June 2023.

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

ADR identification was based on medical review of Study FIREFLY-1 safety population. Review included assessment of AE incidence ≥20% (both individual preferred terms and cluster terms),

treatment-related as determined by investigator, severity, and patient factors associated with disease and medical history. Laboratory abnormalities were considered those that worsened by ≥2 grades from baseline occurring in ≥20% of patients, or Grade 3 or 4 occurring in ≥3% of patients. No additional AEs were identified from the pooled analysis that met sponsor definition for ADRs.

For patients in Arms 1 and 2 of Study FIREFLY-1, the most common ADRs in descending order of frequency were hair color changes, rash (cluster term), fatigue (cluster term), dermatitis acneiform, and dry skin (Table 49 and Table 50).

No patients experienced life-threatening (Grade 4) ADRs. Rash (cluster term) was the most common Grade 3 event (10%). All other events were Grade 1 or Grade 2. Rash (cluster term) was the most common ADR leading to dose interruption (16 patients; 12%) and dose reduction (7 patients; 5%). No patients in Arms 1 or 2 required treatment discontinuation due to an ADR.

Among events occurring at a frequency of < 20% of patients, photosensitivity was assessed as a clinically important event likely associated with tovorafenib. As a known class effect, precautions for exposure to sunlight and use of sun protection were incorporated into the study protocol for FIREFLY-1. Photosensitivity reaction was reported as an ADR in 19 patients (14%). One (0.7%) event was Grade 3, and none were serious.

In addition, growth effects in the form of decrease in growth velocity (PTs growth retardation, growth disorder, and growth failure) were identified as a clinically important event occurring in < 20% of patients and likely to have a causal association with tovorafenib treatment. There were no AEs indicative of defects in bone mineralization or bone integrity and in patients who had bone age performed, there was no evidence of advancement of bone age or premature closure of epiphyses.

Table 49. Adverse Drug Reactions (occurring in ≥20% of patients) Study FIREFLY-1 (arms 1 and 2)

	Tovorafenib (N=137)	
Adverse Drug Reaction	**All Grades (%)**	**Grade 3 or 4 (%)**
Gastrointestinal disorders		
Constipation	23	0
Vomiting	20	2
General disorders and administration site conditions		
Fatigue[a]	45	5
Facial edema[b]	23	0
Infections		
Paronychia	23	2
Metabolism and nutrition disorders		
Decreased appetite	20	3
Nervous system disorders		
Headache	21	0
Respiratory thoracic and mediastinal disorders		
Epistaxis	20	0
Skin and Subcutaneous Tissue disorders		
Hair color changes	76	0
Rash[c]	65	10
Dermatitis acneiform[d]	33	1
Dry skin	33	0
Pruritus	23	1

Source: FIREFLY-1 CSR Table 14.3.2.15, Table 14.3.2.15.1, Table 14.3.2.15.2, Table 14.3.2.15.3; FIREFLY-1 Update CSR Table 14.3.2.3.1, Table 14.3.2.5, Table 14.3.2.8.1, Table 14.3.2.9.1, Table 14.3.2.10.1, Table 14.3.2.11.2

Note: Frequencies of adverse drug reactions are based on all adverse events assessed by the investigator as related to tovorafenib. Grades per National Cancer Institute Common Terminology Criteria for Adverse Events V 5.0.

[a] Includes fatigue, lethargy, and malaise.

[b] Includes face edema, periorbital edema, eye swelling, swelling face, and periorbital swelling.

[c] Includes rash maculo-papular, rash erythematous, rash, rash pustular, drug eruption, rash papular, rash macular, and rash pruritic.

[d] Includes dermatitis acneiform and acne.

Data cutoff date for FIREFLY-1: 05 June 2023

The FDA's Assessment

The FDA's analysis of treatment-emergent adverse reactions by system organ class (SOC) for Arms 1 and 2 of FIREFLY-1 is shown below in Table 50 and can also be found in the USPI for tovorafenib. All 137 patients had at least one treatment-emergent adverse reaction with the most common adverse reactions (>30%) including rash, hair color changes, fatigue, viral infection, vomiting, headache, hemorrhage, pyrexia, dry skin, constipation, nausea, dermatitis acneiform and upper respiratory tract infection. Approximately 61% of patients experienced Grade 3 or 4 toxicity. No patients in Arms 1 or 2 required treatment discontinuation due to an adverse reaction. There were two Grade 5 adverse events of tumor hemorrhage and brain

death; the FDA considered the event of brain death likely to be secondary to disease progression.

Table 50. Treatment-Emergent Adverse Reactions (≥20%) in Arms 1 and 2 of FIREFLY-1

	Tovorafenib N=137	
Adverse Reaction	**All Grades (%)**	**Grade 3 or 4 (%)**
Skin and Subcutaneous Tissue Disorders		
Rash[a]	77	12
Hair color changes	76	0
Dry skin	36	0
Dermatitis acneiform	31	1
Pruritus	26	1
General Disorders		
Fatigue	55	4
Pyrexia	39	4
Edema[b]	26	0
Infections and Infestations		
Viral infection[c]	55	7
Upper respiratory tract infection	31	1.5
Paronychia	26	1.5
Gastrointestinal Disorders		
Vomiting[d]	50	4
Constipation	33	0
Nausea	33	0
Abdominal pain	28	0
Diarrhea[e]	22	1.5
Stomatitis[f]	20	0
Nervous system disorders		
Headache	45	1
Vascular Disorders		
Hemorrhage[g]	42	5*

Source: Reviewer-generated table.

[a] Includes terms erythema multiforme, eczema, rash erythematous, rash macular, rash follicular, rash pruritic, rash maculopapular, rash, rash popular, rash pustular, skin exfoliation, drug eruption, dermatitis, dermatitis bullous.

[b] Includes terms lip edema, periorbital edema, edema peripheral, localized edema, face edema, vulval edema.

[c] Includes terms viral infection, rhinovirus infection, enterovirus infection, viral upper respiratory tract infection, enterocolitis viral, oral herpes, gastroenteritis viral, influenza, influenza like illness, respiratory syncytial virus infection, enterovirus infection, coronavirus infection, COVID-19, SARS-COV-2 test positive, herpes simplex, parainfluenza virus infection, adenoviral upper respiratory infection, viraemia, adenovirus infection, conjunctivitis viral, eye infection viral, metapneumovirus infection, parvovirus infection, respiratory syncytial virus bronchiolitis, respiratory tract infection viral, viral pharyngitis, viral rhinitis, viral tonsillitis.

[d] Includes terms retching, hematemesis.

[e] Includes terms colitis, enterocolitis.

[f] Includes terms mouth ulceration, mucosal inflammation, aphthous ulcer, cheilitis.

[g] Includes terms tumor hemorrhage, gastrointestinal hemorrhage, subdural hemorrhage, epistaxis, intracranial tumor hemorrhage, upper gastrointestinal hemorrhage, lower gastrointestinal hemorrhage, vaginal hemorrhage, gingival bleeding, post procedural hemorrhage, hemoptysis, anal hemorrhage.

*Includes one Grade 5 event.

The FDA agrees that among events occurring at a frequency of <20% in patients enrolled to Arms 1 and 2 of FIREFLY-1, photosensitivity and growth defects are clinically important adverse reactions likely associated with tovorafenib.

- Photosensitivity was observed at a rate of 14% (n=19) with one Grade 3 event and no SAEs. Refer to Section 8.2.5 for additional discussion regarding the FDA's analysis of this safety signal.
- Treatment-emergent adverse events manifesting as reductions in growth velocity (PTs growth retardation, growth disorder and growth failure) were observed in 20 patients ranging in age from 3 to 10 years old in FIREFLY-1. Refer to Section 8.2.5 for further details of the FDA's analysis of this safety signal. Importantly, in patients who had bone age evaluations performed, there was no evidence of advanced bone age or premature closure of the epiphyses, and recovery in growth velocity was observed after interruption of treatment with tovorafenib.

Laboratory Findings

Applicant's Position

The most common laboratory abnormalities (>=50% with any 1 Grade worsening from baseline) were low hemoglobin, hypophosphatemia, increased CPK, increased AST, Increased LDH, and Increased ALT. Most laboratory abnormalities were Grade 1 or 2, had no clinical manifestations, and required no clinical intervention or change in study treatment.

Grade 3 Low hemoglobin, which occurred in 15% of patients, was largely associated with acute intercurrent events such as surgical procedures, acute gastrointestinal illness associated with hematochezia, hospitalizations with excessive phlebotomy, or nutritional deficiencies. Although ALT and AST elevations were common, there were no events of transaminase or bilirubin elevations that met the criteria for Hy's law. Hepatobiliary TEAEs were almost all reports of isolated laboratory abnormalities with exception of 1 patient with a report of ocular icterus with normal bilirubin, 1 patient with reports of ocular icterus and jaundice with a diagnosis of Gilbert's disease, 1 patient with cholelithiasis and a family history of gall bladder disease, and 1 patient with cholecystitis likely of viral origin.

Although preclinical studies identified the thyroid as a potential target organ, no association was established between tovorafenib treatment and abnormalities in thyroid function in human studies.

The FDA's Assessment

The FDA's evaluation of select laboratory abnormalities in Arms 1 and 2 of FIREFLY-1 is shown in Table 51 below and can also be found in the USPI for tovorafenib. The FDA's analysis differs from the Applicant's in that the FDA's analysis is based on worsening from baseline in patients

with a baseline value and at least one post-treatment value available. The most frequently occurring laboratory abnormalities (≥20%) worsening from baseline were decreased hemoglobin, decreased phosphate, increased aspartate aminotransferase (AST), increased creatinine phosphokinase (CPK), increased lactate dehydrogenase (LDH), decreased potassium, increase alanine aminotransferase (ALT), and decreased lymphocytes. The FDA agrees with the Applicant that most laboratory abnormalities were Grade 1 or 2 in severity, had no clinical manifestations, and did not require clinical intervention or modification in administration of tovorafenib.

Table 51. Select Laboratory Abnormalities (≥20%) that Worsened From Baseline in Arms 1 and 2 of FIREFLY-1

	Tovorafenib[2]	
Laboratory Abnormality[1]	**All Grades (%)**	**Grade 3 or 4 (%)**
Hematology		
Decreased hemoglobin	90	15
Decreased lymphocytes	50	2
Decreased leukocytes	31	2
Increased lymphocytes	23	0
Chemistry		
Decreased phosphate	87	25
Increased AST	83	2
Increased creatine phosphokinase	83	11
Increased LDH	73	0
Increased ALT	50	5
Decreased potassium	51	2
Increased bilirubin	22	1
Decreased albumin	24	5
Decreased sodium	20	2

Source: Reviewer-generated table.

[1] Severity as defined by National Cancer Institute CTCAE v5.0

[2] The denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available which ranged from 67 to 137 patients.

Of note, high rates of serum transaminase elevation (83% for AST and 50% for ALT) were observed, though Grade 3 or 4 elevations were uncommon (2% for AST and 5% for ALT). Additionally, all-grade and Grade 3 or 4 elevated bilirubin was observed in 22% and 1% of patients, respectively. Based on the frequency of elevated liver function tests and clinical significance for prescriber decisions and patient management, hepatotoxicity was included as a warning in the USPI for tovorafenib. Further, the FDA agrees with the Applicant that no cases of Hy's law were identified in FIREFLY-1 or the ISS. For additional discussion regarding these liver-related laboratory abnormalities, refer to Section 8.2.5.

Although rhabdomyolysis and myopathy were not observed in the ISS, the FDA **notes that increased CPK documented in Arms 1 and 2 of FIREFLY-1 is a clinically important laboratory**

abnormality for prescriber awareness as it may prompt a treating physician to evaluate for possible muscle damage in a patient being treated with tovorafenib.

Vital Signs

Applicant's Position

There were no clinically notable changes in heart rate or systolic blood pressure (high or low) in children treated with tovorafenib in the pivotal study FIREFLY-1.

Among patients treated in FIRFELY-1, reports of hypertension independent of causality were uncommon (5 patients; 3.6%) and most often associated with other risk factors. Reports of weight gain were also uncommon (10 patients; 7.3%). Patients treated with tovorafenib more commonly reported decreased appetite (39 patients; 28.5%) and weight loss (30 patients; 21.9%).

Overall, the vital sign data collected in the studies presented in this submission were sufficient to evaluate safety of tovorafenib in children 6 months and older. No safety findings associated with vital signs were considered to have an impact on benefit-risk in the proposed indication of relapsed/refractory pLGG.

The FDA's Assessment

The FDA agrees with the Applicant's general analysis of vital signs. Overall, there were no clinically significant trends in blood pressure or heart rate observed. Additionally, patients tended to decrease in weight and the majority experienced a decrease in height percentiles or Z-scores over time during treatment with tovorafenib (refer to Section 8.2.5 for additional discussion). The FDA acknowledges that changes in growth may be observed in some patients with pediatric LGG, which can be associated with growth abnormalities related to dysfunction of the hypothalamic-pituitary axis and resulting endocrinopathies.

Electrocardiograms (ECGs)

Applicant's Position

As of 22 December 2023, 2/136 patients in Arms 1 and 2 had postbaseline abnormal ECG assessments of premature ventricular complexes (PVCs) per central ECG read. One patient had corresponding AEs of ventricular extrasystoles and discontinued study treatment. The second patient had PVCs observed only intermittently and had no corresponding reported Aes. The quality of ECG tracings for this patient was notably poor, and sinus tachycardia was also observed. Ten additional patients reported abnormal ECG findings as Aes. Four patients reported sinus tachycardia, and 1 patient each reported tachycardia, sinus bradycardia, left ventricular hypertrophy, electrocardiogram T wave amplitude decreased, and electrocardiogram QT prolonged. All events were Grade 1 or 2, were not associated with any other Aes, and required no change in study treatment or clinical intervention. All but the left ventricular hypertrophy (by voltage criteria only) had resolved at the time of data cutoff.

The FDA's Assessment

The FDA agrees with the Applicant's position.

QT

Applicant's Position

As of 22 December 2023, no clinically important trends in RR, PR, QRS, or QTcF intervals over time were observed. No patients had a maximum post-baseline QTcF of > 450ms, and no patients had a QTcF change from baseline of > 60ms.
A C-QTc analysis was conducted on ECG data from FIREFLY-1. This assessment demonstrated no clinically significant mean increases in QTc interval (ie, > 20 msec) detected following treatment with tovorafenib at exposures associated with [redacted] (b) (4) 420 mg/m^2 (not to exceed 600 mg) QW.

The FDA's Assessment

The FDA agrees with the Applicant's evaluation of QT and that no clinically significant mean increases in QTc were observed in patients treated with tovorafenib at the RP2D in FIREFLY-1. Refer to the Interdisciplinary Review Team for Cardiac Safety Studies QT Study Review dated December 20, 2023 for full details.

Echocardiograms

Applicant's Position

As of 22 December 2023, there were no clinically meaningful changes in left ventricular ejection fraction (LVEF) or fractional shortening (FS) over time during treatment with tovorafenib. Median change in LVEF and FS from baseline to Cycle 13 (n = 36) was +1.5% and +0.5%, respectively. Among patients with a baseline value and at least 1 post-baseline assessment, no patients had ≥ 10% decrease from baseline in LVEF and an absolute value <50% (clinical lower limit of normal). Most decreases in LVEF or FS were isolated measurements not associated with AEs and no patients required clinical intervention or change in study treatment due to changes in LVEF or FS.

The FDA's Assessment

The FDA agrees with the Applicant's assessment of echocardiogram and that there were no clinically meaningful alterations in left ventricular LVEF findings or fractional shortening observed with tovorafenib treatment in FIREFLY-1.

Immunogenicity

Not applicable.

The FDA's Assessment

No safety issues related to immunogenicity were identified for tovorafenib.

8.2.5. Analysis of Submission-Specific Safety Issues

Applicant's Position

This section provides a summary of other important safety topics for the pediatric low-grade glioma population from study FIREFLY-1. Key safety topics include the prior identified AESIs followed by important safety topics for the pediatric population including those identified from preclinical toxicology studies.

A priori AESIs for FIREFLY-1 included Ventricular arrythmias, Rhabdomyolysis, Intra-tumoral hemorrhage, Ophthalmologic events, and Secondary primary malignancies. None of the pediatric patients receiving tovorafenib in FIREFLY-1 had events of rhabdomyolysis or secondary primary malignancies.

Two (1.5%) patients had ventricular arrythmias (both asymptomatic premature ventricular contractions Grade 1 and Grade 2). One patient discontinued tovorafenib and the second

patient continued on-treatment with full resolution of the PVCs. Neither event required clinical intervention.

Eight (5.8%) patients had events positively adjudicated as potential ophthalmologic events of interest. All events were Grade 1 or 2 and none led to changes in study treatment or discontinuation. All cases were confounded by tumor-effects on the optic pathway or potential concurrent allergic or infectious processes.

Intratumoral hemorrhage occurred in 15 (10.9%) patients and was Grade ≥3 in 6 (4.4%) patients. Three patients discontinued due to tumor hemorrhage and 1 patient had a fatal event of tumor hemorrhage in the setting of disease progression (not related to tovorafenib). Review of severe cases of tumor hemorrhage found that most patients had disease characteristics such as history of prior tumor hemorrhage, leptomeningeal or disseminated disease, aggressive tumor histology, or cystic tumor architecture that likely put them at higher risk for tumor hemorrhage events. The frequency of tumor hemorrhage was assessed by the sponsor as consistent with the natural history of heavily pre-treated pLGG and other patient risk factors.

Table 52. Positively Adjudicated Adverse Events of Special Interest (safety analysis set; arms 1 and 2)

Category	Arm 1 + Arm 2 N=137 n (%)			
Preferred Term	All Grades	Grade 3	Grade 4	Grade 5
Intra-tumoral hemorrhage	15 (10.9)	2 (1.5)	3 (2.2)	1 (0.7)
Tumour haemorrhage	12 (8.8)	2 (1.5)	2 (1.5)	1 (0.7)
Intracranial tumour haemorrhage	3 (2.2)	0	0	0
Subdural haemorrhage[1]	1 (0.7)	0	1 (0.7)	0
Ophthalmologic events	8 (5.8)	0	0	0
Vision blurred	1 (0.7)	0	0	0
Dyschromatopsia	3 (2.2)	0	0	0
Corneal oedema	1 (0.7)	0	0	0
Glaucoma	1 (0.7)	0	0	0
Photopsia	1 (0.7)	0	0	0
Episcleritis	1 (0.7)	0	0	0

Source: Applicant-provided table.

[1] Subdural haemorrhage was post-craniotomy.

8.2.5.1. Skin Toxicity: Rash and Photosensitivity

Treatment-emergent rashes occurred commonly in patients treated with tovorafenib in FIREFLY-1. General Rashes (PTs rash maculo-papular, rash erythematous, rash, rash pustular, drug eruption, rash papular, rash macular, and rash pruritic) occurred in 65% of patients (10% Grade 3) and occurred more commonly in younger patients. Acneiform rashes (PTs dermatitis acneiform and acne) occurred in 33% of patients (1% Grade 3) and occurred more commonly in

the adolescent and young adult populations. Importantly, there were no reports of severe cutaneous adverse reactions (SCARS) such as SJS, TEN, DRESS syndrome or other life threatening skin reactions.

Photosensitivity was reported in 14% of patients and was mostly mild or moderate with only 1 report of Grade 3 photosensitivity.

There were no reports of keratoacanthoma, skin malignancies, or other precursors of skin malignancies.

8.2.5.2. Palatability

Palatability for tovorafenib liquid suspension was acceptable across FIREFLY-1 patients who were treated with this formulation. Overall treatment compliance was 100% of doses with the minimum compliance being 83% of doses. No formal palatability surveys were conducted for FIREFLY-1.

The FDA's Assessment

The FDA generally agrees with the Applicant's summary of their analysis of the prespecified AESIs of ventricular arrhythmias, rhabdomyolysis, ophthalmologic events and secondary primary malignancies, and their description of the clinical management of these AEs in FIREFLY-1. The FDA's analysis of safety issues included all reported adverse events and was not limited to positively adjudicated adverse events. These AESIs were anticipated based upon the review of nonclinical data and clinical data from evaluations of tovorafenib, as well as observation of such toxicity in patients treated with other BRAF inhibitors including dabrafenib, encorafenib and vemurafenib. Due to the single-arm nature of FIREFLY-1, a baseline rate of these toxicities that may be expected to occur in the study population cannot be ascertained. Accordingly, the FDA does not provide attribution for these adverse reactions and instead considers these events to be possibly related to tovorafenib.

The FDA also reviewed the ISS (n=172) for these AESIs and notes there were no additional events of ventricular arrhythmias, rhabdomyolysis/myopathy, or secondary primary malignancies. The FDA notes that keratoacanthoma, skin malignancies or other precursors of skin malignancies were not reported in the ISS. This is a significant finding as primary malignancies, cutaneous and non-cutaneous, have been observed with Type I BRAF inhibitors including dabrafenib, encorafenib and vemurafenib and warranted inclusion of this complication of treatment as a warning in the labels of these drugs. Although additional ophthalmologic events were detected in the ISS, with the leading adverse reactions in the FDA's analysis including visual impairment (15%), blepharitis, dry eye, and photophobia (2% each), all eye disorders identified in the ISS were Grade 1 or 2 in severity.

8.2.5.3. Intracranial Hemorrhage

The FDA has provided a separate analysis of the important safety signal of intracranial hemorrhage for tovorafenib identified in 15 patients in the ISS, all of whom were treated in FIREFLY-1 and represent 11% of the pediatric LGG study population enrolled to Arms 1 and 2. Refer to the table below for the preferred term and the severity of these events. Six (40%) of these 15 patients experienced Grade 3 or higher bleeding. Note, the Grade 5 tumor hemorrhage event occurring in patient (b) (6) is described in further detail in Section 8.2.4.1. The FDA disagrees with the Applicant's conclusion that this event of hemorrhage was solely attributable to disease progression and considers this Grade 5 event as possibly related to tovorafenib.

Table 53. Overview of Intracranial Hemorrhage (n=15) in FIREFLY-1

Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Tumor hemorrhage	6	1	2	2	1
Intracranial tumor hemorrhage	1	1	-	-	-
Subdural hemorrhage	-	-	-	1	-

Source: Reviewer-generated table.

Although some patients with events of hemorrhage had potential confounding factors (e.g., concurrent use of anticoagulants, prior history of intratumoral hemorrhage, simultaneous disease progression), possible attribution to tovorafenib cannot be ruled out in any of these cases. The FDA acknowledges that a specific mechanism for how tovorafenib may increase the risk of intracranial hemorrhage and bleeding in general has not been elucidated; however, these safety signals have been observed with other BRAF inhibitors (e.g., hemorrhage has also been observed with dabrafenib and encorafenib).

The FDA agrees with the Applicant's comments that the more severe cases of tumor hemorrhage were detected in patients with certain high risk disease characteristics including leptomeningeal or disseminated disease, aggressive tumor histology, and presence of cystic tumors. It is unclear, however, whether the natural history of patients with heavily pre-treated pediatric LGG and the high risk features provide a complete explanation for the observation of intracranial hemorrhage at a rate of 11%. The medical literature cites varying rates for spontaneous intratumoral hemorrhage in pediatric LGG, some as low as 1% (Golash et al., 1998) while other publications note higher rates in the range of 8-20% as reported for a study of patients with pilocytic astrocytoma (Donofrio et al., 2020). The natural history of spontaneous tumor bleeding in patients with relapsed or refractory pediatric LGG, particularly to the extent observed in the FIREFLY-1 study population, is not well-defined. Based on a thorough assessment of the narratives for these intracranial hemorrhage events, the potential contribution of tovorafenib to these events cannot be definitively excluded.

8.2.5.4. Hemorrhage

The FDA's review of safety data from Arms 1 and 2 of FIREFLY-1 and the ISS also identified hemorrhage in general as a relevant safety signal for tovorafenib. Overall, hemorrhage occurred in 42% of patients in Arms 1 and 2 of FIREFLY-1 with Grade ≥ 3 events occurring in 5%, and in 37% of patients in the ISS with Grade ≥ 3 events occurring in 4%.

Refer to Table 54 below for the FDA's analysis of hemorrhage in the ISS and the individual preferred terms comprising the grouped term. The most frequent hemorrhagic events were epistaxis (26%; 44 out of 45 events were Grade 1 to 2), intracranial hemorrhage (9%; events ranged from Grade 1 to Grade 5 as described in the previous subsection) and gingival bleeding (5%; all events were Grade 1 to 2). Hemorrhage resulted in interruption of tovorafenib administration in 4% of patients and permanent discontinuation in 2% of patients. Serious adverse events of bleeding occurred in 5% of patients including tumor hemorrhage (n=4), subdural hemorrhage (n=1), gastrointestinal hemorrhage (n=2) and post-procedural hemorrhage (n=1). Based on the review of the patient narratives for these SAEs and considering the safety profile of other similar drugs in class (i.e., dabrafenib and encorafenib), the FDA considered these events to be possibly related to tovorafenib. Given the frequency and potentially severe nature of bleeding events observed in study patients, the USPI for tovorafenib includes a warning for hemorrhage advising prescribers to monitor for signs and symptoms of hemorrhage and to evaluate as clinically indicated.

Table 54. Overview of Hemorrhagic Events in the ISS

	Tovorafenib ISS Safety Population N=172 n (%)		
Event	**All Grades**	**Grades 3-4**	**Grade 5**
Hemorrhage (GT)	64 (37)	7 (4.1)	1 (0.6)
Epistaxis	45 (26)	1 (0.6)	0 (0.0)
Tumor Hemorrhage	12 (7)	4 (2.3)	1 (0.6)
Gingival Bleeding	9 (5)	0	0
Intracranial Tumor Hemorrhage	3 (1.7)	0	0
Vaginal Hemorrhage	2 (1.2)	0	0
Subdural Hemorrhage	1 (0.6)	1 (0.6)	0
Gastrointestinal Hemorrhage	1 (0.6)	1 (0.6)	0
Post Procedural Hemorrhage	1 (0.6)	0	0
Anal Hemorrhage	1 (0.6)	0	0
Hemoptysis	1 (0.6)	0	0
Upper Gastrointestinal Hemorrhage	1 (0.6)	0	0
Lower Gastrointestinal Hemorrhage	1 (0.6)	0	0

Source: ADSL (Subject-Level Analysis Dataset) - 2023-10-25, ADAE (Adverse Event Analysis Dataset) - 2023-10-25. Variables used: USUBJID, POPIRFL, TRTEMFL, AEDECOD, AETOXGRN, AEACN, AEBODSYS, AESER.

8.2.5.5. Skin Toxicity Including Photosensitivity

Skin toxicity is a known adverse reaction observed in patients treated with BRAF inhibitors including dabrafenib and vemurafenib, and photosensitivity has been documented in patients treated with vemurafenib. The FDA agrees with the Applicant's analysis of treatment-emergent skin toxicity in patients treated with tovorafenib in FIREFLY-1. Importantly, as highlighted by the Applicant, there were no reports of severe cutaneous adverse reactions (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, etc.) or other life-threatening skin reactions.

According to the FDA's analysis of skin toxicity in the ISS, 67% of patients developed a rash (see Table 55 below for more detail), most frequently maculopapular in nature, with Grade 3 events in 12%. Rash resulted in dose interruption in 15% of patients and dose reduction in 7% of patients.

Table 55. Overview of Rash in the ISS

	Tovorafenib ISS Safety Population N=172 n (%)	
Event	**All Grades**	**Grades 3-4**
Rash (GT)	116 (67)	20 (12)
Rash Maculo-papular	67 (39)	13 (8)
Eczema	25 (15)	2 (1.2)
Rash	19 (11)	0
Rash Erythematous	14 (8)	1 (0.6)
Rash Papular	8 (4.7)	0
Rash Pustular	8 (4.7)	0
Dermatitis	5 (2.9)	0
Drug Eruption	4 (2.3)	0
Skin Exfoliation	4 (2.3)	0
Rash Macular	4 (2.3)	1 (0.6)
Erythema Multiforme	3 (1.7)	1 (0.6)
Dermatitis Bullous	3 (1.7)	0
Rash Follicular	2 (1.2)	1 (0.6)
Rash Pruritic	1 (0.6)	1 (0.6)

Source: ADSL (Subject-Level Analysis Dataset) - 2023-10-25, ADAE (Adverse Event Analysis Dataset) - 2023-10-25. Variables used: USUBJID, POPIRFL, TRTEMFL, AEDECOD, AETOXGRN, AEACN, AEBODSYS, AESER

Dermatitis acneiform, a well-established adverse reaction observed with other drugs including anticancer drugs, was observed in 26% of the ISS including a Grade 3 reaction in a single patient (0.6%). Notably, dermatitis acneiform was not limited to the adolescent and young adult

population but was also observed in children 1 to 8 years of age in FIREFLY-1. Tovorafenib was dose reduced in 2% of patients due to dermatitis acneiform.

Photosensitivity occurred at a rate of 12% in the ISS, including a Grade 3 event in a single patient (0.6%). There were no dose reductions, interruptions, or drug discontinuations due to photosensitivity.

Skin toxicity including photosensitivity was included as a warning in the USPI for tovorafenib due to the prevalence of these adverse reactions in the ISS and their clinical significance of as they have implications for prescriber decisions and patient management. Prescribers are advised to monitor patients for skin reactions, consider dermatologic consultation and initiate supportive care as indicated, and to recommend patients to use precautionary measures against UV exposure.

8.2.5.6. Hepatotoxicity

The FDA's analysis of safety data from Arms 1 and 2 of FIREFLY-1 and the ISS was remarkable for a high frequency of elevated transaminase levels and a notable level of increased bilirubin. Refer to Table 51 in Section 8.2.4.6 for additional details regarding laboratory abnormalities observed in FIREFLY-1.

As per the FDA's analysis of liver function tests (LFTs) in the ISS, increased aspartate aminotransferase occurred in 74% of patients including Grade 3 elevation in 2%, and increased alanine aminotransferase occurred in 42% of patients with Grade 3 elevation in 4%. Increased bilirubin was observed in 23% of patients with Grade 3 elevation in 1%. Importantly, no cases of Hy's law were reported. The FDA notes that these elevated LFTs were largely isolated laboratory abnormalities that were not associated with other findings concerning for drug-induced liver injury or liver failure. Patients with transaminase elevation in FIREFLY-1 continued treatment with tovorafenib without clinical signs of liver dysfunction. One adult patient with advanced colorectal cancer and liver metastases with baseline elevated bilirubin from Study C28001 experienced a hepatic event (Grade 3 bilirubin elevation; non-SAE) that required treatment discontinuation.

Hepatotoxicity consisting of increased transaminase and bilirubin levels have been observed in patients treated with other BRAF inhibitors including encorafenib and vemurafenib. Based on the frequency of elevated LFTs observed in the ISS and the clinical implications for prescriber decisions and patient management, hepatotoxicity has been included as a warning in the UPSI for tovorafenib and prescribers are advised to monitor LFTs accordingly.

8.2.5.7. Reduction in Growth Velocity

The FDA's analysis of safety data from FIREFLY-1 identified 20 patients who were reported to have growth defects (PTs of growth retardation [n=18], growth disorder [n=1] and growth failure [n=1) that manifested as a reduction in growth velocity (i.e., reductions from baseline in Z-scores for height compared to age and sex-matched normative data), including Grade 3 events in 5% of patients. These 20 patients account ranged in age from 3 to 10 years old and account for 15% of patients 18 years of age or younger (n=136) in FIREFLY-1 which represents the population vulnerable to adverse events on growth. Tovorafenib was permanently discontinued for reduction in growth velocity in two patients.

Based on the data provided in the application, the FDA agrees with the Applicant's position that growth velocity recovered after interruption of tovorafenib treatment with improvement in Z-scores. Also, importantly, among 19 patients who had reductions in growth velocity and had a hand radiograph performed to assess bone age, advanced bone age or premature closure of the epiphyses was not observed. Additionally, there were no indications of defects in bone structure or integrity.

The FDA also acknowledges that some patients with pediatric LGG may develop an endocrinopathy due to tumor location, thereby impacting the patient's given growth trajectory and resulting in reduction in growth velocity; however, as a single-arm trial, the FDA is unable to predict the baseline rate of such growth disruption in the target patient population. As a clinically significant adverse reaction that warrants prescriber awareness, tovorafenib's effect on growth was included as a warning to the USPI.

8.2.5.8. NF1 Associated Tumors

Refer to Section 5.1 for discussion regarding the potential risk of tumor growth in patients with NF1 tumors without a documented BRAF alteration, which is based on nonclinical data. Patients with NF1 were excluded from FIREFLY-1, and only one patient with NF1 and an optic pathway glioma, without BRAF alteration, was treated on study PNOC014. This patient experienced disease progression during cycle 3. There is insufficient clinical information to ascribe the patient's disease progression to tovorafenib compared to the natural history of the patient's disease. However, given the nonclinical data and the high rate of pediatric LGG in patients with NF1, FDA agreed with the Applicant that a warning in the USPI to advise providers of a potential risk of tumor growth in this population is warranted.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Applicant's Position

Patient-reported outcome data were collected for Study FIREFLY-1 including PROMIS and PedsQoL surveys, however no formal analysis has been performed for this application.

The FDA's Assessment

Not applicable as the Applicant did not submit clinical outcome assessment data for the FDA's evaluation. Per the Applicant, although patient reported outcome assessments were administered in FIREFLY-1, interpretation of these data was limited by the high percentage of missing data.

8.2.7. Safety Analyses by Demographic Subgroups

Applicant's Position

Study FIREFLY-1 Arm 1 and Arm 2 contained 3 patients aged <2 years, 27 children 2 to <6 years, 65 patients 6 to <12 years, 27 patients 12 to <16 years and 15 patients 16 to <25 years.

Most of the commonly reported TEAEs generally occurred with comparable frequency across age groups. More commonly reported among younger patients included pyrexia (55.6%, 41.5%, 22.2% and 26.7% among patients ages 2 to < 6 years, 6 to < 12 years, 12 to < 16 years, and 16 to ≤ 25 years, respectively), vomiting (63.0%, 53.8%, 33.3%, and 26.7%, respectively), rash maculo-papular (63.0%, 46.2%, 29.6%, and 26.7%, respectively), and cough (40.7%, 20.0%, 14.8%, and 13.3%, respectively). Anaemia also showed a slight trend toward an increased frequency in younger patients. Dermatitis acneiform was more commonly reported among older patients (11.1%, 24.6%, 51.9%, and 53.3%, respectively), as were fatigue (48.1%, 55.4%, 66.7%, and 60.0%, respectively), nausea (22.2%, 32.3%, 37.0%, and 46.7%, respectively), myalgia (7.4%, 9.2%, 22.2%, and 26.7%, respectively), dizziness (7.4%, 9.2%, 18.5%, and 20.0%, respectively), and arthralgia (7.4%, 9.2%, 1.8%, and 13.3%, respectively), which may be due to reporting by the patient rather than parent/caregiver.

Safety analyses by age did not reveal any evidence of safety signals that would impact benefit-risk in younger children compared to older children and adults.

The FDA's Assessment

The FDA agrees with the Applicant's summary of safety analyses by age.

8.2.8. Specific Safety Studies/Clinical Trials

Applicant's Position

No specific safety studies were performed for this application.

The FDA's Assessment

The FDA agrees with the Applicant's position.

8.2.9. Additional Safety Explorations

8.2.9.1. Human Carcinogenicity or Tumor Development

Applicant's Position

No carcinogenicity studies were conducted for this application.

The FDA's Assessment

The FDA agrees with the Applicant's position.

8.2.9.2. Human Reproduction and Pregnancy

Applicant's Position

Based on findings from animal studies and its mechanism of action, tovorafenib may cause fetal harm when administered to a pregnant woman. Tovorafenib was embryo lethal in rats at doses approximately 0.8-fold the human exposure (b) (4) . Risk to the fetus will be communicated in the product label and use of contraception is advised during treatment with tovorafenib and (b) (4) following discontinuation has been advised.

There are no clinical safety data for pregnancy with exposure to tovorafenib. No pregnancies have occurred in female patients or study participants during treatment with tovorafenib.

It is not known whether tovorafenib is excreted in human breast milk. Because many drugs are secreted in human milk, breastfeeding is not recommended in mothers receiving tovorafenib.

Based on findings in a 3-month toxicology study in rats at doses approximately 0.4-fold the human exposure (b) (4), use of tovorafenib may impact fertility in females and males.

The FDA's Assessment

The FDA agrees with the Applicant's position. Embryofetal toxicity is included as a warning in the product label based on nonclinical findings. Given the findings in animals indicating gonadal toxicity, a relatively small cumulative safety database, and the anticipated long life expectancy in this patient population, the signal of gonadal toxicity will be further characterized through a post-marketing requirement.

8.2.9.3. Pediatrics and Assessment of Effects on Growth

Applicant's Position

Heights were collected with routine vital signs at baseline and at each cycle throughout the duration of study treatment. Patient heights were analyzed using both percentiles and height standard deviation scores (Z-scores) using CDC age and gender normative data as standards.

Overall, there was a trend observed in a decrease from baseline in height percentiles and Z-scores. The median height Z-score at baseline was -0.2 (minimum -4.53, maximum 3.85). Among patients on treatment through Cycle 13 (12 months; n=74 evaluable for height), the median change from baseline in Z-score was -0.7. Among patients on treatment through Cycle 19 (18 months; n=29 evaluable for height), the median change from baseline in Z-score was -0.9 (less than 1 standard deviation change). (FIREFLY-1 Update CSR Table 14.3.4.2, Table 14.3.4.3)

There were 18 (13.1%) patients with reported TEAEs associated with growth effects (PTs growth retardation, growth disorder, and growth failure), including 2 patients who discontinued treatment due to the event. (FIREFLY-1 Update CSR Table 14.3.2.2.1, Table 14.3.2.11.1).

Decrease in growth velocity has been observed in patients treated with tovorafenib. In patients with on-study bone age performed, there is no evidence of advancement of bone age or premature closure of growth plates. Patients from Study FIREFLY-1 and Study PNOC014 who have discontinued tovorafenib show recovery of growth velocity. In this population of children who are not expected to achieve the normative growth potential of children without CNS tumors, most height z-scores varied by less than 1 standard deviation from baseline over the course of treatment. Given observed recovery of growth velocity, the benefit-risk remains positive in the intended treatment population.

The FDA's Assessment

The FDA agrees with the Applicant's analysis of height data collected in FIREFLY-1, citing a general downward trend in height percentiles and Z-scores from baseline in patients treated with tovorafenib. Of note, based on the DCO of June 5, 2023, the FDA's analysis of safety data

identified 20 patients with treatment-emergent reduction in growth velocity. Refer to Section 8.2.5 for additional information.

Given the likely chronic use of tovorafenib in pediatric patients due to the prolonged natural history of pediatric LGG, the FDA has issued a PMR to conduct comprehensive safety analyses from clinical studies that further characterize the serious risk of long-term adverse effects of tovorafenib on growth and development, including growth plate abnormalities. The FDA considers evaluation of the safety of long-term administration to be a priority in further development of tovorafenib for this target population.

8.2.9.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Applicant's Position

There is currently limited experience with overdose of tovorafenib. Weekly doses of up to 800 mg have been administered orally to patients in Study C28001. Although higher doses and dosing frequencies are associated with a higher frequency of common reactions such as rash, no unexpected adverse effects have been reported for patients receiving higher weekly doses.

The effects of administration of doses higher than 800 mg QW have not been studied in Day One-sponsored trials.
Across all clinical studies, there were no cases of overdose with tovorafenib leading to the permanent discontinuation of investigational product and withdrawal of patients from any study.

There is no known specific antidote for overdose with tovorafenib. In the event of a suspected overdose, it is recommended that the patient be monitored and the appropriate supportive clinical care be instituted, as dictated by the patient's clinical status. Given that tovorafenib is extensively protein-bound, it is unlikely that dialysis would be effective in eliminating tovorafenib from the blood.

Tovorafenib is not known to have abuse potential.

Withdrawal and rebound effects of tovorafenib have not been formally studied. However, no rebound growth has been reported in patients who have discontinued tovorafenib for reasons other than progressive disease.

The FDA's Assessment

The FDA agrees with the Applicant's position.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Applicant's Position

Tovorafenib (DAY101) is not currently registered or approved in the US or any other part of the world.

The FDA's Assessment

The FDA agrees with the Applicant's position.

Expectations on Safety in the Postmarket Setting

Applicant's Position

The sponsor plans to more extensively measure growth and development parameters in the ongoing Phase 3 study FIREFLY-2. Current measures include Tanner staging, standardized heights and weights, (b) (4). In the current study FIREFLY-1, monitoring of heights both on and off treatment is planned in the Long Term Follow-up phase to be extended to (b) (4).

The FDA's Assessment

The FDA agrees with the Applicant's comments that further assessment of tovorafenib's effects on growth and development are being conducted in the follow-up phase of FIREFLY-1 and in the ongoing randomized, controlled study FIREFLY-2 in the front-line setting. As previously noted, the FDA has issued a PMR to conduct comprehensive safety analyses from clinical studies that further characterize the serious risk of long-term adverse effects of tovorafenib on growth and development.

8.2.11. Integrated Assessment of Safety

Applicant's Position

The most frequent (>40% incidence) TEAEs reported in Arms 1 and 2 of Study FIREFLY-1 were hair color changes, fatigue, vomiting, headache, and rash maculo-papular. The most common ADRs were hair color changes, rash (cluster term), fatigue (cluster term), dermatitis acneiform, and dry skin. Overall TEAEs, ADRs, and lab abnormalities were similar to approved Type 1 BRAF inhibitors. Lower frequencies of treatment-related pyrexia, weight increased, and diarrhea were reported compared to what has been observed in patients with pediatric low-grade glioma treated with Type I BRAF inhibitors in combination with a MEK inhibitor.

In particular, skin toxicity for tovorafenib was similar to what has been observed in other MAPK therapies and manageable with dose reductions and interruptions. Notable differences to what is observed in Type 1 BRAF inhibitor and MEK inhibitor therapies are the absence of life threatening skin toxicities and precursors to skin malignancies with tovorafenib. Tovorafenib also does not exhibit other toxicities typically associated with MAPK targeted therapies, including clinically significant cardiomyopathy, significant ophthalmologic events, hepatotoxicity, or significant immune compromise.

The AESI profile for tovorafenib in the LGG population indicates low risk of typical MEKi and Type 1 BRAFi class effects. Severe tumor hemorrhage events occurred at a rate deemed consistent with the heavily pre-treated relapsed refractory LGG population.

Patients treated with tovorafenib demonstrate a reduction in growth velocity during treatment, and patients with reported growth data following discontinuation of tovorafenib show recovery of growth velocity. In this population of children not expected to achieve the normative growth potential of children without cancer, most height z-scores varied by less than 1 standard deviation from baseline over the course of treatment. No secondary adverse effects related to bone integrity and pubertal development have been observed in children treated with tovorafenib, and the long-term effects on reversible changes in growth velocity will continue to be monitored.

With a monitorable, reversible, and manageable safety profile, tovorafenib continues to clearly demonstrate a positive benefit-risk profile for patients with pediatric low-grade glioma.

The FDA's Assessment

The most commonly reported (>30% incidence) treatment-emergent adverse reactions observed with tovorafenib treatment in Arms 1 and 2 of FIREFLY-1 were rash, hair color changes, fatigue, viral infection, vomiting, headache, hemorrhage, pyrexia, dry skin, constipation, nausea, dermatitis acneiform and upper respiratory tract infection. Although cross-trial comparisons should be interpreted with caution due to variability in study populations, the FDA agrees that in general, the treatment-emergent adverse reactions in FIREFLY-1 are similar to those observed with in-class products. The most significant safety signals for tovorafenib that are included as warnings in the USPI are hemorrhage, skin toxicity including photosensitivity, hepatotoxicity, and effect on growth. Notably, intracranial hemorrhage was observed in 11% of the patients enrolled in Arms 1 and 2, including a Grade 5 event; therefore, close monitoring of patients with pediatric LGG treated with tovorafenib is warranted.

Additionally, the most frequently occurring (>20% incidence) laboratory abnormalities that worsened from baseline in Arms 1 and 2 of FIREFLY-1 include decreased hemoglobin, decreased phosphate, increased AST, increased CPK, increased LDH, decreased potassium, decreased lymphocytes, increased bilirubin, decreased albumin, decreased leukocytes and increased ALT.

The FDA notes that although Grade 3 or 4 laboratory abnormalities were limited, the rates of decreased hemoglobin, elevated liver function tests and CPK are higher than those observed in clinical trials of approved Type I BRAF inhibitors.

The FDA also notes that although adverse reactions led to dose interruption in approximately 55% of patients and dose reduction in approximately 24% of patients in Arms 1 and 2 of FIREFLY-1, there were fewer drug discontinuations due to adverse reactions (7% of patients). Further, given the predominance of low-severity (Grade 1 or 2) adverse reactions and the prolonged duration of exposure observed in FIREFLY-1, long-term administration of tovorafenib in the intended patient population appears feasible and reasonably safe. In summary, the FDA agrees that overall, the safety profile of tovorafenib is acceptable in the context of patients with relapsed/refractory pediatric LGG, who are anticipated to be treated by pediatric oncologists or neuro-oncologists with experience managing these toxicities.

The youngest patient enrolled in FIREFLY-1 was 11 months old, while the proposed indication for tovorafenib includes patients as young as 6 months of age; therefore, safety data is not available for patients < 11 months old. The FDA determined that the inclusion of patients 6 months to 1 year of age was appropriate based on the totality of the data, including the ability to extrapolate pharmacokinetic data from patients 1 year of age to 6 months of age, in consideration of the maturation of relevant drug metabolizing enzymes and the extent of hepatic and renal clearance of the drug (refer to Section 6 for details regarding drug metabolism and clearance). The FDA also considered that all patients initiating treatment with tovorafenib will be closely monitored by their treating oncologist, and infants in particular will be closely monitored for toxicities associated with the drug.

8.3. Statistical Issues

The FDA's Assessment

Since the approval of this application is based on a single arm trial, the consideration of statistical issues in this section is only applicable to the design and conduct of the single arm trial. There were no major statistical issues in the review of this application. The FDA's efficacy assessment is based on ORR as assessed by BICR per RAPNO-LGG criteria and duration of response, with supportive evidence based on ORR per RANO-LGG criteria. Both RAPNO-LGG and RANO-LGG include a minor response category which represents 25% to less than 50% reduction in target lesion based upon T2/FLAIR measurement. Overall, there was more than 80% agreement between the RAPNO-LGG and RANO-LGG criteria for evaluation of responders. However, the single-arm design of this trial limits the interpretability of certain results (i.e., time to event endpoints such as PFS and OS), given the absence of an active control or comparison to the natural history of disease. Therefore, these reported results are considered descriptive only. For a better understanding of the long-term benefit of tovorafenib through its effect on time-to-event endpoints (i.e., PFS) and to verify the clinical benefit of tovorafenib, a

randomized, multiregional clinical trial is required as a post-marketing requirement to compare tovorafenib to physician's choice of chemotherapy.

8.4. Conclusions and Recommendations

The FDA's Assessment

Based on the evaluation of clinical data from FIREFLY-1, the review team recommends accelerated approval of tovorafenib under the provisions of 21 CFR 314.510 Subpart H for 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.

The FDA's recommendation is based on the favorable benefit-risk assessment for tovorafenib demonstrated by data from FIREFLY-1, a single-arm, open-label, multicenter clinical trial that enrolled patients 6 months to 25 years of age into three non-randomized cohorts including Arm 1 which enrolled patients with relapsed or refractory LGG with an activating BRAF alteration. Pediatric LGGs represent 30% of all childhood brain tumors with an annual incidence of approximately 1600 cases in the United States. Although affected patients generally have a favorable prognosis with a 10-year overall survival rate exceeding 90%, patients unable to undergo complete resection of tumor may experience multiple progression events associated with significant morbidity and possibly death. Patients with relapsed or refractory disease without a targetable genomic alteration are generally treated with chemotherapy, and in the course of their disease, many experience tumor and/or treatment-related complications which can include cognitive impairment, endocrinopathy, secondary malignancy, and growth abnormality. The combination of dabrafenib and trametinib is approved for the treatment of pediatric patients 1 year of age and older with LGG with a BRAF V600E mutation who require systemic therapy; however, there are currently no FDA-approved treatments for patients with pediatric LGG harboring a BRAF fusion, including the KIAA1549:BRAF fusion which is the leading oncogenic driver in these tumors.

The FDA considers ORR and DOR to be endpoints that are reasonably likely to predict clinical benefit in patients with relapsed or refractory pediatric LGG with BRAF fusions or rearrangements, or BRAF V600 mutations. In Arm 1 of FIREFLY-1, the observed response rate of 51% (95% CI: 40, 63), inclusive of complete, partial, and minor responses along with durability of response as demonstrated by a median duration of response of 13.8 months, according to blinded independent central review as per RAPNO criteria, represents a clinically meaningful treatment effect. Similar response rates were observed in patients with BRAF fusions and BRAF V600E mutations, as well as patients previously treated with a MAPK pathway inhibitor and those with multiple prior lines of systemic therapy. The FDA has previously considered only partial and complete responses in its calculation of ORR given uncertainties regarding the clinical meaningfulness of minor responses. However, in consideration of current scientific consensus regarding appropriate measurement and response criteria for pediatric LGG, and of data provided in the application supporting the clinical meaningfulness of minor responses in

pediatric LGG, the FDA determined that including minor responses in the response rate calculation was appropriate.

The FDA determined that the inclusion of patients 6 months to 1 year of age in the indication statement was appropriate based on the totality of the data, including the ability to extrapolate pharmacokinetic data from patients 1 year of age to 6 months of age, in consideration of the maturation of relevant drug metabolizing enzymes and the extent of hepatic and renal clearance of the drug. The FDA also considered that all patients initiating treatment with tovorafenib, and infants in particular, will be closely monitored for signs of toxicities associated with the drug by their treating neuro-oncologist as part of routine standard of care. Finally, the FDA considered that although few patients less than one year of age will be eligible for tovorafenib based on disease rarity and the need for prior treatment, there is a high unmet medical need in this population; in the context of a favorable benefit-risk assessment, inclusion of these patients in the indication statement is warranted.

Supportive data for tovorafenib treatment in patients with pediatric LGG with the aforementioned BRAF alterations includes clinical data from PNOC014, preclinical data demonstrating strong mechanistic rationale, and evidence of effectiveness of other drugs from a related pharmacologic class for a similar indication.

In order to obtain the information needed to verify the clinical benefit of tovorafenib in patients with pediatric LGG harboring BRAF fusion or rearrangement, or BRAF V600 mutation, a clinical trial will be conducted as a PMR to provide additional data to further characterize the overall response rate, duration of response and to assess progression-free survival. To fulfill this PMR, the Applicant intends to submit data from FIREFLY-2, an ongoing randomized controlled trial comparing tovorafenib to standard of care chemotherapy in the front-line setting of RAF-altered pediatric LGG. Based on communications during the review period, this trial is well underway (refer to Section 3).

The safety findings in FIREFLY-1 (n=137) and the integrated safety population consisting of patients treated with tovorafenib at the recommended Phase 2 dose (n=172) overlap with the known safety profile of other BRAF inhibitors. Although hemorrhage in general is a known potential complication of treatment with BRAF-inhibitors, the FDA notes that intracranial hemorrhage is a particularly relevant and potentially severe safety signal observed at a clinically significant rate in the intended patient population for tovorafenib. Other key adverse reactions included skin toxicity, hepatotoxicity, and reduction in growth velocity, which are detailed in the warnings and precautions section of the drug label. Close monitoring of patients is advised, particularly in those less than 12 months of age, and FDA has included specific label recommendations to mitigate risks, including monitoring of liver function tests prior to initiation of tovorafenib and throughout treatment. Importantly, pediatric oncologists or neuro-oncologists who are anticipated to treat patients with pediatric LGG have experience in managing such toxicities. Overall, tovorafenib has a safety profile that is acceptable in the

context of patients with relapsed or refractory pediatric LGG, a potentially life-threatening disease. Additional safety data from FIREFLY-2 will also be submitted as PMRs to further inform the safety profile of tovorafenib in the intended population, including the long-term adverse effects of tovorafenib on growth and development of pediatric patients, and the potential for gonadal toxicity.

A companion diagnostic for tovorafenib was not available at the time of approval, but is under development. Given the availability of local tests to identify BRAF alterations, the magnitude and durability of responses observed, and the unmet medical need in this population, the review team considers that tovorafenib should be approved in the absence of a companion diagnostic, with the Applicant's commitment to develop such a test. The final product labeling will reflect the lack of an approved companion diagnostic for the selection of patients for treatment with tovorafenib.

In conclusion, the submitted data meets the statutory standard for demonstration of substantial evidence of effectiveness, and the benefit-risk assessment for tovorafenib is favorable. The review team considers the ORR, which is large in magnitude, along with durability of responses observed in FIREFLY-1 to be clinically meaningful and supportive of accelerated approval for tovorafenib for the treatment patients with relapsed or refractory pediatric LGG harboring BRAF fusion or rearrangement, or BRAF V600 mutation. The ORR and DOR observed with tovorafenib are similar to other therapies available in the relapsed setting, though evolving response criteria, and limited data to establish response rates to chemotherapy for the indicated population with BRAF fusions or rearrangements, or BRAF V600E mutations, make comparisons to literature challenging. The route and frequency of administration offer a meaningful advantage over available therapy by limiting disruptions to school attendance and decreasing caregiver burden with frequent visits for infusions. Furthermore, the safety profile of tovorafenib may offer an advantage over the toxicities associated with commonly used chemotherapy agents for patients with pediatric LGG (e.g., severe myelosuppression, neurotoxicity).

Notably, tovorafenib represents the first targeted agent to be approved for the treatment of patients with pediatric LGG harboring BRAF fusions, including the KIAA1549:BRAF fusion that is the leading oncogenic driver of pediatric LGG. Based on the favorable benefit-risk assessment for this population with a serious, life-threatening disease, accelerated approval is recommended for the following indication:

> *OJEMDA is a kinase inhibitor indicated for the treatment of patients 6 months of age and older with relapsed or refractory pediatric LGG harboring a BRAF fusion or rearrangement, or BRAF V600 mutation.*

The recommended dosage regimen for tovorafenib is 380 mg/m^2 orally once weekly with a maximum recommended dosage of 600 mg once weekly.

X	X
Primary Statistical Reviewer Somak Chatterjee	Statistical Team Leader Xiaoxue Li
X	X
Primary Clinical Reviewer Sonia Singh	Clinical Team Leader Diana Bradford

9. Advisory Committee Meeting and Other External Consultations

The FDA's Assessment

The FDA did not refer this application to an advisory committee as no significant efficacy or safety issues were identified during the review that required external input for the proposed indication.

10. Pediatrics

Applicant's Position

All relevant information from the pediatric population is presented in prior sections.

The FDA's Assessment

The FDA agrees with the Applicant's position. Since this application was not intended for the treatment of an adult cancer, it was not subject to the amended provisions of PREA under FDARA to conduct a molecularly targeted investigation in pediatric patients and would be subject to the original provisions of PREA. Because the Applicant obtained orphan designation for tovorafenib for the treatment of malignant glioma, the application is exempt from PREA requirements.

11. Labeling Recommendations

Applicant's Position

Not applicable.

The FDA's Assessment

The format, language, and content of the proposed labeling was evaluated and revised for consistency with 21 Code of Federal Regulations (CFR), labeling guidances and current labeling practices of the Office of Oncologic Diseases. The table below summarizes key labeling changes. The FDA has provided a selected summary of the proposed labeling in the middle column; refer to original product labeling for complete details.

Table 56. Summary of Significant Labeling Changes (high level changes and not direct quotations)

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
1 INDICATIONS AND USAGE	TRADENAME is indicated for the treatment of pediatric patients 6 months of age and older with relapsed or refractory pediatric low-grade glioma (LGG) harboring a BRAF fusion or rearrangement, or BRAF V600 mutation.	Minor editorial revisions. Inclusion of accelerated approval text.
2 DOSAGE AND ADMINISTRATION		Editorial revisions for clarity and brevity.
2.1 Patient Selection		Inclusion of cross reference to new warning, section 5.5 NF1 Associated Tumors
2.3 Administration		Added instructions for missed or vomited dose.
2.4 Dosage Modifications for Adverse Reactions		Table 5 Recommended Dosage Modifications for Adverse Reactions revisions for consistency with the study protocol. Addition of dosage modifications for the management of hepatotoxicity.
3. DOSAGE FORMS AND STRENGTHS	Tablets Powder for Oral Suspension	Revised to "oral suspension" for consistency with FDA SPL Dosage Forms

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
5 WARNINGS AND PRECAUTIONS	Proposed warnings for (b) (4), effect on growth, and embryofetal toxicity.	New subsection added: 5.1 Hemorrhage due to the incidence and severity of hemorrhagic events observed in FIREFLY-1 (b) (4) New subsection added: 5.3 Hepatotoxicity due to the incidence and severity of ALT and AST elevations. Applicant added new warning subsection 5.5 NF1 Associated Tumors. The duration of contraception for female patients of reproductive potential was informed both by potential drug-drug interactions and the potential for embryofetal toxicity.
6 ADVERSE REACTIONS		Editorial revisions for clarity, brevity and consistency with oncology labeling practices.
7 DRUG INTERACTIONS		Section 7 information put into tabular format for ease of prescriber reference.
8 USE IN SPECIFIC POPULATIONS		Editorial revisions for consistency with PLLR guidance. New subsection 8.7 Renal Impairment added.
(b) (4)		(b) (4)
12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action		(b) (4) deleted for consistency with 21 CFR 201.57(c)(2)(iv), Indications or uses must not be implied or suggested in other sections of the labeling if not included in INDICATIONS AND USAGE.

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
12.2 Pharmacodynamics		Inclusion of *Exposure-Response Relationships* specific to height-for-age risk.
12.3 Pharmacokinetics		Minor editorial revisions.
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility		Inclusion of additional details in male and female reproductive organs from non-clinical studies.
13.2 Animal Toxicology and/or Pharmacology		New subsection added to describe neurofibromatosis Type 1-loss of function (NF1-LOF) suggesting activation of the MAP kinase pathway. This data supports the new warning, 5.5.
14 CLINICAL STUDIES		Editorial revisions for clarity and brevity. Deleted (b) (4) as this information is not included in labeling.
16 HOW SUPPLIED/STORAGE AND HANDLING		Minor revisions for clarity.
17 PATIENT COUNSELING INFORMATION		Minor revisions for clarity and consistency with section 5.

Source: Reviewer-generated table.

12. Risk Evaluation and Mitigation Strategies

The FDA's Assessment

The risks of tovorafenib are considered acceptable in the indication patient population due to the serious and potentially life-threatening nature of relapsed or refractory pediatric LGG. The safe use of tovorafenib can be adequately implemented in the post-market setting through product labeling. No additional risk management strategies are recommended.

13. Postmarketing Requirements and Commitment

The FDA's Assessment

The following PMR and PMCs will be included in the approval letters. Refer to the approval letters for requested milestones.

Clinical PMRs

- Conduct a multiregional, randomized clinical trial comparing tovorafenib to physician's choice of chemotherapy in pediatric patients with low grade glioma with RAF fusions or rearrangements, or V600 mutations, intended to verify and describe the clinical benefit of tovorafenib through assessment of overall response rate as a primary endpoint and progression-free survival and duration of response, as determined by blinded independent central review, as key secondary endpoints.
- Conduct comprehensive safety analyses from clinical studies that further characterize the known serious risk of long-term adverse effects of tovorafenib on growth and development, including but not limited to growth plate abnormalities, in a sufficient number of pediatric patients. Monitor patients for growth and development using age-appropriate screening tools. Include evaluations of growth as measured by height, weight, height velocity and height standard deviation scores, age at adrenarche if applicable, age at menarche if applicable (females) and Tanner stage. Monitor patients until discontinuation of study treatment or a minimum of 5 years from start of treatment, whichever occurs first.
    - Conduct comprehensive safety analyses from clinical studies that further characterize the potential serious risk of gonadal toxicity in a sufficient number of adolescent and young adult patients treated with tovorafenib. Include evaluations of pubertal development and hormonal evaluation in appropriate patients. Monitor patients for a minimum of 5 years from start of treatment. Post-treatment follow-up assessments including reproductive hormone measurements should be obtained at regularly scheduled intervals and after treatment cessation to assess time to gonadal function recovery. Include, in the interim report, a comprehensive safety analysis characterizing gonadal toxicity after all patients have been monitored for a minimum of 12 months from the start of study treatment.

Clinical Pharmacology PMRs

- Conduct a clinical pharmacokinetic trial of tovorafenib with a strong CYP2C8 inhibitor to evaluate the potential increased drug toxicity and provide dosage recommendations for tovorafenib when used concomitantly with strong and moderate CYP2C8 inhibitors. Design and conduct the trial in accordance with the FDA Guidance for Industry titled "Clinical Drug

Interaction Studies —Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."

- Conduct a clinical pharmacokinetic trial of multi-dose tovorafenib on sensitive substrates of CYP3A4, CYP2C8, CYP1A2, CYP2B6, CYP2C9, and CYP2C19 to evaluate the potential for increased toxicity or reduced efficacy of these substrate drugs and provide appropriate drug interaction management strategies for tovorafenib when used concomitantly with these substrates. Design and conduct the trial in accordance with the FDA Guidance for Industry titled "Clinical Drug Interaction Studies —Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."
- Conduct a clinical pharmacokinetic trial of multi-dose tovorafenib on substrates of BCRP to evaluate the potential for increased toxicity of BCRP substrates and provide appropriate drug interaction management strategies for tovorafenib when used concomitantly with BCRP substrates. Design and conduct the trial in accordance with the FDA Guidance for Industry titled "Clinical Drug Interaction Studies —Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."

Nonclinical PMRs

- Conduct a carcinogenicity study in mice to evaluate the potential serious risk of carcinogenicity.
- Conduct a carcinogenicity study in rats to evaluate the potential serious risk of carcinogenicity. Submit a carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

Clinical PMCs

- Conduct an appropriate analytical and clinical validation study to support the development of an in vitro diagnostic device using clinical trial data that demonstrates that the device is essential to the safe and effective use of tovorafenib for 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.
- Complete the FIREFLY-1 trial, including your planned additional follow-up for the 137 patients with relapsed or refractory low-grade glioma harboring a BRAF alteration enrolled to Arms 1 and 2 of FIREFLY-1 and treated with tovorafenib, to further characterize the overall response rate and duration of response as per Response Assessment in Pediatric Neuro-oncology (RAPNO) criteria including assessment by an independent review committee (IRC) for patients enrolled to Arm 1.

Clinical Pharmacology PMC

- Conduct a clinical pharmacokinetic trial with a strong or moderate CYP2C8 inducer with tovorafenib to evaluate the effect of a strong or moderate CYP2C8 inducer on decreasing the systemic exposure of tovorafenib and provide dosage recommendations for tovorafenib when used concomitantly with CYP2C8 inducers. Design and conduct the trial in accordance with the FDA Guidance for Industry titled "Clinical Drug Interaction Studies —Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."

CMC PMC

(b) (4)

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:		Is a PMC/PMR needed? No
□	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	_X_ Yes __ No
□	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	__ Yes _X_ No
□	Other considerations (e.g.: PK/PD), if applicable:	__ Yes _X_ No

14. Division Director (DHOT) (NME ONLY)

X _____

15. Division Director (OCP)

X _____

16. Division Director (OB)

X _____

17. Division Director (Clinical)

X

18. Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X _____

19. Appendices

19.1. References

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19.2. Financial Disclosure

Covered Clinical Study: FIREFLY-1/DAY101-001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 270		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 1		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

The FDA's Assessment

In accordance with the Code of Federal Regulations (CFR) Title 21, Part 54, the Applicant submitted a financial disclosure certification document (FDA Form 3454) in Module 1.3.4. The document includes a list of all principal investigators, including sub-investigators, who participated in FIREFLY-1. According to the Applicant, there was one sub-investigator, (b) (6)

(b) (6) . The Applicant confirmed that this sub-investigator did not remain an investigator of FIREFLY-1 or any other Day One-sponsored clinical study after joining Day One. The Applicant also states that despite exercising due diligence, they were unable to obtain some of the financial information described in 21 CFR 52.4(a)(2) needed for (b) (6), a sub-investigator at the (b) (6); however, the Applicant was able to confirm that (b) (6) does not have a financial arrangement with cumulative monetary value of $25,000 or more.

In Module 1.3.4, the Applicant highlights the following to support the claim that any potential bias that may result from the concerns mentioned above was minimized:

- Routine internal site audits to ensure data integrity and to detect investigator bias
- Study design elements including multiple investigators, multiple study sites, and objective tests to evaluate the safety and efficacy of tovorafenib
- Study monitoring
- An endpoint assessed by a blinded observer other than the investigator
- Predetermined statistical analysis plan

In the FDA's assessment, the steps taken to minimize any potential investigator bias of the clinical trial results were sufficient.

Additionally, the Applicant confirmed that there were no investigators who participated or are participating in FIREFLY-1 who have financial interest or arrangements as described in 21 CFR 52.4(a)(3). As such, FDA Form 3455 was not submitted.

19.3. Nonclinical Pharmacology/Toxicology

19.3.1. Toxicology Tables

Table 57. Repeat-Dose Toxicity: Pivotal Studies

Report Title: A 4-Week Oral Gavage Toxicity Study in Sprague-Dawley Rats with a 4-Week Recovery				**Test Article:** Tovorafenib			
Species/Strain: Rat/Sprague-Dawley		**Duration of Dosing:** 4 weeks (Q2D; 15 doses)			**Study No.:** P024-09-05		
Initial Age: 9 to 10 weeks		**Duration of Postdose:** 4 weeks			**Location in CTD:** 4.2.3.2		
Date of First Dose: 15 Sep 2009		**Method of Administration:** Oral gavage					
Special Features: hormone analysis		**Vehicle/Formulation:** 1% NaCMC and 0.2% Tween 80 in reverse-osmosis deionized water			**GLP Compliance:** Yes		
No Observed Adverse Effect Level: 150 mg/kg Q2D (males); not determined (females)							
Dose (mg/kg)	**0 (Control)**		**50**		**150**		**500**	
Number of Animals (main/recovery/TK)	**M: 10/5/3**	**F: 10/5/3**	**M: 10/5/12**	**F: 10/5/12**	**M: 10/5/12**	**F: 10/5/12**	**M: 10/5/12**	**F: 10/5/12**
Toxicokinetics:								
Day 29								
C_{max} (ng/mL)	NA	NA	2660	4680	2810	6230	3700	8700
AUC_{0-48} (ng.h/mL)	NA	NA	31,700	83,500	50,800	107,000	84,400	184,000
Noteworthy Findings:								
Died or Sacrificed Moribund	0	0	0	1[a]	0	1[a]	0	0
Body Weight	-	-	-	-	-	-	-	-
Food Consumption	-	-	-	-	-	-	-	-
Clinical Observations	-	-	-	-	-	-	-	-
Ophthalmoscopy	-	-	-	-	-	-	-	-
Hematology[b]								
Hemoglobin (g/dL)	D15: - D31: -	D15: 15.29 D31: 14.01	D15: - D31: -	D15: - 12⁑ D31: - 14⁑	D15: - D31: -	D15: - 14⁑ D31: - 16⁑	D15: - D31: -	D15: - 24⁑ D31: - 28⁑
Hematocrit (%)	D15: - D31: -	D15: 44.08 D31: 43.13	D15: - D31: -	D15: - 13* D31: - 15*	D15: - D31: -	D15: - 15* D31: - 17*	D15: - D31: -	D15: - 25* D31: - 29*
Red blood cell count (10^6/µL)	D15: - D31: 8.294	D15: 8.012 D31: 7.945	D15: - D31: -	D15: - 11⁑ D31: - 18*	D15: - D31: -5	D15: - 14⁑ D31: - 21*	D15: - D31: -10⁑	D15: - 23⁑ D31: - 37*
Reticulocytes (10^9/L)	D15: - D31: 160.29	D15: 163.10 D31: 140.05	D15: - D31: -	D15: - 51* D31: - 32⁑	D15: - D31: -25*	D15: - 61* D31: - 26⁑	D15: - D31: -30*	D15: - 59* D31: +22

Report Title: A 4-Week Oral Gavage Toxicity Study in Sprague-Dawley Rats with a 4-Week Recovery			**Test Article:** Tovorafenib				
Species/Strain: Rat/Sprague-Dawley		**Duration of Dosing:** 4 weeks (Q2D; 15 doses)			**Study No.:** P024-09-05		
Initial Age: 9 to 10 weeks		**Duration of Postdose:** 4 weeks			**Location in CTD:** 4.2.3.2		
Date of First Dose: 15 Sep 2009		**Method of Administration:** Oral gavage					
Special Features: hormone analysis		**Vehicle/Formulation:** 1% NaCMC and 0.2% Tween 80 in reverse-osmosis deionized water			**GLP Compliance:** Yes		
No Observed Adverse Effect Level: 150 mg/kg Q2D (males); not determined (females)							
Dose (mg/kg)	**0 (Control)**		**50**		**150**		**500**	
Number of Animals (main/recovery/TK)	**M: 10/5/3**	**F: 10/5/3**	**M: 10/5/12**	**F: 10/5/12**	**M: 10/5/12**	**F: 10/5/12**	**M: 10/5/12**	**F: 10/5/12**
White blood cell count (10^3/µL)	D15: - D31: -	D15: 11.16 D31: 9.13	D15: - D31: -	D15: -15 D31: -14	D15: - D31: -	D15: - 34⁑ D31: - 26⁑	D15: - D31: -	D15: - 31⁑ D31: - 21⁑
Lymphocytes (10^3/µL)	D15: - D31: -	D15: 9.682 D31:7.593	D15: - D31: -	D15: -15 D31: -12	D15: - D31: -	D15: - 37⁑ D31: - 30⁑	D15: - D31: -	D15: - 45⁑ D31: - 36⁑
Coagulation	-	-	-	-	-	-	-	-
Serum Chemistry[b]								
Alanine aminotransferase (U/L)	-	31.7	-	+70⁑	-	+129⁑	-	+132⁑
Aspartate aminotransferase (U/L)	-	102.3	-	+42⁑	-	+77⁑	-	+99⁑
Total bilirubin (mg/dL)	0.11	0.14	-	+50⁑	+55⁑	+107⁑	+127⁑	+150⁑
Phosphorus (mg/dL)	8.91	8.25	-	-25*	-12⁑	-23*	-11⁑	-27*
Globulin (g/dL)	2.95	3.23	-	+20⁑	-	+28⁑	+17⁑	+33⁑
Albumin:Globulin ratio	-	1.07	-	-	-	-	-	-16⁑
Urinalysis								
Leukocytes[c]								
Negative	-	10/10	-	4/10	-	1/10	-	0/10
Trace	-	0/10	-	4/10	-	6/10	-	1/10
Small	-	0/10	-	2/10	-	1/10	-	4/10
Moderate	-	0/10	-	0/10	-	2/10	-	5/10
Thyroid hormones[b]								
Triiodothyronine	-	83	-	+25*	-	+34*	-	+36*
Thyroxine	2.64	1.96	+21	+33	+29*	+68*	+59*	+58*
Organ Weights								
Ovary (number examined)	NA	10	NA	9	NA	9	NA	10
Absolute weight (g)	NA	0.0886	NA	0.1100	NA	0.1331	NA	0.1376
Relative to brain weight	NA	0.0455	NA	0.0581	NA	0.0688	NA	0.0705
Relative to body weight	NA	0.0357	NA	0.0451	NA	0.0562	NA	0.0567

Report Title: A 4-Week Oral Gavage Toxicity Study in Sprague-Dawley Rats with a 4-Week Recovery				**Test Article:** Tovorafenib			
Species/Strain: Rat/Sprague-Dawley		**Duration of Dosing:** 4 weeks (Q2D; 15 doses)			**Study No.:** P024-09-05		
Initial Age: 9 to 10 weeks		**Duration of Postdose:** 4 weeks			**Location in CTD:** 4.2.3.2		
Date of First Dose: 15 Sep 2009		**Method of Administration:** Oral gavage					
Special Features: hormone analysis		**Vehicle/Formulation:** 1% NaCMC and 0.2% Tween 80 in reverse-osmosis deionized water			**GLP Compliance:** Yes		
No Observed Adverse Effect Level: 150 mg/kg Q2D (males); not determined (females)							
Dose (mg/kg)	**0 (Control)**		**50**		**150**		**500**	
Number of Animals (main/recovery/TK)	**M: 10/5/3**	**F: 10/5/3**	**M: 10/5/12**	**F: 10/5/12**	**M: 10/5/12**	**F: 10/5/12**	**M: 10/5/12**	**F: 10/5/12**
Gross Pathology (number examined)	NA	10	NA	9	NA	9	NA	10
Ovary: focus, dark, bilateral	NA	0	NA	7	NA	9	NA	9
Ovary: enlarged	NA	0	NA	2	NA	5	NA	8
Histopathology (number examined)	10	10	10	9	10	9	10	10
Bone, femur								
Bone marrow precursor depletion, focal	0	0	0	3	0	2	1	6
Minimal	0	0	0	3	0	1	0	3
Mild	0	0	0	0	0	1	0	3
Marked	0	0	0	0	0	0	1	0
Hemorrhage, medullary cavity	0	0	0	0	0	0	1	0
Moderate	0	0	0	0	0	0	1	0
Bone, tibia								
Bone marrow precursor depletion, focal	0	0	0	1	0	2	2	5
Minimal	0	0	0	1	0	0	1	1
Mild	0	0	0	0	0	1	0	4
Moderate	0	0	0	0	0	1	1	0
Hemorrhage, medullary cavity	0	0	0	0	0	0	1	0
Mild	0	0	0	0	0	0	1	0
Bone, sternum								
Bone marrow precursor depletion, focal	0	0	0	0	0	0	0	2[d]
Minimal	0	0	0	0	0	0	0	1
Mild	0	0	0	0	0	0	0	1
Ovary	NA		NA		NA		NA	
Corpus hemorrhagicum, increased size/number	NA	0	NA	9	NA	9	NA	9
Minimal	NA	0	NA	5	NA	1	NA	1
Mild	NA	0	NA	3	NA	5	NA	4
Moderate	NA	0	NA	1	NA	3	NA	4

Report Title: A 4-Week Oral Gavage Toxicity Study in Sprague-Dawley Rats with a 4-Week Recovery			**Test Article:** Tovorafenib					
Species/Strain: Rat/Sprague-Dawley		**Duration of Dosing:** 4 weeks (Q2D; 15 doses)			**Study No.:** P024-09-05			
Initial Age: 9 to 10 weeks		**Duration of Postdose:** 4 weeks			**Location in CTD:** 4.2.3.2			
Date of First Dose: 15 Sep 2009		**Method of Administration:** Oral gavage						
Special Features: hormone analysis		**Vehicle/Formulation:** 1% NaCMC and 0.2% Tween 80 in reverse-osmosis deionized water			**GLP Compliance:** Yes			
No Observed Adverse Effect Level: 150 mg/kg Q2D (males); not determined (females)								
Dose (mg/kg)	**0 (Control)**		**50**		**150**		**500**	
Number of Animals (main/recovery/TK)	**M: 10/5/3**	**F: 10/5/3**	**M: 10/5/12**	**F: 10/5/12**	**M: 10/5/12**	**F: 10/5/12**	**M: 10/5/12**	**F: 10/5/12**
Hemorrhage	NA	0	NA	0	NA	1	NA	4
Minimal	NA	0	NA	0	NA	0	NA	2
Mild	NA	0	NA	0	NA	1	NA	1
Marked	NA	0	NA	0	NA	0	NA	1
Vagina	NA		NA		NA		NA	
Increased thickness, mucosa	NA	0	NA	1	NA	4	NA	10
Minimal	NA	0	NA	1	NA	4	NA	1
Mild	NA	0	NA	0	NA	0	NA	4
Moderate	NA	0	NA	0	NA	0	NA	5
Intestine, duodenum								
Crypt microabscess	0	0	0	0	0	0	1	5
Minimal	0	0	0	0	0	0	1	5
Intestine, ileum								
Crypt ectasia, multifocal	0	0	NE	NE	NE	NE	0	2
Minimal	0	0	NE	NE	NE	NE	0	2
Postdose Evaluation: Number Evaluated	5	5	5	5	5	5	5	5
Organ Weights								
Ovary (number examined)	NA	5	NA	5	NA	5	NA	5
Absolute weight (g)	NA	0.0900	NA	0.0952	NA	0.1062	NA	0.1136
Relative to brain weight	NA	0.0452	NA	0.0496	NA	0.0546	NA	0.0594
Relative to body weight	NA	0.0314	NA	0.0346	NA	0.0402	NA	0.0424
Gross Pathology (number examined)	NA	5	NA	5	NA	5	NA	5
Ovary: focus, dark, bilateral	NA	0	NA	1	NA	1	NA	2

Report Title: A 4-Week Oral Gavage Toxicity Study in Sprague-Dawley Rats with a 4-Week Recovery							**Test Article:** Tovorafenib	
Species/Strain: Rat/Sprague-Dawley		**Duration of Dosing:** 4 weeks (Q2D; 15 doses)					**Study No.:** P024-09-05	
Initial Age: 9 to 10 weeks		**Duration of Postdose:** 4 weeks					**Location in CTD:** 4.2.3.2	
Date of First Dose: 15 Sep 2009		**Method of Administration:** Oral gavage						
Special Features: hormone analysis		**Vehicle/Formulation:** 1% NaCMC and 0.2% Tween 80 in reverse-osmosis deionized water					**GLP Compliance:** Yes	
No Observed Adverse Effect Level: 150 mg/kg Q2D (males); not determined (females)								
Dose (mg/kg)	**0 (Control)**		**50**		**150**		**500**	
Number of Animals (main/recovery/TK)	**M: 10/5/3**	**F: 10/5/3**	**M: 10/5/12**	**F: 10/5/12**	**M: 10/5/12**	**F: 10/5/12**	**M: 10/5/12**	**F: 10/5/12**
Histopathology								
Ovary (number examined)	NA	5	NA	5	NA	5	NA	5
Corpus hemorrhagicum, increased size/number	NA	0	NA	1	NA	1	NA	3
Minimal	NA	0	NA	1	NA	1	NA	3

- No noteworthy findings

* P = < .05 ANOVA with Dunnett's t-Test compared with control group of same gender

⁑ P = < .05 Kruskal-Wallis with Dunn's procedure compared with control group of same gender

[a] Gavage error as evidenced by esophageal perforation; not tovorafenib-related

[b] For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

[c] Incidence expressed as the number of animals that had the result listed over the total number of animals in the group.

[d] Number examined was 8 for this group for this tissue.

Abbreviations: D# = Day number; NA = not applicable; NaCMC = sodium carboxymethylcellulose; NE = not evaluated; Q2D = every 2 days

Report Title: A 3-Month Repeat-Dose Oral Gavage Toxicity and Toxicokinetic Study of MLN2480 in Sprague-Dawley Rats with a 2-Week Recovery							**Test Article:** Tovorafenib	
Species/Strain: Rat/Sprague-Dawley		**Duration of Dosing:** 3 months (Q2D)					**Study No.:** 20060186	
Initial Age: 8 to 10 weeks		**Duration of Postdose:** 2 weeks					**Location in CTD:** 4.2.3.2	
Date of First Dose: 06 Nov 2014		**Method of Administration:** Oral gavage						
Special Features: none		**Vehicle/Formulation:** 1% NaCMC and 0.2% Tween® 80 in reverse-osmosis deionized water					**GLP Compliance:** Yes	
No Observed Adverse Effect Level: 50 mg/kg Q2D (males); not determined (females)								
Dose (mg/kg)	**0 (Control)**		**50**		**150**		**500**	
Number of Animals (main/recovery)	**M: 10/5**	**F: 10/5**	**M: 10/5**	**F: 10/5**	**M: 10/5**	**F: 10/5**	**M: 10/5**	**F: 10/5**
Toxicokinetics [a]:								
Day 91								
C_{max} (ng/mL)	NA	NA	891	1840	1390	2270	1970	3860

Report Title: A 3-Month Repeat-Dose Oral Gavage Toxicity and Toxicokinetic Study of MLN2480 in Sprague-Dawley Rats with a 2-Week Recovery					**Test Article:** Tovorafenib			
Species/Strain: Rat/Sprague-Dawley		**Duration of Dosing:** 3 months (Q2D)			**Study No.:** 20060186			
Initial Age: 8 to 10 weeks		**Duration of Postdose:** 2 weeks			**Location in CTD:** 4.2.3.2			
Date of First Dose: 06 Nov 2014		**Method of Administration:** Oral gavage						
Special Features: none		**Vehicle/Formulation:** 1% NaCMC and 0.2% Tween® 80 in reverse-osmosis deionized water			**GLP Compliance:** Yes			
No Observed Adverse Effect Level: 50 mg/kg Q2D (males); not determined (females)								
Dose (mg/kg)	**0 (Control)**		**50**		**150**		**500**	
Number of Animals (main/recovery)	**M: 10/5**	**F: 10/5**	**M: 10/5**	**F: 10/5**	**M: 10/5**	**F: 10/5**	**M: 10/5**	**F: 10/5**
AUC_{0-24} (ng.h/mL)	NA	NA	18,400	29,700	24,000	48,000	41,000	73,600
Noteworthy Findings:								
Died or Sacrificed Moribund	0	0	0	0	0	1[b]	0	0
Body Weight (g)								
Day 53	563.80	-	519.80*	-	522.93*	-	519.60*	-
Day 88	621.87	-	564.87*	-	579.87*	-	558.27*	-
Food Consumption (g/animal/day)								
Day 1 to Day 8	28.07	-	26.33*	-	26.14*	-	24.87*	-
Day 43 to Day 50	30.20	-	27.07*	-	29.15*	-	26.80*	-
Day 85 to Day 91	28.80	-	27.20	-	29.10	-	26.20*	-
Clinical Observations	-	-	-	-	-	-	-	-
Ophthalmoscopy	-	-	-	-	-	-	-	-
Hematology[c]								
Hemoglobin (g/dL)	14.64	14.38	-4	-16*	-8*	-25*	-8*	-35*
Hematocrit (%)	44.58	42.46	-4	-17*	-9*	-25*	-8*	-35*
Red blood cell count (10^6/µL)	8.362	7.804	-10*	-23*	-15*	-34*	-19*	-45*
Reticulocytes (10^9/L)	204.26	189.87	-16	-23	-7	-23	-12	-25
Mean cell volume (fL)	53.32	54.43	+7	+7*	+9*	+13*	+14*	+20*
Mean cell hemoglobin (pg)	17.56	18.44	+7	+8*	+9*	+13*	+13*	+20*
Red cell distribution width (%)	13.49	12.18	-	+7*	+4	+13*	+4	+23*
Platelets (10^3/µL)	-	890.4	-	-	-	+17	-	+18
Monocytes (10^3/µL)	0.26	0.17	-42*	-59*	-46*	-65*	-58*	-59*
Neutrophils (10^3/µL)	1.61	-	-34	-	-27	-	-27	-
Coagulation	-	-	-	-	-	-	-	-
Serum Chemistry[c]								
Creatine kinase (U/L)	354.44	322.90	+40	+37%	+51%	+37%	+50%	+51%

Report Title: A 3-Month Repeat-Dose Oral Gavage Toxicity and Toxicokinetic Study of MLN2480 in Sprague-Dawley Rats with a 2-Week Recovery				**Test Article:** Tovorafenib			
Species/Strain: Rat/Sprague-Dawley		**Duration of Dosing:** 3 months (Q2D)				**Study No.:** 20060186	
Initial Age: 8 to 10 weeks		**Duration of Postdose:** 2 weeks				**Location in CTD:** 4.2.3.2	
Date of First Dose: 06 Nov 2014		**Method of Administration:** Oral gavage					
Special Features: none		**Vehicle/Formulation:** 1% NaCMC and 0.2% Tween® 80 in reverse-osmosis deionized water				**GLP Compliance:** Yes	
No Observed Adverse Effect Level: 50 mg/kg Q2D (males); not determined (females)							
Dose (mg/kg)	**0 (Control)**		**50**		**150**		**500**	
Number of Animals (main/recovery)	**M: 10/5**	**F: 10/5**	**M: 10/5**	**F: 10/5**	**M: 10/5**	**F: 10/5**	**M: 10/5**	**F: 10/5**
Alanine aminotransferase (U/L)	43.9	42.5	-	+56	+68*	-	+26	+142*
Aspartate aminotransferase (U/L)	105.2	141.5	+19%	+59	+88*	+22	+68*	+104*
Total bilirubin (mg/dL)	0.11	0.13	+45	+69*	+82*	+69*	+91*	+115*
Alkaline phosphatase (U/L)	61.8	32.4	-21	-30*	-7	-16*	-11	-30*
Phosphorus (mg/dL)	6.91	6.50	-9	-16*	-11*	-19*	-16*	-32*
Cholesterol (mg/dL	51.0	-	+25	-	+42	-	+52*	-
Total protein (g/dL)	5.83	6.44	+5	+14*	+10*	+19*	+14*	+25*
Albumin (g/dL)	2.97	3.52	+5	+12*	+7	+10*	+9*	+14*
Globulin (g/dL)	2.87	2.92	+5	+17*	+13*	+30*	+18*	+37*
Urinalysis	-	-	-	-	-	-	-	-
Organ Weights[c]								
Epididymis (number examined)	10	NA	10	NA	10	NA	10	NA
Absolute weight (g)	1.6361	NA	-	NA	-15*	NA	-20.0*	NA
Relative to body weight	0.2755	NA	-	NA	-10	NA	-12.1	NA
Relative to brain weight	73.2182	NA	-	NA	-12	NA	-18.4*	NA
Heart (number examined)	10	10	10	10	10	9	10	10
Absolute weight (g)	-	1.0852	-	-	-	-	-	+34.9*
Relative to body weight	-	0.3418	-	-	-	-	-	+44.1*
Relative to brain weight	-	52.5789	-	-	-	-	-	+39.9*
Thymus (number examined)	10	10	10	10	10	9	10	10
Absolute weight (g)	0.3167	-	-31.9*	-	-21.9	-	-38.5*	-
Relative to body weight	0.0533	-	-24.6	-	-18.0	-	-32.3	-

Report Title: A 3-Month Repeat-Dose Oral Gavage Toxicity and Toxicokinetic Study of MLN2480 in Sprague-Dawley Rats with a 2-Week Recovery					**Test Article:** Tovorafenib			
Species/Strain: Rat/Sprague-Dawley		**Duration of Dosing:** 3 months (Q2D)			**Study No.:** 20060186			
Initial Age: 8 to 10 weeks		**Duration of Postdose:** 2 weeks			**Location in CTD:** 4.2.3.2			
Date of First Dose: 06 Nov 2014		**Method of Administration:** Oral gavage						
Special Features: none		**Vehicle/Formulation:** 1% NaCMC and 0.2% Tween® 80 in reverse-osmosis deionized water			**GLP Compliance:** Yes			
No Observed Adverse Effect Level: 50 mg/kg Q2D (males); not determined (females)								
Dose (mg/kg)	**0 (Control)**		**50**		**150**		**500**	
Number of Animals (main/recovery)	**M: 10/5**	**F: 10/5**	**M: 10/5**	**F: 10/5**	**M: 10/5**	**F: 10/5**	**M: 10/5**	**F: 10/5**
Relative to brain weight	14.3573	-	-30.8	-	-20.4	-	-38.3*	-
Testes (number examined)	10	NA	10	NA	10	NA	10	NA
Absolute weight (g)	3.6597	NA	-	NA	-19.5*	NA	-23.3*	NA
Relative to body weight	0.6172	NA	-	NA	-14.7*	NA	-15.9*	NA
Relative to brain weight	163.9092	NA	-	NA	-16.8*	NA	-22.0*	NA
Spleen (number examined)	10	10	10	10	10	9	10	10
Absolute weight (g)	0.8518	-	-	-	-	-	-25.6*	-
Relative to body weight	0.1431	-	-	-	-	-	-18.2*	-
Relative to brain weight	38.1309	-	-	-	-	-	-24.4*	-
Gross Pathology	-	-	-	-	-	-	-	-
Histopathology (number examined)	10	10	10	10	10	9	10	10
Epididymis		NA		NA		NA		NA
Reduced sperm, luminal	0	NA	2	NA	0	NA	4	NA
Minimal	0	NA	1	NA	0	NA	3	NA
Mild	0	NA	1	NA	0	NA	1	NA
Testis		NA		NA		NA		NA
Degeneration/atrophy, tubule	0	NA	2	NA	2	NA	5	NA
Minimal	0	NA	1	NA	2	NA	3	NA
Mild	0	NA	1	NA	0	NA	2	NA
Ovary	NA		NA		NA		NA	
Cystic follicles	NA	0	NA	8	NA	8	NA	10
Minimal	NA	0	NA	6	NA	2	NA	1
Mild	NA	0	NA	2	NA	3	NA	6
Moderate	NA	0	NA	0	NA	3	NA	2
Marked	NA	0	NA	0	NA	0	NA	1

Report Title: A 3-Month Repeat-Dose Oral Gavage Toxicity and Toxicokinetic Study of MLN2480 in Sprague-Dawley Rats with a 2-Week Recovery							**Test Article:** Tovorafenib	
Species/Strain: Rat/Sprague-Dawley		**Duration of Dosing:** 3 months (Q2D)					**Study No.:** 20060186	
Initial Age: 8 to 10 weeks		**Duration of Postdose:** 2 weeks					**Location in CTD:** 4.2.3.2	
Date of First Dose: 06 Nov 2014		**Method of Administration:** Oral gavage						
Special Features: none		**Vehicle/Formulation:** 1% NaCMC and 0.2% Tween® 80 in reverse-osmosis deionized water					**GLP Compliance:** Yes	
No Observed Adverse Effect Level: 50 mg/kg Q2D (males); not determined (females)								
Dose (mg/kg)	**0 (Control)**		**50**		**150**		**500**	
Number of Animals (main/recovery)	**M: 10/5**	**F: 10/5**	**M: 10/5**	**F: 10/5**	**M: 10/5**	**F: 10/5**	**M: 10/5**	**F: 10/5**
Decreased corpora lutea	NA	0	NA	3	NA	4	NA	9
Minimal	NA	0	NA	0	NA	0	NA	1
Mild	NA	0	NA	3	NA	0	NA	1
Moderate	NA	0	NA	0	NA	1	NA	3
Marked	NA	0	NA	0	NA	1	NA	0
Severe	NA	0	NA	0	NA	2	NA	4
Hyperplasia, interstitial cells	NA	0	NA	4	NA	4	NA	10
Minimal	NA	0	NA	4	NA	0	NA	3
Mild	NA	0	NA	0	NA	3	NA	4
Moderate	NA	0	NA	0	NA	1	NA	3
Thyroid gland								
Atrophy, follicular cell	0	3	1	3	4	7	9	7
Minimal	0	2	1	0	1	0	1	2
Mild	0	1	0	2	3	3	3	1
Moderate	0	0	0	1	0	4	5	4
Thymus								
Depletion, lymphoid	2	1	2	1	0	1	7	5
Minimal	2	1	2	1	0	0	6	5
Mild	0	0	0	0	0	1	1	0
Mesenteric lymph node								
Depletion, lymphoid	1	2	1	1	1	3	7	5
Minimal	1	2	1	1	0	2	4	2
Mild	0	0	0	0	1	1	3	3
Spleen								
Increased hematopoiesis	0	1	1	0	2	3	1	2
Minimal	0	1	1	0	2	3	1	2
Postdose Evaluation: Number Evaluated	5	5	5	5	5	5	5	5
Body Weight (g)								
Day 92	626.20	-	563.00	-	570.80	-	547.20	-

Report Title: A 3-Month Repeat-Dose Oral Gavage Toxicity and Toxicokinetic Study of MLN2480 in Sprague-Dawley Rats with a 2-Week Recovery							**Test Article:** Tovorafenib	
Species/Strain: Rat/Sprague-Dawley		**Duration of Dosing:** 3 months (Q2D)					**Study No.:** 20060186	
Initial Age: 8 to 10 weeks		**Duration of Postdose:** 2 weeks					**Location in CTD:** 4.2.3.2	
Date of First Dose: 06 Nov 2014		**Method of Administration:** Oral gavage						
Special Features: none		**Vehicle/Formulation:** 1% NaCMC and 0.2% Tween® 80 in reverse-osmosis deionized water					**GLP Compliance:** Yes	
No Observed Adverse Effect Level: 50 mg/kg Q2D (males); not determined (females)								
Dose (mg/kg)	**0 (Control)**		**50**		**150**		**500**	
Number of Animals (main/recovery)	**M: 10/5**	**F: 10/5**	**M: 10/5**	**F: 10/5**	**M: 10/5**	**F: 10/5**	**M: 10/5**	**F: 10/5**
Day 102	640.20	-	573.40	-	580.40	-	542.20	-
Food Consumption (g/animal/day)								
Day 92 to Day 99	30.40	-	27.20	-	30.40	-	24.80	-
Hematology[c]								
Hemoglobin (g/dL)	-	14.54	-	-	-	-	-	-5
Hematocrit (%)	-	43.54	-	-	-	-	-	-3
Red blood cell count (10^6/µL)	-	7.958	-	-	-	-	-	-16
Mean cell volume (fL)	52.10	54.72	+5	+8*	+9*	+10*	+14*	+15*
Mean cell hemoglobin (pg)	17.02	18.28	+5	+7*	+9*	+9*	+14*	+14*
Red cell distribution width (%)	-	11.66	-	-	-	+5	-	+7
Serum Chemistry[c]								
Total bilirubin (mg/dL)	-	0.13	-	-	-	-	-	+54
Alkaline phosphatase	62.2	31.4	-14	-18	-9	-	-23	-43*
Total protein (g/dL)	-	6.66	-	+6	-	+4	-	+6
Globulin (g/dL)	-	3.08	-	+6	-	+3	-	+12*
Organ Weights[c] (number weighed)	5	5	5	5	5	5	5	5
Testes		NA		NA		NA		NA
Absolute weight (g)	3.6546	NA	-	NA	-8.8	NA	-18.3*	NA
Relative to body weight	0.6031	NA	-	NA	-0.5	NA	-3.8	NA
Relative to brain weight	157.5522	NA	-	NA	-2.6	NA	-11.9*	NA
Heart								
Absolute weight (g)	-	1.0160	-	-	-	+13.6	-	+10.9
Relative to body weight	-	0.3374	-	-	-	+17.1*	-	+20.4*
Relative to brain weight	-	50.6292	-	-	-	+18.6*	-	+11.1
Histopathology (number examined)	5	5	5	5	5	5	5	5

Report Title: A 3-Month Repeat-Dose Oral Gavage Toxicity and Toxicokinetic Study of MLN2480 in Sprague-Dawley Rats with a 2-Week Recovery					**Test Article:** Tovorafenib			
Species/Strain: Rat/Sprague-Dawley		**Duration of Dosing:** 3 months (Q2D)			**Study No.:** 20060186			
Initial Age: 8 to 10 weeks		**Duration of Postdose:** 2 weeks			**Location in CTD:** 4.2.3.2			
Date of First Dose: 06 Nov 2014		**Method of Administration:** Oral gavage						
Special Features: none		**Vehicle/Formulation:** 1% NaCMC and 0.2% Tween® 80 in reverse-osmosis deionized water			**GLP Compliance:** Yes			
No Observed Adverse Effect Level: 50 mg/kg Q2D (males); not determined (females)								
Dose (mg/kg)	**0 (Control)**		**50**		**150**		**500**	
Number of Animals (main/recovery)	**M: 10/5**	**F: 10/5**	**M: 10/5**	**F: 10/5**	**M: 10/5**	**F: 10/5**	**M: 10/5**	**F: 10/5**
Ovary	NA		NA		NA		NA	
Cystic follicles	NA	0	NA	4	NA	3	NA	4
Minimal	NA	0	NA	1	NA	1	NA	1
Mild	NA	0	NA	3	NA	1	NA	2
Moderate	NA	0	NA	0	NA	1	NA	1
Decreased corpora lutea	NA	0	NA	3	NA	2	NA	3
Mild	NA	0	NA	1	NA	0	NA	0
Moderate	NA	0	NA	0	NA	1	NA	0
Marked	NA	0	NA	2	NA	1	NA	2
Severe	NA	0	NA	0	NA	0	NA	1
Hyperplasia, interstitial cells	NA	1	NA	4	NA	2	NA	3
Minimal	NA	0	NA	1	NA	0	NA	0
Mild	NA	1	NA	3	NA	2	NA	3
Thyroid gland								
Atrophy, follicular cell	0	1	1	2	1	3	4	4
Minimal	0	0	1	1	0	1	0	1
Mild	0	1	0	1	0	1	2	1
Moderate	0	0	0	0	1	1	2	2
Mesenteric lymph node								
Depletion, lymphoid	1	0	2	2	1	0	5	4
Minimal	1	0	1	1	0	0	1	3
Mild	0	0	1	1	1	0	4	1

Report Title: A 3-Month Repeat-Dose Oral Gavage Toxicity and Toxicokinetic Study of MLN2480 in Sprague-Dawley Rats with a 2-Week Recovery				**Test Article:** Tovorafenib			
Species/Strain: Rat/Sprague-Dawley		**Duration of Dosing:** 3 months (Q2D)		**Study No.:** 20060186			
Initial Age: 8 to 10 weeks		**Duration of Postdose:** 2 weeks		**Location in CTD:** 4.2.3.2			
Date of First Dose: 06 Nov 2014		**Method of Administration:** Oral gavage					
Special Features: none		**Vehicle/Formulation:** 1% NaCMC and 0.2% Tween® 80 in reverse-osmosis deionized water		**GLP Compliance:** Yes			
No Observed Adverse Effect Level: 50 mg/kg Q2D (males); not determined (females)							
Dose (mg/kg)	**0 (Control)**		**50**		**150**		**500**	
Number of Animals (main/recovery)	**M: 10/5**	**F: 10/5**	**M: 10/5**	**F: 10/5**	**M: 10/5**	**F: 10/5**	**M: 10/5**	**F: 10/5**
Spleen								
Increased hematopoiesis	1	1	2	3	3	3	4	3
Minimal	1	1	2	3	3	3	2	1
Mild	0	0	0	0	0	0	2	2

- No noteworthy findings

* P = < .05 ANOVA with Dunnett's/Dunn's t-Test compared with control group of same gender

[a] TK samples were collected from main study rats and a composite TK profile was generated.

[b] Gavage error; not tovorafenib-related

[c] For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

Abbreviations: NA = not applicable; NaCMC = sodium carboxymethylcellulose; Q2D = every 2 days

Report Title: A 4-Week Oral Gavage Toxicity Study in Cynomolgus Monkeys with a 4-Week Recovery				**Test Article:** Tovorafenib			
Species/Strain: Monkey/Cynomolgus		**Duration of Dosing:** 4 weeks (Q2D; 15 doses)		**Study No.:** P024-09-03			
Initial Age: Not reported		**Duration of Postdose:** 4 weeks		**Location in CTD:** 4.2.3.2			
Date of First Dose: 16 Jun 2009		**Method of Administration:** Oral gavage					
Special Features: hormone analysis		**Vehicle/Formulation:** 100% PEG400		**GLP Compliance:** Yes			
No Observed Adverse Effect Level: 3 mg/kg Q2D							
Dose (mg/kg)	**0 (Control)**		**3**		**10**		**30**	
Number of Animals (main/recovery)	**M: 4/2**	**F: 4/2**	**M: 4/2**	**F: 4/2**	**M: 4/2**	**F: 4/2**	**M: 4/2**	**F: 4/2**
Toxicokinetics:								
Day 29								
C_{max} (ng/mL)	NA	NA	1150	1330	3910	3820	8490	6480
AUC_{0-48} (ng.h/mL)	NA	NA	19,100	24,600	94,400	84,400	222,000	179,000
Noteworthy Findings:								
Died or Sacrificed Moribund	0	0	0	0	0	0	0	0
Body Weight (kg)[a]								
Day 30	-	2.70	-	-	-	-	-	2.33*

Report Title: A 4-Week Oral Gavage Toxicity Study in Cynomolgus Monkeys with a 4-Week Recovery				**Test Article:** Tovorafenib			
Species/Strain: Monkey/Cynomolgus		**Duration of Dosing:** 4 weeks (Q2D; 15 doses)		**Study No.:** P024-09-03			
Initial Age: Not reported		**Duration of Postdose:** 4 weeks		**Location in CTD:** 4.2.3.2			
Date of First Dose: 16 Jun 2009		**Method of Administration:** Oral gavage					
Special Features: hormone analysis		**Vehicle/Formulation:** 100% PEG400		**GLP Compliance:** Yes			
No Observed Adverse Effect Level: 3 mg/kg Q2D							
Dose (mg/kg)	**0 (Control)**		**3**		**10**		**30**	
Number of Animals (main/recovery)	**M: 4/2**	**F: 4/2**	**M: 4/2**	**F: 4/2**	**M: 4/2**	**F: 4/2**	**M: 4/2**	**F: 4/2**
Food Consumption								
Low, Day 1 through Day 30[b]	2/180	22/180	-	-	-	-	27/180	53/180
Clinical Observations[c]								
Dehydration	0	0	0	0	0	0	1	2
Hunched posture	0	0	0	0	0	0	1	0
Soft feces	6	3	5	6	6	6	6	6
Ophthalmoscopy	-	-	-	-	-	-	-	-
Electrocardiography	-	-	-	-	-	-	-	-
Hematology[d]								
Hemoglobin (g/dL)	D15: 12.68 D31: 11.75	D15: 12.23 D31: 11.65	D15: -6 D31: -12*	D15: -7 D31: -7	D15: -9* D31: -15*	D15: -5 D31: -15*	D15: -15* D31: -29*	D15: -11 D31: -32*
Hematocrit (%)	D15: 41.13 D31: 37.95	D15: 40.40 D31: 37.27	D15: -7* D31: -13**	D15: -10* D31: -9*	D15: -10* D31: -13**	D15: -6 D31: -15*	D15: -16* D31: -28**	D15: -11* D31: -30*
Red blood cell count (10^6/µL)	D15: 5.237 D31: 4.935	D15: 5.060 D31: 4.835	D15: -9* D31: -15*	D15: -8 D31: -9	D15: -7 D31: -13*	D15: -4 D31: -15*	D15: -13* D31: -26*	D15: -10* D31: -29*
Reticulocytes (10^9/L)	D15: 111.18 D31: 53.47	D15: 95.63 D31: 33.83	D15: -13 D31: +13	D15: -23 D31: +39	D15: -54** D31: +26	D15: -56* D31: +25	D15: -82** D31: +40	D15: -78* D31: +164
White blood cell count (10^3/µL)	D15: 11.40 D31: 12.98	D15: 12.00 D31: 13.00	D15: +11 D31: -	D15: -9 D31: -27	D15: - D31: +20	D15: +11 D31: +28	D15: +37 D31: +41	D15: +53** D31: +35
Neutrophils (10^3/µL)	D15: 4.580 D31: 7.035	D15: 6.008 D31: 7.682	D15: +16 D31: -	D15: -18 D31: -41	D15: +19 D31: +24	D15: -22 D31: +25	D15: +34 D31: +82*	D15: +45 D31: +73
Coagulation	-	-	-	-	-	-	-	-
Serum Chemistry[d]								

Report Title: A 4-Week Oral Gavage Toxicity Study in Cynomolgus Monkeys with a 4-Week Recovery				**Test Article:** Tovorafenib			
Species/Strain: Monkey/Cynomolgus		**Duration of Dosing:** 4 weeks (Q2D; 15 doses)		**Study No.:** P024-09-03			
Initial Age: Not reported		**Duration of Postdose:** 4 weeks		**Location in CTD:** 4.2.3.2			
Date of First Dose: 16 Jun 2009		**Method of Administration:** Oral gavage					
Special Features: hormone analysis		**Vehicle/Formulation:** 100% PEG400		**GLP Compliance:** Yes			
No Observed Adverse Effect Level: 3 mg/kg Q2D							
Dose (mg/kg)	**0 (Control)**		**3**		**10**		**30**	
Number of Animals (main/recovery)	**M: 4/2**	**F: 4/2**	**M: 4/2**	**F: 4/2**	**M: 4/2**	**F: 4/2**	**M: 4/2**	**F: 4/2**
Alanine aminotransferase (U/L)	52.7	36.0	-	-	+31	+73	+72*	+148*
Aspartate aminotransferase (U/L)	48.5	41.0	-	-	+81⁑	+98	+223⁑	+269⁑
Albumin (g/dL)	3.98	3.85	-	-	-7	-5	-15	-21⁑
Globulin (g/dL)	2.83	2.98	-	-	-	-	+21*	+25
Albumin:Globulin ratio	1.40	1.30	-	-	-9	-8	-27⁑	-33
Calcium (mg/dL)	9.80	9.93	-	-	-4	-11*	-9	-15*
Phosphorus (mg/dL)	5.80	4.25	-	-	-34*	-5	-49*	-30⁑
Urinalysis	-	-	-	-	-	-	-	-
Thyroid hormones[d]								
Parathyroid hormone (pg/mL)	74.83	57.02	+46	-	+77	+237*	+104	+337*
Organ Weights[d]								
Thymus								
Absolute weight (g)	3.620	1.715	-	-	-	-	-57*	-80
Relative to brain weight	0.053	0.028	-	-	-	-	-57*	-82
Relative to body weight	0.133	0.065	-	-	-	-	-55	-77
Gross Pathology (number examined)	4	4	4	4	4	4	4	4
Thymus, small	0	1[e]	0	1[e]	0	0	3	4
Histopathology (number examined)	4	4	4	4	4	4	4	4
Bone marrow sternum								
Hypocellularity, erythroid	0	0	0	0	0	1	2	2
Mild	0	0	0	0	0	0	1	0
Moderate	0	0	0	0	0	1	1	2
Hypercellularity, myeloid	0	0	0	0	2	2	4	4
Minimal	0	0	0	0	0	1	0	0
Mild	0	0	0	0	2	0	3	1
Moderate	0	0	0	0	0	1	1	3
Intestine, cecum								

Report Title: A 4-Week Oral Gavage Toxicity Study in Cynomolgus Monkeys with a 4-Week Recovery				**Test Article:** Tovorafenib			
Species/Strain: Monkey/Cynomolgus		**Duration of Dosing:** 4 weeks (Q2D; 15 doses)		**Study No.:** P024-09-03			
Initial Age: Not reported		**Duration of Postdose:** 4 weeks		**Location in CTD:** 4.2.3.2			
Date of First Dose: 16 Jun 2009		**Method of Administration:** Oral gavage					
Special Features: hormone analysis		**Vehicle/Formulation:** 100% PEG400		**GLP Compliance:** Yes			
No Observed Adverse Effect Level: 3 mg/kg Q2D							
Dose (mg/kg)	**0 (Control)**		**3**		**10**		**30**	
Number of Animals (main/recovery)	**M: 4/2**	**F: 4/2**	**M: 4/2**	**F: 4/2**	**M: 4/2**	**F: 4/2**	**M: 4/2**	**F: 4/2**
Infiltration, mixed cell, lamina propria	0	0	0	0	0	0	0	1
Minimal	0	0	0	0	0	0	0	1
Accumulation, neutrophilic, lumen	0	0	0	0	0	0	0	1
Minimal	0	0	0	0	0	0	0	1
Intestine, colon								
Infiltration, mixed cell, lamina propria	0	0	0	0	0	0	1	1
Minimal	0	0	0	0	0	0	1	1
Intestine, rectum								
Infiltration, mixed cell, lamina propria	0	0	0	0	0	0	1	3
Minimal	0	0	0	0	0	0	1	2
Mild	0	0	0	0	0	0	0	1
Ulceration	0	0	0	0	0	0	1	0
Mild	0	0	0	0	0	0	1	0
Thymus								
Decreased thickness (cortex and medulla)	0	0	0	0	0	0	4	4
Moderate	0	0	0	0	0	0	3	2
Marked	0	0	0	0	0	0	1	2
Thyroid gland								
Decreased size and numbers, follicles	0	0	0	0	0	0	2	3
Minimal	0	0	0	0	0	0	1	0
Mild	0	0	0	0	0	0	1	3
Fibrosis	0	0	0	0	0	0	2	3
Minimal	0	0	0	0	0	0	2	3
Hemorrhage	0	0	0	0	0	0	1	0
Minimal	0	0	0	0	0	0	1	0
Postdose Evaluation: Number Evaluated								
Clinical Observations[c]								

Report Title: A 4-Week Oral Gavage Toxicity Study in Cynomolgus Monkeys with a 4-Week Recovery				**Test Article:** Tovorafenib			
Species/Strain: Monkey/Cynomolgus		**Duration of Dosing:** 4 weeks (Q2D; 15 doses)		**Study No.:** P024-09-03			
Initial Age: Not reported		**Duration of Postdose:** 4 weeks		**Location in CTD:** 4.2.3.2			
Date of First Dose: 16 Jun 2009		**Method of Administration:** Oral gavage					
Special Features: hormone analysis		**Vehicle/Formulation:** 100% PEG400		**GLP Compliance:** Yes			
No Observed Adverse Effect Level: 3 mg/kg Q2D							
Dose (mg/kg)	**0 (Control)**		**3**		**10**		**30**	
Number of Animals (main/recovery)	**M: 4/2**	**F: 4/2**	**M: 4/2**	**F: 4/2**	**M: 4/2**	**F: 4/2**	**M: 4/2**	**F: 4/2**
Soft feces	0	0	0	1	0	1	2	1
Organ Weights[f]								
Thymus								
Absolute weight (g)	-	1.715/5.010	-	-	-	-	-	0.85
Relative to brain weight	-	0.028/0.075	-	-	-	-	-	0.01
Relative to body weight	-	0.065/0.160	-	-	-	-	-	0.03
Gross Pathology (number examined)	2	2	2	2	2	2	2	2
Thymus, small	0	0	0	0	0	0	1[e]	1
Histopathology (number examined)	2	2	2	2	2	2	2	2
Thymus								
Decreased thickness (cortex and medulla)	0	0	0	0	0	0	0	1
Mild	0	0	0	0	0	0	0	1

- No noteworthy findings

* P = < .05 ANOVA with Dunnett's t-Test compared with control group of same gender

⁑ P = < .05 Kruskal-Wallis with Dunn's procedure compared with control group of same gender

[a] Decreased body weight versus pretest observed in 6 (1 males and 5 females) of 12 animals at 30 mg/kg Q2D on Day 28

[b] Expressed as number of observations of low (<50% ration consumed) food consumption/total number of scheduled observations for the group.

[c] Total number of affected animals with the sign on 1 or more occasions during the applicable phase (dosing or recovery) of the study

[d] For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

[e] Consistent with normal physiologic involution and not considered tovorafenib-related

[f] 1 of 2 recovery females had decreased absolute and relative thymus weights at Day 59 compared with mean control females on Days 31 and 59. Actual mean values for controls are reported (Day 31/Day59) as is the actual value for the 1 affected female in the high-dose group (animal number 4105).

Abbreviations: NA = not applicable; Q2D = every 2 days.

Report Title: A 3-Month Repeat-Dose Oral Gavage Toxicity and Toxicokinetic Study of MLN2480 in Cynomolgus Monkeys with a 2-Week Recovery				**Test Article:** Tovorafenib			
Species/Strain: Monkey/Cynomolgus		**Duration of Dosing:** 3 months (Q2D)		**Study No.:** 20060187			
Initial Age: 2.3 to 3.9 years		**Duration of Postdose:** 4 weeks		**Location in CTD:** 4.2.3.2			
Date of First Dose: 06 Nov 2014		**Method of Administration:** Oral gavage					
		Vehicle/Formulation: 100% PEG400		**GLP Compliance:** Yes			
Special Features: thyroid hormone analysis (thyroxine and thyroid stimulating hormone)							
No Observed Adverse Effect Level: 3 mg/kg Q2D (males); not determined (females)							
Dose (mg/kg)	**0 (Control)**		**3**		**10**		**20**	
Number of Animals (main/recovery)	**M: 4/2**	**F: 4/2**	**M: 4/0**	**F: 4/0**	**M: 4/2**	**F: 4/2**	**M: 4/2**	**F: 4/2**
Toxicokinetics:								
Day 65								
C_{max} (ng/mL)	NA	NA	1120	1090	3300	2530	5590	4700
AUC_{0-24} (ng.h/mL)	NA	NA	19,100	16,900	57,800	43,400	107,000	86,500
Day 91								
C_{max} (ng/mL)	NA	NA	1210	1150	ND	ND	ND	ND
AUC_{0-24} (ng.h/mL)	NA	NA	19,100	16,400	ND	ND	ND	ND
Noteworthy Findings:								
Died or Sacrificed Moribund	0	0	0	0	0	3[1]	0	2[a]
Body Weight (kg)[b]								
Day 2	-	2.60	-	2.43	-	2.53	-	2.48
Day 58	-	2.82	-	2.45*	-	2.43*	-	2.62*
Day 90[c]	-	2.75	-	2.40*	-	2.65	-	2.60
Food Consumption	-	-	-	-	-	-[d]	-	-[d]
Clinical Observations								
Sacrificed moribund females	lethargy, weak appearance, hunched posture, liquid feces, dehydration							
Pale skin[e]	0	0	0	2	4	3	6	4
Ophthalmoscopy	-	-	-	-	-	-	-	-
Electrocardiography	-	-	-	-	-	-	-	-
Hematology[f]								
Hemoglobin (g/dL)	13.03	12.87	-13	-17*	-26*	-29*	-29*	-37*
Hematocrit (%)	40.22	39.87	-15*	-19*	-26*	-28*	-26*	-34*
Red blood cell count (10^6/µL)	5.410	5.255	-14	-16	-28*	-30*	-28*	-36*
Reticulocytes (10^9/L)	74.63	71.82	-24	-28	+37	-1	+15	+48
Red cell distribution width (%)	13.37	13.35	-	-	+13*	-	+19*	+22*
White blood cell count (10^3/µL)	13.28	13.79	-	-	-	+73	+128*	+296
Neutrophils (10^3/µL)	6.44	6.49	-	-	-	-	+170	+389

Report Title: A 3-Month Repeat-Dose Oral Gavage Toxicity and Toxicokinetic Study of MLN2480 in Cynomolgus Monkeys with a 2-Week Recovery				**Test Article:** Tovorafenib			
Species/Strain: Monkey/Cynomolgus		**Duration of Dosing:** 3 months (Q2D)		**Study No.:** 20060187			
Initial Age: 2.3 to 3.9 years		**Duration of Postdose:** 4 weeks		**Location in CTD:** 4.2.3.2			
Date of First Dose: 06 Nov 2014		**Method of Administration:** Oral gavage					
		Vehicle/Formulation: 100% PEG400		**GLP Compliance:** Yes			
Special Features: thyroid hormone analysis (thyroxine and thyroid stimulating hormone)							
No Observed Adverse Effect Level: 3 mg/kg Q2D (males); not determined (females)							
Dose (mg/kg)	**0 (Control)**		**3**		**10**		**20**	
Number of Animals (main/recovery)	**M: 4/2**	**F: 4/2**	**M: 4/0**	**F: 4/0**	**M: 4/2**	**F: 4/2**	**M: 4/2**	**F: 4/2**
Monocytes (10^3/µL)	0.40	0.43	-	-	-	-	+136	+194
Lymphocytes (10^3/µL)	6.27	6.70	-	-	-	+85	+89	+162
Eosinophils (10^3/µL)	0.09	0.08	-	-	+325	-	+150	+650
Basophils (10^3/µL)	0.04	0.05	-	-	-	-	+400*	+1200
Large unstained cells (10^3/µL)	0.04	0.05	-	-	-	-	+575*	+280*
Coagulation								
Fibrinogen (mg/dL)[g]	423	466	-	479	-	-	753	-
Serum Chemistry[h]								
Alkaline phosphatase (U/L)	516.3	353.5	-39	-	-61*	-54	-68*	-58
Albumin (g/dL)	3.93	4.10	+4	-10	-5	-10	-17*	-17
Total protein (g/dL)	6.50	6.55	+5	+1	<+1	+5	-5	-3
Globulin (g/dL)	2.57	2.45	+6	+20	+8	+29	+14	+22
Albumin:Globulin ratio	1.57	1.67	-4	-14	-11	-28	-28	-31
Calcium (mg/dL)	9.63	9.73	+2	-5	-6	-8	-13*	-9*
Total bilirubin (mg/dL)	0.18	0.18	-	-	-	-	+67	+94*
Urinalysis	-	-	-	-	-	-	-	-
Thyroid hormones	-	-	-	-	-	-	-	-
Organ Weights	-	-	-	-	-	-	-	-
Gross Pathology (number examined at scheduled termination)	4	4	4	4	4	1	4	2
Colon: focus, dark, mucosa	0	0	0	0	1	0	0	1
Histopathology (scheduled termination)								
Bone marrow sternum (number examined)	4	4	4	4	4	1	4	2
Increased myeloid to erythroid ratio	0	0	2	1	1	1	1	2
Minimal	0	0	2	1	1	1	0	0
Mild	0	0	0	0	0	0	0	1

Report Title: A 3-Month Repeat-Dose Oral Gavage Toxicity and Toxicokinetic Study of MLN2480 in Cynomolgus Monkeys with a 2-Week Recovery				**Test Article:** Tovorafenib			
Species/Strain: Monkey/Cynomolgus		**Duration of Dosing:** 3 months (Q2D)		**Study No.:** 20060187			
Initial Age: 2.3 to 3.9 years		**Duration of Postdose:** 4 weeks		**Location in CTD:** 4.2.3.2			
Date of First Dose: 06 Nov 2014		**Method of Administration:** Oral gavage					
		Vehicle/Formulation: 100% PEG400		**GLP Compliance:** Yes			
Special Features: thyroid hormone analysis (thyroxine and thyroid stimulating hormone)							
No Observed Adverse Effect Level: 3 mg/kg Q2D (males); not determined (females)							
Dose (mg/kg)	**0 (Control)**		**3**		**10**		**20**	
Number of Animals (main/recovery)	**M: 4/2**	**F: 4/2**	**M: 4/0**	**F: 4/0**	**M: 4/2**	**F: 4/2**	**M: 4/2**	**F: 4/2**
Moderate	0	0	0	0	0	0	1	1
Esophagus (number examined)	4	4	4	3	4	1	4	2
Degeneration, epithelial	0	0	0	0	1	0	0	1
Minimal	0	0	0	0	1	0	0	1
Salivary gland, sublingual (number examined)	4	4	4	4	4	1	4	2
Inflammation, mixed cell	0	0	0	0	0	1	0	1
Minimal	0	0	0	0	0	1	0	1
Intestine, colon (number examined)	4	4	4	4	4	1	4	2
Infiltration, eosinophilic	0	0	0	0	0	0	1	1
Minimal	0	0	0	0	0	0	1	1
Postdose Evaluation: Number Evaluated	2	2	0	0	2	2	2	2
All parameters	-	-	-	-	-	-	-	-

- No noteworthy findings

* P = < .05 ANOVA with Dunnett's/Dunn's compared with control group of same gender

[a] Due to moribundity requiring euthanasia of these animals, and the deteriorating condition of the surviving mid and high dose females, the remaining main study animals at 10 and 20 mg/kg were necropsied early on Day 72 (males) and 70 (females). The recovery phase for these dose groups also began on Day 72 (males) and 70 (females).

[b] Females at ≥10 mg/kg that were euthanized early had a mean of 10.4% body weight loss

[c] End of the dosing phase for the 3 mg/kg dose group; approximately 3 weeks into the recovery phase for the 10 and 20 mg/kg dose groups.

[d] Decreased food consumption was observed only in the unscheduled early euthanized females during veterinary assessments.

[e] Transient; highest incidence reported for any single day over the duration of the study

[f] For controls, group means on Day 66 are shown, and statistical significance is indicated for comparisons of tovorafenib-treated group mean on Day 66 to the control group mean of the same gender on Day 66. However, percent change was determined by comparison of the tovorafenib-treated group mean on Day 66 to the Day -7 mean

for the same group. Percent changes on Day 66 at ≥ 10 mg/kg do not include animals euthanized early on Days 47, 61, or 63. Changes at 3 mg/kg on Day 92 were generally similar to changes on Day 66.

[g] Highest value regardless of day for controls reported; 1 female at 3 mg/kg and 1 male at 10 mg/kg on Day 66 had values higher than highest gender-specific control value, and the value for each animal is reported

[h] For controls, group means on Day 66 are shown. For treated groups, percent differences from controls are shown for Day 66. Statistical significance is based on actual data (not on the percent differences).

Abbreviations: ND = no data; Q2D = every 2 days.

19.3.2. Additional Safety Summary Tables

Table 58. Extent of Exposure, Study C28001 (safety population)

	Dose Escalation Phase			Dose Expansion Phase			
Parameter	Q2D Total N=30	QW Total N=20	Total N=50	PK Cohort N=20[a,b]	Q2D Total N=80[b]	QW Total N=19	Total N=99
Number of treated cycles [c]							
Mean (SD)	3.1 (6.67)	2.1 (2.13)	2.7 (5.32)	6.7 (12.77)	4.9 (8.59)	3.1 (1.99)	4.6 (7.80)
Median	2.0	1.0	2.0	2.0	2.0	2.0	2.0
Min, max	1, 38	1, 10	1, 38	1, 49	1, 49	1, 8	1, 49
Total amount of dose received (mg)							
Mean (SD)	5580.7 (16925.50)	3950.0 (3622.66)	4928.4 (13239.52)	11326.0 (20772.38)	10041.8 (15539.56)	6368.4 (4594.33)	9336.8 (14165.15)
Median	2800.0	2400.0	2600.0	4700.0	5600.0	4800.0	5400.0
Min, max	180, 94640	600, 15600	180, 94640	400, 92800	400, 95340	1200, 17400	400, 95340
Total number of doses received							
Mean (SD)	33.5 (83.44)	7.1 (8.37)	22.9 (65.71)	53.9 (83.85)	53.6 (89.22)	10.8 (7.70)	45.4 (81.95)
Median	20.0	4.0	11.0	23.5	28.0	8.0	25.0
Min, max	2, 471	1, 39	1, 471	2, 334	2, 675	2, 29	2, 675
Relative dose intensity (%) [d]							
Mean (SD)	82.9 (22.02)	77.8 (23.62)	80.8 (22.57)	76.3 (26.28)	80.5 (21.07)	84.0 (16.26)	81.2 (20.21)
Median	95.5	75.0	90.9	88.0	88.6	87.5	88.0
Min, max	18, 100	25, 100	18, 100	18, 100	18, 100	50, 100	18, 100

[a] One patient in the PK cohort had Cycle 50 dosing data recorded under Cycle 49 as the electronic data capture was designed for visits only up to Cycle 49. This therefore had a minor effect on the calculations for number of treated cycles and relative dose intensity for the PK cohort.

[b] Two patients in the Q2D total group of the Dose Expansion phase, including 1 patient in the PK cohort, switched to a weekly dosing starting with Cycles 5 and 4, respectively.

[c] A treated cycle was defined as a cycle in which the patient received any amount of study drug.

[d] Relative dose intensity (%) = 100 × [total amount of dose received (mg)/(prescribed total dose per day × prescribed total number of treated days per cycle × number of treated cycles)]. One patient who received tovorafenib Q2D in the Dose Escalation phase switched from a 22-day regimen to a 28-day regimen. For this patient relative dose intensity (%)

= 100 × [total amount of dose received (mg)/(prescribed total dose per day × [prescribed total number of treated days per 22 days cycle × number of treated 22-day cycles + prescribed total number of treated days per 28 days cycle*number of treated 28 days cycles])].

Note: Percentages were based on the total number of patients in the safety population. Source: C28001 CSR, in-text Table 12.b

Abbreviations: Max = maximum; Min = minimum; PK = pharmacokinetics; Q2D = every other day (QOD); QW = weekly; SD = standard deviation.

Table 59. Demographic Characteristics, Study C28001 (safety population)

	Dose Escalation Phase			Dose Expansion Phase			
Characteristic	Q2D Total N=30	QW Total N=20	Total N=50	PK Cohort N=20	Q2D Total N=80	QW Total N=19	Total N=99
Sex, n (%)							
Male	14 (47)	9 (45)	23 (46)	12 (60)	43 (54)	10 (53)	53 (54)
Female	16 (53)	11 (55)	27 (54)	8 (40)	37 (46)	9 (47)	46 (46
Ethnicity, n (%)							
Hispanic or Latino	7 (23)	7 (35)	14 (28)	1 (5)	2 (3)	0	2 (2)
Not Hispanic or Latino	12 (40)	13 (65)	25 (50)	17 (85)	74 (93)	18 (95)	92 (93
Not reported	11 (37)	0	11 (22)	2 (10)	4 (5)	1 (5)	5 (5)
Race, n (%)							
White	26 (87)	18 (90)	44 (88)	19 (95)	78 (98)	19 (100)	97 (98)
Black or African American	3 (10)	2 (10)	5 (10)	0	0	0	0
Asian	0	0	0	1 (5)	1 (1)	0	1 (1)
Other	1 (3)	0	1 (2)	0	0	0	0
Not Reported	0	0	0	0	1 (1)	0	1 (1)
Age (years) [a]							
n	30	20	50	20	80	19	99
Mean (SD)	63.2 (10.98)	58.7 (10.06)	61.4 (10.75)	65.1 (14.67)	62.2 (13.34)	66.1 (11.13)	63.0 (12.98
Median	65.5	60.5	62.5	65.0	65.0	70.0	66.0
Min, Max	37, 83	39, 74	37, 83	33, 94	31, 94	41, 83	31, 94

Source: C28001 CSR in-text Table 11.b

[a] Age at date of informed consent.

Note: Percentages were based on the total number of patients with non-missing values in the safety population.

Abbreviations: Max = maximum; Min = minimum; PK = pharmacokinetic; Q2D = every other day (QOD); QW = weekly; SD = standard deviation.

Table 60. Primary Cancer Diagnosis, Years Since Diagnosis, and Disease Stage at Study Entry, Study C28001 (safety population)

	Dose Escalation Phase			Dose Expansion Phase			
Characteristic	**Q2D Total N=30**	**QW Total N=20**	**Total N=50**	**PK Cohort N=20**	**Q2D Total N=80**	**QW Total N=19**	**Total N=99**
Primary diagnosis, n (%)							
Anal	1 (3)	0	1 (2)	0	0	0	0
Brain	0	1 (5)	1 (2)	0	0	0	0
Breast	0	1 (5)	1 (2)	0	0	0	0
Colon	12 (40)	6 (30)	18 (36)	0	0	0	0
Colorectal	2 (7)	0	2 (4)	0	0	0	0
Endometrial	1 (3)	1 (5)	2 (4)	1 (5)	1 (1)	0	1 (1)
Gall Bladder	1 (3)	0	1 (2)	0	0	0	0
Gastric	0	0	0	1 (5)	1 (1)	0	1 (1)
Liver	0	0	0	1 (5)	1 (1)	0	1 (1)
Melanoma	0	4 (20)	4 (8)	12 (60)	62 (78)	19 (100)	81 (82)
Non-small cell lung cancer	2 (7)	0	2 (4)	0	0	0	0
Ovarian	1 (3)	0	1 (2)	0	0	0	0
Pancreatic	2 (7)	1 (5)	3 (6)	0	0	0	0
Rectal	0	1 (5)	1 (2)	0	0	0	0
Sarcoma	0	1 (5)	1 (2)	0	0	0	0
Skin	0	0	0	1 (5)	1 (1)	0	1 (1)
small cell lung cancer	1 (3)	0	1 (2)	0	0	0	0
Soft tissue	0	0	0	0	1 (1)	0	1 (1)
Thyroid	1 (3)	2 (10)	3 (6)	0	0	0	0
Other	6 (20)	2 (10)	8 (16)	4 (20)	13 (16)	0	13 (13)
Years since diagnosis [a]							
n	30	20	50	20	79	19	98
Mean (SD)	4.08 (4.688)	5.37 (3.919)	4.60 (4.402)	5.15 (7.102)	4.95 (5.202)	3.92 (3.145)	4.75 (4.875)
Median	2.45	4.40	3.02	2.86	3.16	3.14	3.15
Min, max	0.1, 23.1	1.3, 15.9	0.1, 23.1	0.2, 29.9	0.1, 29.9	0.2, 15.0	0.1, 29.9
Disease stage at study entry, n (%)							
I	0	1 (5)	1 (2)	0	0	0	0
II	0	0	0	1 (5)	1 (1)	0	1 (1)
III	0	1 (5)	1 (2)	0	0	1 (5)	1 (1)

	Dose Escalation Phase			Dose Expansion Phase			
Characteristic	Q2D Total N=30	QW Total N=20	Total N=50	PK Cohort N=20	Q2D Total N=80	QW Total N=19	Total N=99
IIIA	0	0	0	0	1 (1)	0	1 (1)
IIIB	1 (3)	2 (10)	3 (6)	0	0	2 (11)	2 (2)
IIIC	0	1 (5)	1 (2)	1 (5)	4 (5)	1 (5)	5 (5)
IV	21 (70)	9 (45)	30 (60)	16 (80)	60 (75)	12 (63)	72 (73)
IVA	0	0	0	1 (5)	1 (1)	1 (5)	2 (2)
IVB	1 (3)	2 (10)	3 (6)	0	2 (3)	0	2 (2)
IVC	1 (3)	1 (5)	2 (4)	0	5 (6)	2 (11)	7 (7)
Not available	6 (20)	3 (15)	9 (18)	1 (5)	6 (8)	0	6 (6)

Source: C28001 CSR in-text Table 11.c

[a] Years since initial diagnosis = (first dose date – date of initial diagnosis)/365.25.

Note: Percentages were based on the total number of patients with non-missing values in the safety population.

Abbreviations: Max = maximum; Min = minimum; PK = pharmacokinetic; Q2D = every other day (QOD); QW = weekly; SD = standard deviation.

Table 61. Proportion of Patients with Prior Therapy or Surgery, Study C28001 (safety population)

	Dose Escalation Phase			Dose Expansion Phase			
Characteristic	Q2D Total N=30 n (%)	QW Total N=20 n (%)	Total N=50 n (%)	PK Cohort N=20 n (%)	Q2D Total N=80 n (%)	QW Total N=19 n (%)	Total N=99 n (%)
Prior antineoplastic therapy	**NA**	**19 (95)**	**19 (38)**	**16 (80)**	**52 (65)**	**15 (79)**	**67 (68)**
Number of regimens							
1	NA	2 (11)	2 (11)	5 (31)	15 (29)	3 (20)	18 (27)
2	NA	2 (11)	2 (11)	5 (31)	21 (40)	5 (33)	26 (39)
3	NA	5 (26)	5 (26)	1 (6)	6 (12)	3 (20)	9 (13)
4 or more	NA	10 (53)	10 (53)	5 (31)	10 (19)	4 (27)	14 (21)
Best response to last therapy							
Complete response	NA	0	0	0	0	0	0
Partial response	NA	1 (5)	1 (5)	1 (6)	5 (10)	2 (13)	7 (10)
Stable disease	NA	5 (26)	5 (26)	3 (19)	10 (19)	2 (13)	12 (18)
Progressive disease	NA	10 (53)	10 (53)	7 (44)	29 (56)	10 (67)	39 (58)
Unable to assess	NA	1 (5)	1 (5)	2 (13)	3 (6)	0	3 (4)
Unknown	NA	2 (11)	2 (11)	3 (19)	5 (10)	1 (7)	6 (9)
Prior radiation therapy	**NA**	**14 (70)**	**14 (28)**	**8 (40)**	**33 (41)**	**8 (42)**	**41 (41)**
Best response to last therapy							
Complete response	NA	1 (7)	1 (7)	0	0	1 (13)	1 (2)
Partial response	NA	0	0	1 (13)	5 (15)	0	5 (12)
Stable disease	NA	1 (7)	1 (7)	0	1 (3)	1 (13)	2 (5)
Progressive disease	NA	4 (29)	4 (29)	0	10 (30)	0	10 (24)
Unable to assess	NA	0	0	0	0	0	0
Unknown	NA	5 (36)	5 (36)	7 (88)	12 (36)	4 (50)	16 (39)
Symptom relief	NA	3 (21)	3 (21)	0	5 (15)	2 (25)	7 (17)
Prior surgery	**NA**	**20 (100)**	**20 (40)**	**14 (70)**	**69 (86)**	**19 (100)**	**88 (89)**

Source: C28001 CSR in-text Table 11.d

Note: Only the patients for whom the information about the prior therapy/radiation/surgery was collected were included in this table. Percentages were based on the total number of patients in the safety population, except for best response to the last therapy for which percentages were based on the total number of patients in the safety population with prior therapy or prior radiation therapy, respectively.

Abbreviations: NA = not applicable; PK = pharmacokinetic; Q2D = every other day (QOD); QW = weekly.

Table 62. Serious Adverse Events (occurring in ≥2 patients in the all dosing regimen pool) (FIREFLY-1 and C28001 pooled data safety analysis set)

	QW Dosing					
		C28001		QW Dosing Regimen Pool	Q2D Dosing C28001	All Dosing Regimen Pool
MedDRA Preferred Term	FF-1 420 mg/m² N=139 n (%)	400 mg/ 600 mg N=35 n (%)	800 mg N=4 n (%)	N=178 n (%)	N=110 n (%)	N=288 n (%)
Any SAE	47 (33.8)	15 (42.9)	3 (75.0)	65 (36.5)	50 (45.5)	115 (39.9)
Dyspnoea	0	5 (14.3)	0	5 (2.8)	4 (3.6)	9 (3.1)
Sepsis	2 (1.4)	0	0	2 (1.1)	4 (3.6)	6 (2.1)
Pneumonia	2 (1.4)	1 (2.9)	0	3 (1.7)	2 (1.8)	5 (1.7)
Rash maculo-papular	2 (1.4)	1 (2.9)	0	3 (1.7)	2 (1.8)	5 (1.7)
Anaemia	2 (1.4)	1 (2.9)	0	3 (1.7)	2 (1.8)	5 (1.7)
Seizure	5 (3.6)	0	0	5 (2.8)	0	5 (1.7)
Pyrexia	5 (3.6)	0	0	5 (2.8)	0	5 (1.7)
Atrial fibrillation	0	0	0	0	4 (3.6)	4 (1.4)
Pleural effusion	0	1 (2.9)	0	1 (0.6)	3 (2.7)	4 (1.4)
Rash macular	0	1 (2.9)	0	1 (0.6)	3 (2.7)	4 (1.4)
Acute kidney injury	1 (0.7)	0	0	1 (0.6)	3 (2.7)	4 (1.4)
Vomiting	4 (2.9)	0	0	4 (2.2)	0	4 (1.4)
Headache	4 (2.9)	0	0	4 (2.2)	0	4 (1.4)
Hydrocephalus	4 (2.9)	0	0	4 (2.2)	0	4 (1.4)
Dehydration	3 (2.2)	0	1 (25.0)	4 (2.2)	0	4 (1.4)
Lower respiratory tract infection	0	1 (2.9)	0	1 (0.6)	2 (1.8)	3 (1.0)
Pulmonary embolism	1 (0.7)	0	0	1 (0.6)	2 (1.8)	3 (1.0)
Tumour haemorrhage	2 (1.4)	0	0	2 (1.1)	1 (0.9)	3 (1.0)
Hyponatraemia	3 (2.2)	0	0	3 (1.7)	0	3 (1.0)
Clostridium difficile colitis	1 (0.7)	0	0	1 (0.6)	1 (0.9)	2 (0.7)
Otitis media	2 (1.4)	0	0	2 (1.1)	0	2 (0.7)
Upper respiratory tract infection	2 (1.4)	0	0	2 (1.1)	0	2 (0.7)
Viral infection	2 (1.4)	0	0	2 (1.1)	0	2 (0.7)
Viral upper respiratory tract infection	2 (1.4)	0	0	2 (1.1)	0	2 (0.7)
Abdominal pain	1 (0.7)	0	0	1 (0.6)	1 (0.9)	2 (0.7)
Ascites	2 (1.4)	0	0	2 (1.1)	0	2 (0.7)
Constipation	0	0	0	0	2 (1.8)	2 (0.7)
Gastrointestinal haemorrhage	1 (0.7)	0	0	1 (0.6)	1 (0.9)	2 (0.7)
Gastrooesophageal reflux disease	0	1 (2.9)	0	1 (0.6)	1 (0.9)	2 (0.7)
Nausea	0	2 (5.7)	0	2 (1.1)	0	2 (0.7)
Rectal haemorrhage	0	0	0	0	2 (1.8)	2 (0.7)

	QW Dosing					
		C28001				
MedDRA Preferred Term	FF-1 420 mg/m² N=139 n (%)	400 mg/ 600 mg N=35 n (%)	800 mg N=4 n (%)	QW Dosing Regimen Pool N=178 n (%)	Q2D Dosing C28001 N=110 n (%)	All Dosing Regimen Pool N=288 n (%)
Haemoptysis	0	0	1 (25.0)	1 (0.6)	1 (0.9)	2 (0.7)
Respiratory failure	0	0	0	0	2 (1.8)	2 (0.7)
Ataxia	1 (0.7)	0	0	1 (0.6)	1 (0.9)	2 (0.7)
Hypothermia	2 (1.4)	0	0	2 (1.1)	0	2 (0.7)
Decreased appetite	2 (1.4)	0	0	2 (1.1)	0	2 (0.7)
Metastatic malignant melanoma	0	0	0	0	2 (1.8)	2 (0.7)
Hyperbilirubinaemia	0	0	1 (25.0)	1 (0.6)	1 (0.9)	2 (0.7)
Shunt malfunction	2 (1.4)	0	0	2 (1.1)	0	2 (0.7)
Flank pain	0	0	0	0	2 (1.8)	2 (0.7)
Device malfunction	2 (1.4)	0	0	2 (1.1)	0	2 (0.7)
Anxiety	2 (1.4)	0	0	2 (1.1)	0	2 (0.7)
Hypotension	1 (0.7)	0	0	1 (0.6)	1 (0.9)	2 (0.7)

Source: Modified from ISS Table 1.4.6

Note: MedDRA version 23.1.

Data cutoff date for FIREFLY-1: 22 December 2022

Abbreviations: FF-1 = FIREFLY-1; MedDRA = Medical Dictionary for Regulatory Activities; Q2D = every other day; QW = once weekly; SAE = serious adverse event.

Table 63. Adverse Events Leading to Study Treatment Discontinuation (FIREFLY-1 and C28001 pooled data safety analysis set)

	QW Dosing					
		C28001				
MedDRA Preferred Term	FF-1 420 mg/m² N=139 n (%)	400 mg/ 600 mg N=35 n (%)	800 mg N=4 n (%)	QW Dosing Regimen Pool N=178 n (%)	Q2D Dosing C28001 N=110 n (%)	All Dosing Regimen Pool N=288 n (%)
Any AE leading to study treatment discontinuation	6 (4.3)	6 (17.1)	0	12 (6.7)	19 (17.3)	31 (10.8)
Rash maculo-papular	1 (0.7)	0	0	1 (0.6)	3 (2.7)	4 (1.4)
Sepsis	0	0	0	0	2 (1.8)	2 (0.7)
Dyspnoea	0	2 (5.7)	0	2 (1.1)	0	2 (0.7)
Erythema multiforme	0	1 (2.9)	0	1 (0.6)	0	1 (0.3)
Psoriasis	0	0	0	0	1 (0.9)	1 (0.3)
Rash	0	0	0	0	1 (0.9)	1 (0.3)
Rash macular	0	0	0	0	1 (0.9)	1 (0.3)
Rash popular	0	0	0	0	1 (0.9)	1 (0.3)
Dyspnoea exertional	0	0	0	0	1 (0.9)	1 (0.3)

	QW Dosing					
		C28001				
MedDRA Preferred Term	FF-1 420 mg/m² N=139 n (%)	400 mg/ 600 mg N=35 n (%)	800 mg N=4 n (%)	QW Dosing Regimen Pool N=178 n (%)	Q2D Dosing C28001 N=110 n (%)	All Dosing Regimen Pool N=288 n (%)
Restrictive pulmonary disease	0	0	0	0	1 (0.9)	1 (0.3)
Eosinophilia	1 (0.7)	0	0	1 (0.6)	0	1 (0.3)
Haemolysis	1 (0.7)	0	0	1 (0.6)	0	1 (0.3)
Cardiac failure	0	0	0	0	1 (0.9)	1 (0.3)
Ventricular extrasystoles	1 (0.7)	0	0	1 (0.6)	0	1 (0.3)
Stomatitis	1 (0.7)	0	0	1 (0.6)	0	1 (0.3)
Chest pain	0	0	0	0	1 (0.9)	1 (0.3)
Hepatotoxicity	0	0	0	0	1 (0.9)	1 (0.3)
Hyperbilirubinaemia	0	1 (2.9)	0	1 (0.6)	0	1 (0.3)
Growth retardation	1 (0.7)	0	0	1 (0.6)	0	1 (0.3)
Myalgia	0	0	0	0	1 (0.9)	1 (0.3)
Melanocytic naevus	0	0	0	0	1 (0.9)	1 (0.3)
Tumour haemorrhage	1 (0.7)	0	0	1 (0.6)	0	1 (0.3)
Acute kidney injury	0	0	0	0	1 (0.9)	1 (0.3)
Haemoptysis	0	0	0	0	1 (0.9)	1 (0.3)
Respiratory failure	0	0	0	0	1 (0.9)	1 (0.3)
Escherichia sepsis	0	0	0	0	1 (0.9)	1 (0.3)
Pneumonia	0	0	0	0	1 (0.9)	1 (0.3)
Auto-immune haemolytic anaemia	1 (0.7)	0	0	1 (0.6)	0	1 (0.3)
Atrial flutter	0	1 (2.9)	0	1 (0.6)	0	1 (0.3)
Diverticular perforation	0	0	0	0	1 (0.9)	1 (0.3)
Gastrointestinal haemorrhage	0	0	0	0	1 (0.9)	1 (0.3)
Fatigue	0	1 (2.9)	0	1 (0.6)	0	1 (0.3)
Shunt malfunction	1 (0.7)	0	0	1 (0.6)	0	1 (0.3)
Guillain-Barre syndrome	0	0	0	0	1 (0.9)	1 (0.3)

Source: Modified from ISS Table 1.4.8

Note: MedDRA version 23.1. Data cutoff date for FIREFLY-1: 22 December 2022

Abbreviations: AE = adverse event; FF-1 = FIREFLY-1; MedDRA = Medical Dictionary for Regulatory Activities; Q2D = every other day; QW = once weekly.

19.4. OCP Appendices (technical documents supporting OCP recommendations)

19.4.1. Population PK Analysis

19.4.1.1. Executive Summary

The FDA's Assessment

The PK of tovorafenib was characterized by a one-compartment model with first order absorption for PFOS or transit-compartment absorption for tablets followed by first order clearance. The population PK model described the observed data reasonably well. No intrinsic or extrinsic factors are likely to have clinically meaningful impact on exposure except for body surface area (BSA) which supported BSA based dosing in pediatric patients. In addition, tovorafenib's use in patients 6 months and older is supported by (1) body size allometry in the popPK model to account for PK differences across age and to support BSA-based dosing and (2) the ontogeny of the main metabolizing enzymes (aldehyde oxidase and CYP2C8) appearing to mature after 6 months of age.

19.4.1.2. Population PK Assessment Summary

Applicant's Position

A population PK analysis based on pooled data from healthy adult participants and adult and pediatric patients with cancer in Studies C28001, C28002, (b) (4) 205140, and FIREFLY-1 was performed to characterize the PK of tovorafenib across studies, to evaluate the impact of intrinsic and extrinsic factors on tovorafenib PK, and to derive individual model-predicted PK parameters for subsequent E-R analyses.

The key findings of these analyses include:

- The tovorafenib concentration-time course was described by a one-compartment model with three-transit absorption model (designated as Ka [Tablet]) for the tablet formulation and first-order absorption model with no transit compartment (designated as Ka [PfR]) for the PfR formulation.
- Body surface area was included as a covariate of tovorafenib CL/F and apparent central volume of distribution (Vc/F). Apparent clearance was associated with sex, where males were estimated to have a 21.5% higher CL/F than females. For participants who received the tablet formulation, the consumption of high-fat food decreased the absorption rate constant (Ka [Tablet]) by 54.3% compared to those in the fasted state.

Table 64.

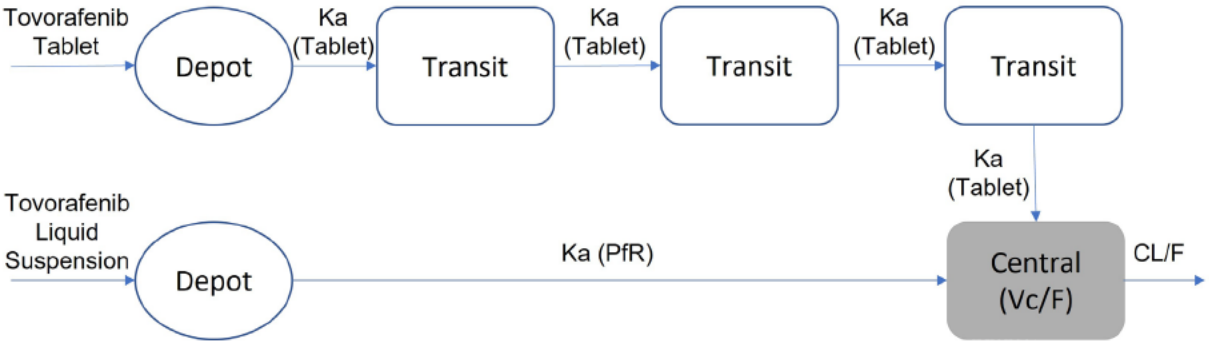
General Information		
Objectives of PPK Analysis		• *Characterize the PK of tovorafenib across studies* • *Evaluate the impact of intrinsic and extrinsic factors on tovorafenib PK* • *Derive individual model-predicted PK parameters for subsequent E-R analyses*
Study Included		*Studies C28001, C28002, (b) (4) 205140, and FIREFLY-1*
Dose(s) Included		*20 mg – 280 mg Q2D; 400 mg – 800 mg QW; 420 mg/m² QW (not to exceed 600 mg); single doses of 100 and 300 mg*
Population Included		*Healthy adult participants, adult and pediatric patients with cancer*
Population Characteristics (Table 65, Table 66, Table 67)	General	*Age: median 48 years (range: 1 – 94 years)* *Weight: median 64.9 kg (range: 9.20 – 186 kg)* *N = 174 (51%) male* *N = 258 (75.7%) White; N = 37 (10.9%) Black/Asian/ other/multiple; N = 46 (13.5%) unknown*
	Organ Impairment	*Hepatic (NCI): N = 274 (80.4%) normal; N = 52 (15.2%) mild; N = 1 (0.3%) moderate; N = 14 (4.1%) unknown* *Renal (eGFR): N = 212 (62.2%) normal; N = 108 (31.7%) mild; N = 21 (6.2%) moderate*
	Pediatrics	*N = 3 (0.9%) 1 month to < 2 years* *N = 27 (7.9%) 2 to < 6 years* *N = 66 (19.4%) 6 to < 12 years* *N = 36 (10.6%) 12 to < 18 years* *Weight [FIREFLY-1] median 32.9 kg (range: 9.20 - 98.3 kg)* *Note: includes 6 young adults enrolled in FIREFLY-1.*
No. of Patients, PK Samples, and BLQ		*N = 341 subjects with N = 3,915 samples. N = 132 samples pre-first dose BLQ and N=6 postdose BLQ samples*
Sampling Schedule	Rich Sampling	***Study C28001 Dose Escalation*** *C1D1 (predose and 30 minutes and 1, 2, 4, 6, and 8 hours postdose), C1D2 (24 hours postdose), C1D3 (48 hours postdose), C1D9 (predose), C1D15 (predose), C1D21 (predose and 30 minutes and 1, 2, 4, 6, and 8 hours postdose), C1D22 (24 hours postdose), C2D1 (48 hours postdose)* ***Study C28001 Dose Expansion*** *C1D1 (predose), C1D2 (24 hours postdose), C1D3 (48 hours postdose), C1 additional sample 1, C1D21 (predose), C1D22 (24 hours postdose), C1 additional sample 2, and C2D1 (48 hours postdose)* ***Study C28002*** *Arm 1: C1D10 (predose and 30 minutes and 1, 2, 4, 6, 8, 24, and 48 hours postdose)* *Arm 2: C1D10 (predose and 30 minutes and 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours postdose)* *Arm 3: C1D15 (predose and 30 minutes and 1, 2, 4, 6, 8, 24, and 48 hours postdose)* *Arm 4: C1D16 (predose and 30 minutes and 1, 2, 4, 6, 8, 24, and 144 hours postdose)* *Arm 5: C1D16 (predose and 30 minutes and 1, 2, 4, 6, 8, 24, and 144 hours postdose)* *Expansion (QW) PK as Arm 3*

		Study (b) (4) 2015140 *Predose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 60, 72, 96, and 120 hours postdose*
	In ITT Population (Study FIREFLY-1)	*C1D1 (1, 2 and 4 hours postdose)* *C1D15 (a sample between 1 and 4 hours postdose)* *C2D1 (predose)* *C4D1 (a sample between 1 and 4 hours postdose)* *C4, C7, C10 and C13 (a sample between 1 and 4 hours postdose)*
Covariates Evaluated	Static	*Sex, age, weight, BSA, albumin, ALP, AST, ALT, bilirubin, creatinine, crCL, eGFR, race, ethnicity, disease type, renal impairment, hepatic impairment, H2 receptor antagonist, antacid*
	Time-varying	*Regimen/formulation, concomitant medication use*

Final Model	**Summary**	**Acceptability [FDA's comments]**
Software and Version	*NONMEM Version 7.4.3*	Yes
Model Structure (Figure 20)	*One-compartment model with three-transit absorption model (designated as Ka [Tablet]) for the tablet formulation and first-order absorption model with no transit compartment (designated as Ka [PfR]) for the PfR formulation, and first-order elimination.*	Yes
Model Parameter Estimates	*Table 36*	Yes
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	*All parameters, including those characterizing the covariate effects, were estimated with good precision, with %RSE consistently below 30%.*	Yes
BLQ for Parameter Accuracy	*N = 1 BLQ observation after administration of the first dose ("postdose BLQ") in Study C28001, 2 BLQ observations in Study (b) (4) 205140, and 3 BLQ observations in Study FIREFLY-1.*	Yes
GOF, VPC	Figure 21 *(GOF for base/final model)* Figure 22 *(pcVPC for final model)*	Yes
Significant Covariates and Clinical Relevance	Figure 23 *BSA was selected for body size scaling. BSA was included as a covariate of tovorafenib CL/F and Vc/F.* *The final model included the effect of sex (male vs. female) on CL/F and prandial status (fasted vs. fed) on the Ka of the tablet formulation. Based on univariate analysis, the food and formulation effects on tovorafenib exposure (AUC, C_{max}, and C_{min}) were within the 0.8 to 1.25 exposure ratio interval and were not considered clinically meaningful. Males were estimated to have a 21.5% higher CL/F than females, which was not considered clinically meaningful.*	Yes Several factors of interest have limited to no information for characterizing the impact on PK, including moderate-to-severe hepatic impairment, severe renal impairment, and moderate-to-strong CYP2C8 inhibitors/inducers.
Analysis Based on Simulation	*Not applicable.*	

Labeling Language	Description	Acceptability [FDA's comments]
12.3 PK	*Description* *Specific Populations: PK differences are not clinically relevant based on age (range: 1 to 94 years), sex, race, mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1x to 1.5x ULN and any AST), and mild (eGFR ≥ 60 to 89 mL/min/1.73 m²) or moderate (eGFR ≥ 30 to 59 mL/min/1.73 m²) renal impairment, after accounting for BSA.*	Yes

Figure 20. Schematic of the PopPK Model for Tovorafenib



CL/F = apparent clearance; Ka (Tablet) = transit absorption rate constant for tablet formulation; Ka (PfR) = absorption rate constant for PfR; PfR = powder for reconstitution; PopPK = population pharmacokinetic; Vc/F = apparent central volume of distribution

Table 65. Table 66 Summary of Baseline Continuous Covariates

Covariate	Statistic	Study C28001 (N=125)	Study C28002 (N=66)	(b) (4) 205140 (N=12)	FIREFLY-1 (N=138)	Overall (N=341)
Age (years)	Mean (SD)	63.4 (11.9)	60.1 (11.0)	42.5 (7.15)	9.26 (4.58)	40.1 (27.4)
	Median [range]	65.0 [33.0, 94.0]	62.0 [24.0, 78.0]	41.0 [35.0, 54.0]	9.00 [1.00, 24.0]	48.0 [1.00, 94.0]
Height (cm)	Mean (SD)	170 (9.80)	166 (8.77)	167 (11.2)	134 (24.0)	154 (24.0)
	Median [range]	169 [137, 193]	166 [147, 191]	163 [151, 184]	134 [72.0, 178]	161 [72.0, 193]
	Missing (%)	1 (0.8%)	2 (3.0%)	-	-	3 (0.9%)
Weight (kg)	Mean (SD)	81.3 (20.1)	74.0 (17.5)	77.4 (12.9)	37.7 (18.8)	62.1 (27.7)
	Median [range]	79.0 [42.5, 186]	71.5 [44.0, 138]	77.8 [58.3, 98.5]	32.9 [9.20, 98.3]	64.9 [9.20, 186]
	Missing (%)	-	1 (1.5%)	-	-	1 (0.3%)
BMI (kg/m^2)	Mean (SD)	28.2 (6.17)	26.6 (5.39)	27.6 (2.17)	19.6 (4.59)	24.4 (6.63)
	Median [range]	26.9 [17.1, 53.9]	26.7 [16.6, 46.1]	28.5 [24.2, 30.4]	18.9 [10.9, 34.3]	24.2 [10.9, 53.9]
	Missing (%)	1 (0.8%)	2 (3.0%)	-	-	3 (0.9%)
BSA (m^2)	Mean (SD)	1.91 (0.245)	1.82 (0.226)	1.86 (0.217)	1.17 (0.387)	1.59 (0.467)
	Median [range]	1.89 [1.38, 2.92]	1.81 [1.39, 2.44]	1.83 [1.54, 2.22]	1.12 [0.440, 2.19]	1.70 [0.440, 2.92]
	Missing (%)	1 (0.8%)	2 (3.0%)	-	-	3 (0.9%)
Albumin (g/L)	Mean (SD)	36.8 (4.95)	37.8 (4.81)	43.3 (2.05)	42.0 (5.08)	39.3 (5.48)
	Median [range]	37.0 [26.0, 49.0]	38.0 [26.0, 47.0]	43.5 [39.0, 46.0]	42.0 [13.0, 56.0]	39.0 [13.0, 56.0]
Alkaline phosphatase (U/L)	Mean (SD)	131 (97.1)	137 (89.2)	60.3 (19.9)	205 (92.4)	160 (100)
	Median [range]	96.0 [39.0, 689]	104 [52.0, 519]	59.5 [36.0, 110]	198 [54.0, 715]	130 [36.0, 715]
Alanine aminotransferase (U/L)	Mean (SD)	31.8 (19.6)	25.4 (12.0)	18.4 (6.37)	23.7 (15.7)	26.8 (16.8)
	Median [range]	27.0 [7.00, 127]	24.5 [7.00, 62.0]	18.5 [8.00, 29.0]	20.0 [5.00, 102]	22.0 [5.00, 127]
Aspartate aminotransferase (U/L)	Mean (SD)	30.5 (18.3)	30.7 (17.1)	18.3 (2.87)	29.4 (10.1)	29.6 (15.0)
	Median [range]	25.0 [8.00, 123]	25.5 [10.0, 103]	18.5 [13.0, 22.0]	28.0 [7.00, 80.0]	26.0 [7.00, 123]
	Missing (%)	-	-	-	1 (0.7%)	1 (0.3%)
Bilirubin (µmol/L)	Mean (SD)	9.92 (5.20)	9.09 (4.86)	8.98 (2.93)	6.40 (3.83)	8.27 (4.81)
	Median [range]	8.55 [3.00, 30.8]	8.55 [1.71, 30.4]	8.55 [5.13, 13.7]	5.13 [1.71, 25.7]	6.92 [1.71, 30.8]
	Missing (%)	-	13 (19.7%)	-	-	13 (3.8%)
Creatinine (µmol/L)	Mean (SD)	80.9 (25.8)	72.5 (19.8)	76.6 (14.3)	40.6 (15.1)	62.8 (27.6)
	Median [range]	78.0 [26.5, 168]	69.5 [38.9, 130]	79.6 [53.1, 97.3]	38.0 [8.84, 92.8]	61.9 [8.84, 168]
	Mean (SD)	95.8 (40.0)	98.8 (44.4)	115 (26.3)	139 (52.4)	115 (50.1)

Covariate	Statistic	Study C28001 (N=125)	Study C28002 (N=66)	(b) (4) 205140 (N=12)	FIREFLY-1 (N=138)	Overall (N=341)
Creatinine clearance (mL/min)	Median [range]	88.8 [25.2, 252]	90.1 [41.6, 265]	117 [71.9, 153]	127 [52.1, 368]	107 [25.2, 368]
	Missing (%)	-	1 (1.5%)	-	-	1 (0.3%)
eGFR (mL/min/1.73 m^2)	Mean (SD)	87.7 (31.6)	93.2 (28.0)	89.0 (16.2)	132 (40.1)	107 (40.1)
	Median [range]	81.9 [35.7, 240]	86.8 [52.1, 178]	90.8 [65.2, 116]	126 [67.8, 375]	100 [35.7, 375]

BMI=body mass index; BSA=body surface area; eGFR=estimated glomerular filtration rate; N=number of subjects with available information; SD=standard deviation

Table 67. Summary of Time-Varying Continuous or Categorical Covariates

Covariate	Value	C28001	C28002	(b) (4) 205140	FIREFLY-1	Overall
Regimen/ formulation	N	125	66	35	140	366
	Regimen G	0 (0%)	0 (0%)	11 (31.4%)	0 (0%)	11 (3.9%)
	Regimen H	0 (0%)	0 (0%)	12 (34.3%)	0 (0%)	12 (4.2%)
	Regimen I	0 (0%)	0 (0%)	12 (34.3%)	0 (0%)	12 (4.2%)
	T1	106 (84.8%)	32 (48.5%)	0 (0%)	0 (0%)	138 (37.7%)
	T2	19 (15.2%)	34 (51.5%)	0 (0%)	108 (77.1%)	161 (44.0%)
	PfR	0 (0%)	0 (0%)	0 (0%)	32 (22.9%)	32 (8.7%)
CYP2C19 strong inhibitor	N	127	67	12	139	345
	No	123 (96.9%)	65 (97.0%)	12 (100%)	138 (99.3%)	338 (98.0%)
	Yes	4 (3.1%)	2 (3.0%)	0 (0%)	1 (0.7%)	7 (2.0%)
CYP2C19 moderate inhibitor	N	132	71	12	143	358
	No	104 (78.8%)	59 (83.1%)	12 (100%)	133 (93.0%)	308 (86.0%)
	Yes	28 (21.2%)	12 (16.9%)	0 (0%)	10 (7.0%)	50 (14.0%)
CYP2C8 weak inhibitor	N	127	67	12	147	353
	No	123 (96.9%)	65 (97.0%)	12 (100%)	132 (89.8%)	332 (94.1%)
	Yes	4 (3.1%)	2 (3.0%)	0 (0%)	15 (10.2%)	21 (5.9%)
CYP2C8 weak inducer	N	133	67	12	142	354
	No	125 (94.0%)	66 (98.5%)	12 (100%)	138 (97.2%)	341 (96.3%)
	Yes	8 (6.0%)	1 (1.5%)	0 (0%)	4 (2.8%)	13 (3.7%)
CYP2C9 strong inhibitor	N	125	66	12	140	343
	No	125 (100%)	66 (100%)	12 (100%)	138 (98.6%)	341 (99.4%)
	Yes	0 (0%)	0 (0%)	0 (0%)	2 (1.4%)	2 (0.6%)

Covariate	Value	C28001	C28002	(b) (4) 205140	FIREFLY-1	Overall
CYP2C9 moderate inhibitor	N	129	68	12	139	348
	No	124 (96.1%)	66 (97.1%)	12 (100%)	138 (99.3%)	340 (97.7%)
	Yes	5 (3.9%)	2 (2.9%)	0 (0%)	1 (0.7%)	8 (2.3%)
CYP2C9 weak inhibitor	N	125	68	12	139	344
	No	124 (99.2%)	66 (97.1%)	12 (100%)	136 (97.8%)	338 (98.3%)
	Yes	1 (0.8%)	2 (2.9%)	0 (0%)	3 (2.2%)	6 (1.7%)
CYP3A strong inhibitor	N	130	67	12	147	356
	No	124 (95.4%)	66 (98.5%)	12 (100%)	132 (89.8%)	334 (93.8%)
	Yes	6 (4.6%)	1 (1.5%)	0 (0%)	15 (10.2%)	22 (6.2%)
CYP3A moderate inhibitor	N	130	70	12	140	352
	No	120 (92.3%)	66 (94.3%)	12 (100%)	137 (97.9%)	335 (95.2%)
	Yes	10 (7.7%)	4 (5.7%)	0 (0%)	3 (2.1%)	17 (4.8%)
CYP3A weak inhibitor	N	136	83	12	147	378
	No	97 (71.3%)	51 (61.4%)	12 (100%)	136 (92.5%)	296 (78.3%)
	Yes	39 (28.7%)	32 (38.6%)	0 (0%)	11 (7.5%)	82 (21.7%)
CYP3A weak inducer	N	145	89	12	152	398
	No	109 (75.2%)	61 (68.5%)	12 (100%)	123 (80.9%)	305 (76.6%)
	Yes	36 (24.8%)	28 (31.5%)	0 (0%)	29 (19.1%)	93 (23.4%)
Proton pump inhibitor	N	141	75	12	151	379
	no PPI	95 (67.4%)	57 (76.0%)	0 (0%)	134 (88.7%)	286 (75.5%)
	PPI	46 (32.6%)	18 (24.0%)	0 (0%)	17 (11.3%)	81 (21.4%)
	Missing	0 (0%)	0 (0%)	12 (100%)	0 (0%)	12 (3.2%)

CYP = cytochrome P450; N = number of subjects with available information; PfR = powder for reconstitution; PPI = proton pump inhibitor

Notes: Numeric columns formatted as count (% of total). Concomitant medications were classified as CYP inhibitors or inducers based on the Drug Interactions Database [(b) (4)].

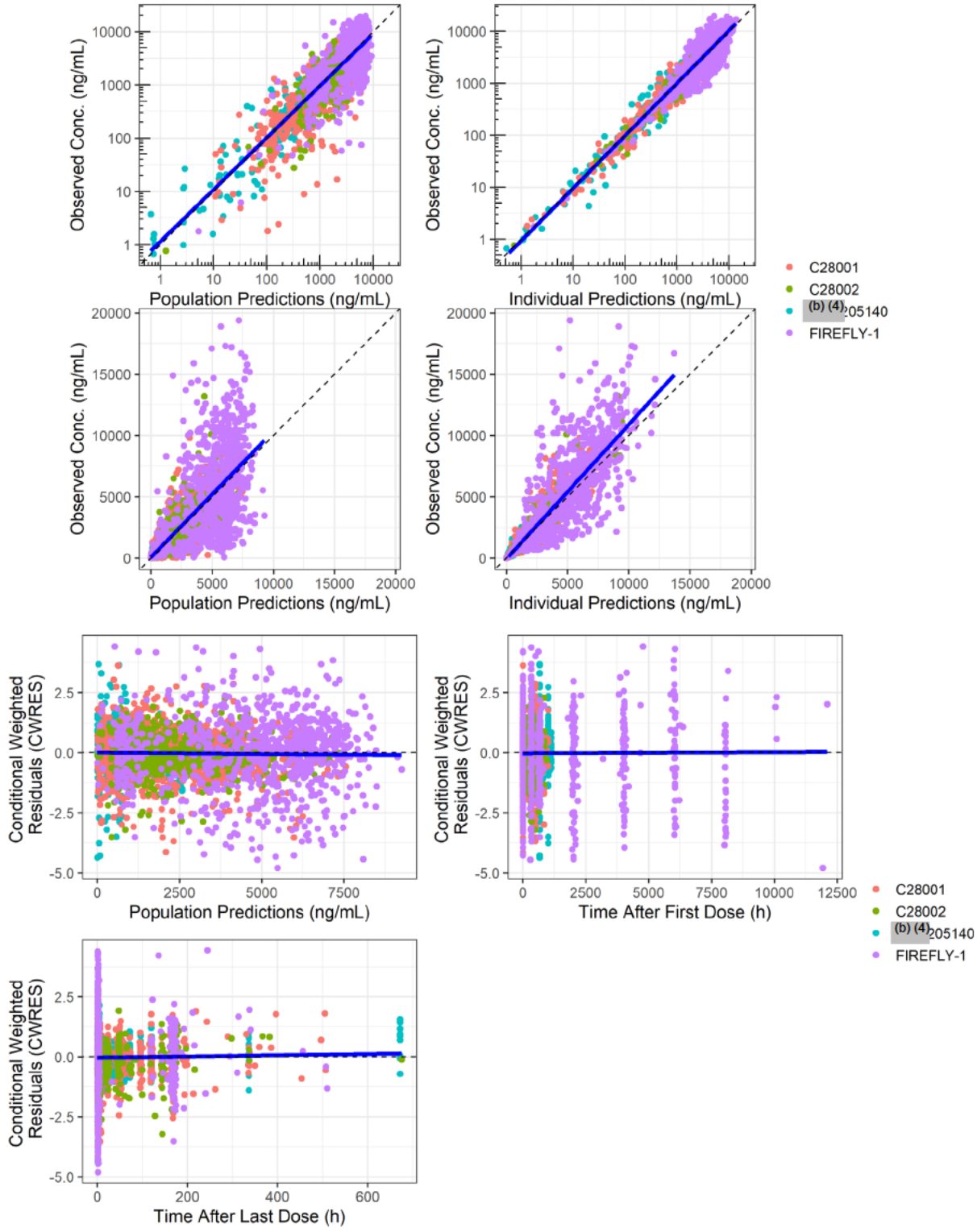
Table 68. Final Model Parameter Estimates for Tovorafenib Pharmacokinetics

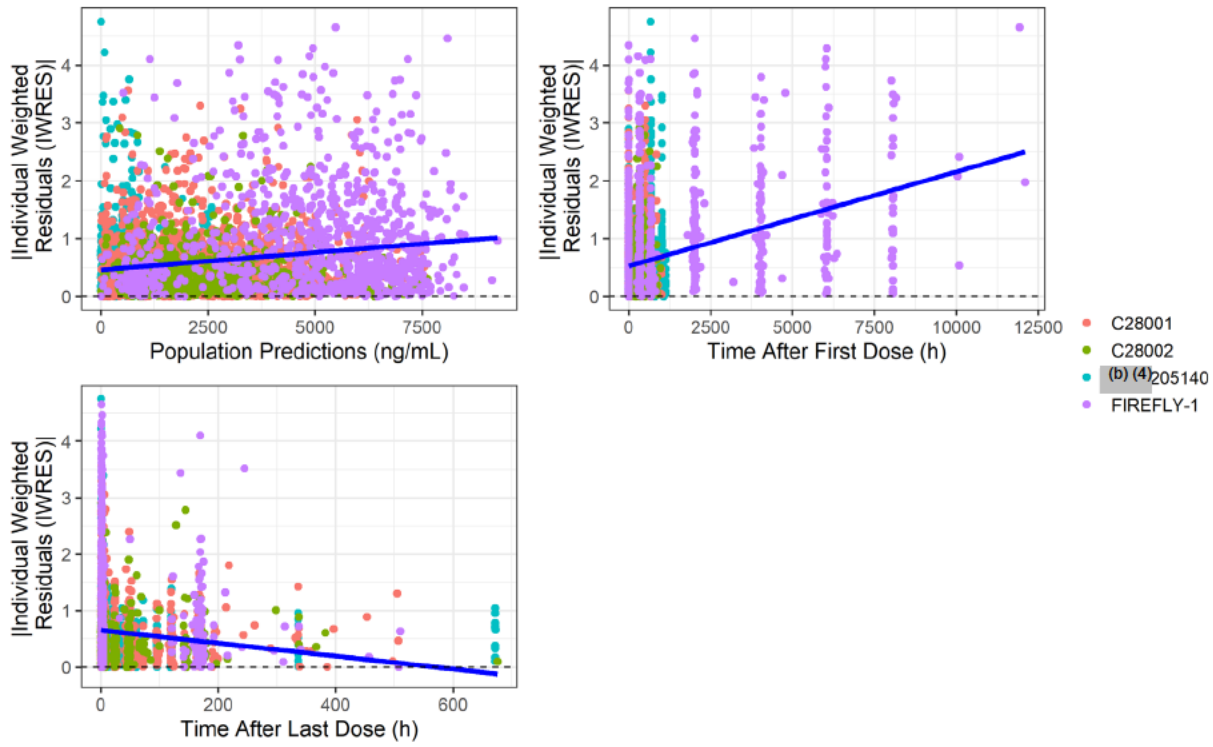
Parameters	Estimates	%RSE	95% CI	SIR 95% CI	
Parameters					
CL/F (L/hr)	1.20	3.93	1.11 – 1.30	1.15 – 1.27	
Vc/F (L)	118	1.92	114 – 123	114 – 122	
Ka (Tablet) (hr^{-1})	3.31	3.39	3.09 – 3.53	3.11 – 3.55	
Ka (PfR) (hr^{-1})	0.81	27.2	0.378 – 1.24	0.585 – 1.11	
BSA on CL/F	1.04	7.45	0.886 – 1.19	0.929 – 1.14	
BSA on Vc/F	1.30	5.50	1.16 – 1.44	1.19 – 1.41	
Sex on CL/F	0.215	32.4	0.0786 – 0.352	0.136 – 0.295	
Food effect (Regimen I) on Ka (Tablet)	-0.543	10.9	-0.659, -0.428	-0.579, -0.507	
Random effects	**Estimates**	**%RSE**	**95 % CI**	**SIR 95% CI**	**Shrinkage (%)**
IIV on CL/F	0.0896	11.0	0.0703 – 0.109	0.0742 – 0.109	12.0
Covariance of CL/F and Vc/F	0.0337	25.5	0.0169 – 0.0506	0.0218 – 0.0468	
IIV on Vc/F	0.0575	18.5	0.0366 – 0.0783	0.0441 – 0.0736	25.0
IIV on Ka (tablet)	0.2850	11.7	0.22 – 0.35	0.232 – 0.347	16.8
IIV on Ka (PfR)	0.9170	26.5	0.441 – 1.39	0.546 – 1.56	14.6
Residual error	**Estimates**	**%RSE**	**95%CI**	**SIR 95% CI**	**Shrinkage (%)**
Additive error on log scale (equivalent to proportional error on linear scale)	0.321	3.49	0.299 – 0.343	0.313 – 0.329	9.36

BSA = body surface area; CI = confidence interval; CL/F = apparent clearance; IIV = inter-individual variability; Ka (Tablet) = transit rate constant for tablet formulation; Ka (PfR) = transit rate constant for PfR; PfR = powder for reconstitution; PK = pharmacokinetics; RSE = relative standard error; SIR = sampling importance resampling; Vc/F = apparent central volume of distribution.

Note: The typical individual is a female subject with a BSA = $1.70 m^2$, who received tablet formulation under fasted/any meal condition.

Figure 21. Goodness-of-Fit Plots for the Base Model by Study



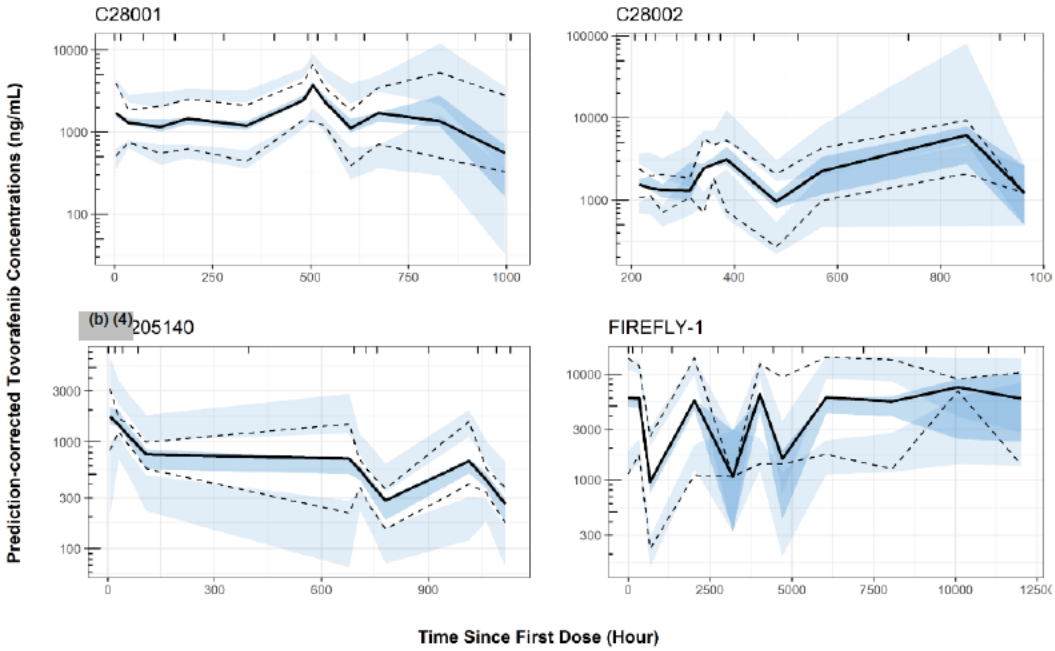


Notes: The dots are the individual observed plasma tovorafenib concentrations, and the blue line is the linear regression line.The dashed lines are the line of identity in the observed concentrations versus predicted concentrations plots. The Y- and X-axes of the two upper plots are presented on a log scale. All other plots are presented on a linear scale.

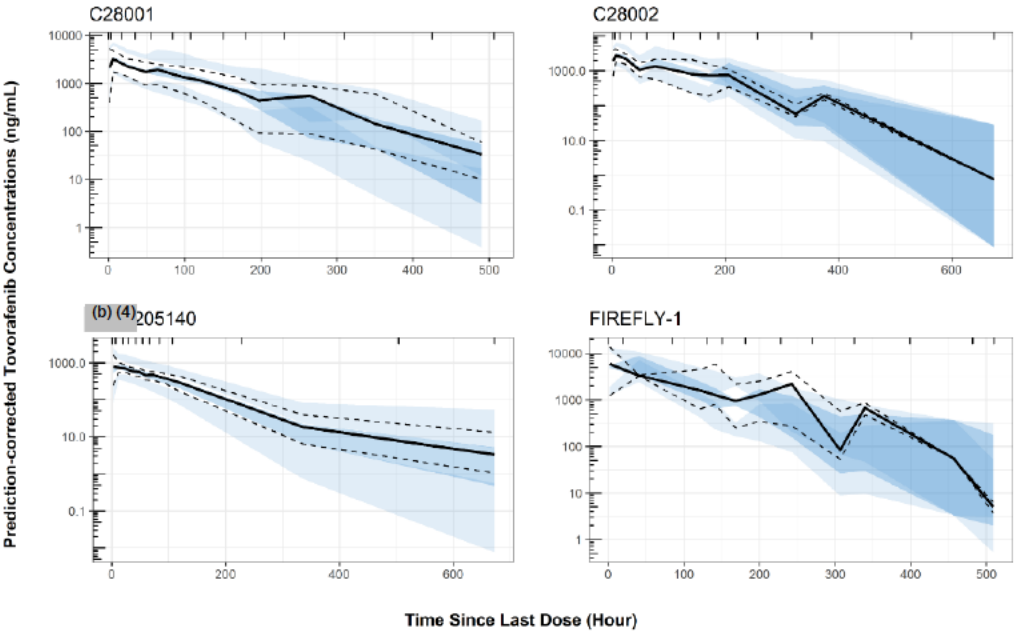
Conc. = concentration.

Figure 22. Prediction-Corrected Visual Predictive Check for the Final PopPK Model Stratified by Study

Time Since First Dose



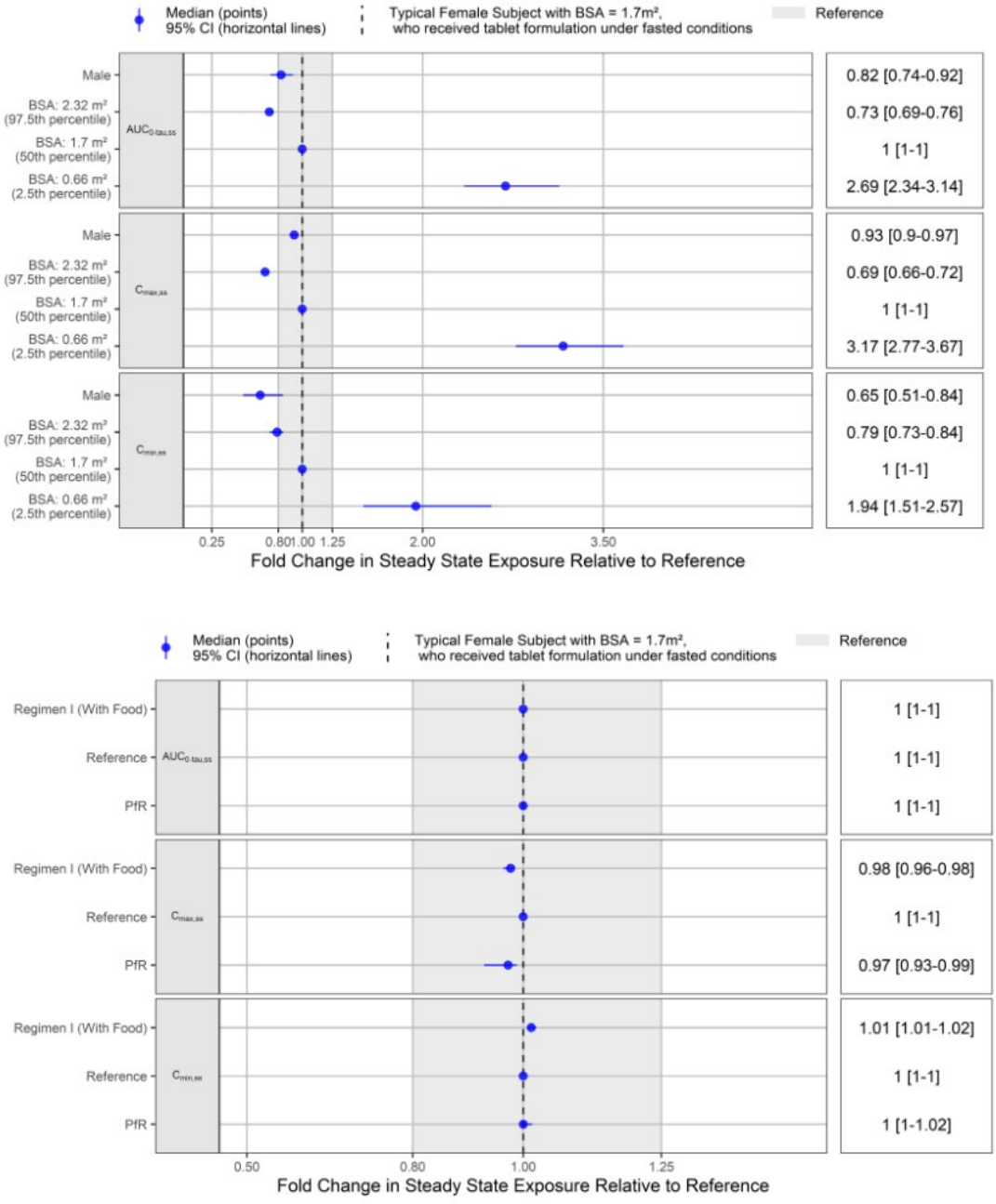
Time Since Last Dose



Notes: The solid line is the observed median; the dashed lines are the observed p5 and p95. The blue shaded area is the 90% CI of the simulated median, p5 and p95.

Abbreviations: CI = confidence interval; p5 = 5th percentile; p95 = 95th percentile; PopPK = population pharmacokinetic

Figure 23. Relative Impact of Covariates on Tovorafenib Steady-State Exposure at 600 mg Once Weekly in the Evaluable Subjects for PopPK Analysis



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Note: For continuous covariates (ie, BSA), the values represent the 5th and 95th percentiles of the observed covariate values in the study. The gray-shaded region represents the clinically insignificant region. The symbols represent median ±95% CI. The typical individual is a female subject with a BSA = 1.70 m^2, who received tablet formulation under fasted/any meal conditions. A flat dose of 600 mg was used in the simulations.

$AUC_{0\text{-}tau,ss}$ = area under the curve at steady state; BSA = body surface area; CI = confidence interval; $C_{max,ss}$ = steady state maximum plasma concentration; $C_{min,ss}$ = steady state minimum plasma concentration.

The FDA's Assessment

FDA agrees with Applicant's position.

19.4.1.3. PPK Review Issues

The FDA's Assessment

PK data in pediatric patients under 2 years of age are limited, which included 2 patients 1 year of age, and 1 patient 11 months of age whose exposures were within the range of other patients. It was thus not possible to empirically assess the potential ontogenic effect on apparent drug clearance. Tovorafenib is mainly eliminated via metabolism. Based on in vitro phenotyping study data and biotransformation pathway information determined from the human AME (absorption, metabolism and excretion) study, the contribution of CYP2C8 and aldehyde oxidase accounts for 49% and 23% of the metabolism, respectively. Published literature reports suggest maturation of these two enzymes beyond 6 months of age, with a plateau reached at around 1 to 2 years of age. While this cannot be confirmed with the current data, considering the unmet medical need for pLGG in infants aged between 6 months and 1 year of age for whom there is no approved therapy, BSA-based dosing is deemed reasonable in this age group. This approach, supported by data from pediatric patients aged 1 year or older, is expected to account for clearance difference due to body size and align exposure levels in infants aged between 6 months and 1 year of age with other pediatric patients. Close monitoring for safety is considered necessary to mitigate risk in this patient subgroup given the lack of clinical data.

19.4.1.4. Reviewer's Independent Analysis

The FDA's Assessment

None.

19.4.2. Exposure-Response Analysis

19.4.2.1. Exposure-Response (efficacy) Executive Summary

The FDA's Assessment

Although a single dose level (420 mg/m^2) not to exceed 600 mg was intended in FIREFLY-1, the actual doses in the study ranged from 290 to 476 mg/m^2 due to dosing variability and the maximum dose limit. Lack of positive E-R relationships for ORR based on RAPNO-LGG, RANO-LGG or RAPNO-LGG was observed among all evaluated exposure metrics (e.g., first-cycle exposure and time-averaged exposure), which supports that a 10% reduction from 420 mg/m^2 dose is unlikely to compromise efficacy. Leveraging the E-R relationship of efficacy and safety together with other evidence (see 6.3.2.2), FDA recommends 380 mg/m^2 QW (not to exceed 600 mg).

19.4.2.2. Exposure-Response (efficacy) Assessment Summary

Applicant's Position

Exposure-efficacy analysis using data from Arm 1 of FIREFLY-1 study was performed to evaluate the relationship between tovorafenib exposure and efficacy endpoints (ie, tumor response and tumor size). Tumor response was assessed by an IRC based on the RANO-HGG criteria and tumor size was assessed by the SPPD at each visit. The key findings of these analyses include:

Table 69.

General Information		
Goal of ER analysis		*To provide E-R relationship analysis that characterizes exposure-efficacy relationships in patients in Arm 1 of Study FIREFLY-1 for the following efficacy endpoints:* • *Tumor response (RANO-HGG by IRC)* • *Tumor size (SPPD)*
Study Included		*Arm 1 of FIREFLY-1 study*
Endpoints		• *Tumor response as assessed by IRC based on the RANO-HGG criteria (ie, complete and partial response [responder] versus stable disease, progressive disease, and not evaluable [non-responder]).* • *Tumor size time course data from each participant were modelled using either predicted tovorafenib concentration (Claret et al model) or steady-state tovorafenib exposure (C_{min}, C_{max}, and AUC; Wang et al model). In addition, simplified models based on the maximum or mean SPPD percent change from baseline for each patient were also explored.*
No. of Patients (total, and with individual PK)		*N = 69 (tumor response)* *N = 67 (tumor size – SPPD). Two subjects were excluded from the analysis as they had only baseline tumor size information.* *Individual PK was simulated using the final population PK model.*
Population Characteristics (Table 65)	General	***Tumor Response:*** *Age median: 8 years (range: 2 – 21 years)* *Weight median: 31.5 kg (range: 14.2 – 93.4 kg)* *N = 36 (52.2%) male* *N = 36 (52.2%) White; N = 33 (47.8%) Asian/Black/ other/unknown/multiple*
	Pediatrics	*N = 14 (20.3%) 2 - < 6 years* *N = 36 (52.2%) 6 - < 12 years* *N = 16 (23.2%) 12 - < 18 years*
		(b) (4)
Exposure Metrics Explored (range)		C_{min}, C_{max}, AUC_{ss}, *TAE*
Covariates Evaluated		*In the absence of a relationship between tumor response and exposure, no covariate analysis was performed.*
Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	***Exposure-Tumor Response: Logistic Regression***	Yes

	Development of a robust longitudinal model to characterize the change of tumor size over time was deemed unfeasible due to limited time-course data and large variability in the tumor size data.	
Model Parameter Estimates	Table 66	Yes
Model Evaluation	*Not applicable*	
Covariates and Clinical Relevance	*In the absence of a relationship between tumor response and exposure, no covariate analysis was performed.*	Yes
Simulation for Specific Population	*Not applicable*	
Visualization of E-R relationships	Table 67	Figure 11 illustrates additional E-R relationships for ORR based on RAPNO-LGG or RANO-LGG, and ORR by RAPNO-LGG with time-averaged exposure.
Overall Clinical Relevance for ER	*There was no statistically significant relationship in any of the models for all exposure metrics considered (ie, C_{min}, AUC_{ss}, TAE, and C_{max})*	Yes All E-R analysis showed clinically insignificant relationship.
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	Not applicable	"The exposure-response relationship for overall response rate based on RAPNO-LGG (Response Assessment in Pediatric Neuro-Oncology), and RANO-LGG (Response Assessment in Pediatric Neuro-Oncology) were not clinically significant over the dosage range of 290 to 476 mg/m^2 (0.76-1.25 times the approved recommended dosage)" was added to provide support for the recommended dosage in the labeling.

Table 70. Summary of Covariates for Tumor Response Data Analysis

Covariate	Overall (N=69)
Mutation	
BRAF FUSION: Other	8 (11.6%)
BRAF V600E Mutation	10 (14.5%)
KIAA1549:BRAF Fusion	51 (73.9%)
Mutation lumped	
BRAF FUSION: Other/KIAA1549:BRAF Fusion	59 (85.5%)
BRAF V600E Mutation	10 (14.5%)
Sex	
Female	33 (47.8%)
Male	36 (52.2%)
Weight (kg)	
Mean (SD)	36.4 (17.2)
Median [Min, Max]	31.5 [14.2, 93.4]
BSA (m^2)	
Mean (SD)	1.15 (0.342)
Median [Min, Max]	1.07 [0.630, 2.07]
Age (years)	
Mean (SD)	9.06 (4.08)
Median [Min, Max]	8.00 [2.00, 21.0]
Age category	
Children (2 to <6 years)	14 (20.3%)
Children (6 to <12 Years)	36 (52.2%)
Adolescent (12 to <18 years)	16 (23.2%)
Adult (≥18 years)	3 (4.3%)
Age category lumped	
Children (2 to <6 years)	14 (20.3%)
Children (6 to <12 Years)	36 (52.2%)
Adolescent and adult (≥12 years)	19 (27.5%)
Race	
Asian	4 (5.8%)
Black/African American	2 (2.9%)
Other/Unknown/Multiple	27 (39.1%)
White	36 (52.2%)
Race lumped	
Asian, Black, and Other/Unknown/Multiple	33 (47.8%)
White	36 (52.2%)

Abbreviations: BRAF=v-raf murine sarcoma viral oncogene homolog B; BSA=body surface area; max=maximum; min=minimum; N=number of subjects; SD=standard deviation.

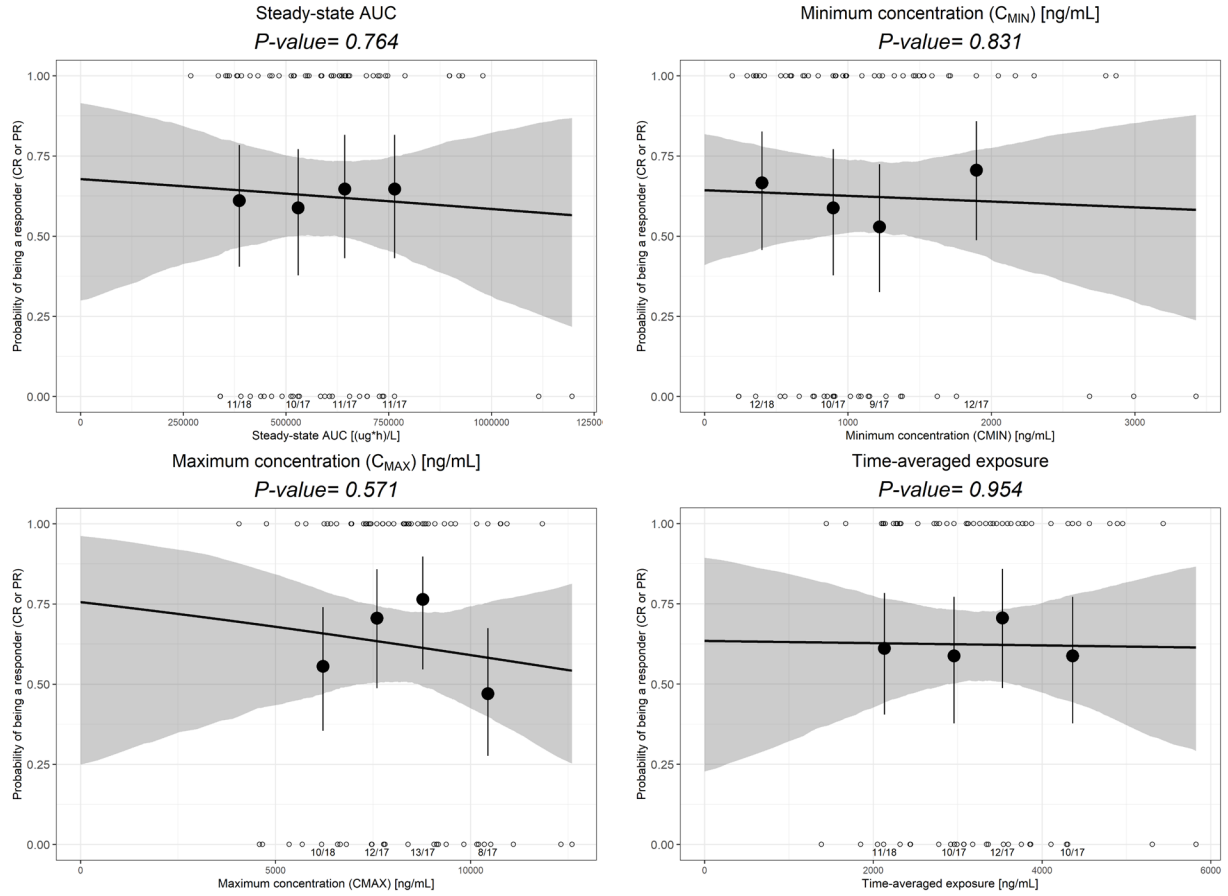
Table 71. Summary of Logistic Regression Model Outcome by Exposure Metrics

Exposure Metric	Slope (%RSE)	95% CI for Slope	P-Value	Log-Likelihood	AIC	Number of Subjects
AUC_{ss} [(µg•h)/L]	-4.02e-07 (332)	(-3.06e-06, 2.27e-06)	0.764	-45.7	95.3	69
C_{min} [ng/mL]	-7.52e-05 (469)	(-0.00077, 0.00064)	0.831	-45.7	95.4	69
C_{max} [ng/mL]	-7.63e-05 (177)	(-0.000348, 0.000189)	0.571	-45.6	95.1	69
TAE [ng/mL]	-1.5e-05 (1730)	(-0.000524, 0.000501)	0.954	-45.7	95.4	69

Notes: The p-value is an ANOVA test comparing the logistic regression fit against the null that probability is independent of exposures based on the likelihood ratio test.

Abbreviations: %RSE = percent relative standard error; AIC = Akaike information criterion; ANOVA = analysis of variance; AUC_{ss} = steady-state area under the plasma concentration-time curve; CI = confidence interval; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; TAE = time-averaged exposure.

Figure 24. Probability of Response Stratified by Exposure Metrics



Notes: Open circles at y = 0 represent non-responders, and open circles at y = 1 represent responders. Subjects are stratified into exposure quartiles. Black circles are the observed proportions of responders per exposure quartile, also shown as numerical values above the x-axis. Black vertical lines are the 95% CI of the probability of being a responder. Black curved lines are the linear logistic regression fit, and the gray shaded region represents the corresponding 95% CI. The numbers above the x-axis represent the number of responders out of the total number of subjects within each exposure quartiles. The p-value is an ANOVA test comparing the logistic regression fit against the null that probability is independent of exposures based on the likelihood ratio test.

Abbreviations: ANOVA = analysis of variance; AUC = area under the plasma concentration-time curve; C_{MIN} = minimum concentration; C_{MAX} = maximum concentration; TAE = time-averaged exposure; CI = confidence interval; CR = complete response; PR = partial response.

19.4.2.3. Exposure-Response (safety) Executive Summary

The FDA's Assessment

The E-R analysis for safety included dosages ranging from 20 BID to 800 mg QW. The positive E-R relationships were noted for TEAEs (i.e., Gr2+ TEAE, Gr3+ TEAE) and some of the commonly occurring AEs (i.e., skin rash, CPK elevation, ALT elevation, and eye events) with a steeper slope in the pediatric subgroup. Analysis with respect to impact on growth was requested for the clinical significance in the intended patient population, which suggested a partial restoration of growth with a dose reduction, based on PK-PD modeling and simulation. Leveraging the E-R

relationships for efficacy and safety together with other evidence (see Section 6.3.2.2), FDA recommends 380 mg/m^2 QW (not to exceed 600 mg).

19.4.2.4. Exposure-Response (safety) Assessment Summary

Applicant's Position

Exposure-safety analyses were performed using data from Studies C28001 and FIREFLY-1 to evaluate the relationship between tovorafenib exposure and safety endpoints that included both categorical variables (NCI-CTCAE): fatigue, skin rash, anemia, myalgia, nausea and/or vomiting, elevated ALT, elevated AST, elevated bilirubin, and elevated CPK) and longitudinal safety biomarkers (hemoglobin, ALT, AST, CPK). Study (b) (4) 205140 was also included for longitudinal safety biomarkers. The key findings of these analyses include:

Exposure-Adverse Events

- Logistic regression analysis identified statistically significant positive correlations between minimum plasma concentration (C_{min}) and reporting of the following AEs: Grade ≥ 2 or Grade ≥ 3 skin rash, Grade ≥ 2 elevated ALT, Grade ≥ 2 or Grade ≥ 3 elevated AST, and Grade ≥ 2 fatigue. Positive correlations were also noted between TAE and reporting of the following AEs: Grade ≥ 2 anemia, Grade ≥ 2 or Grade ≥ 3 elevated CPK, and Grade ≥ 2 myalgia. Higher C_{min} or TAE was associated with higher probability of these AEs being reported.
- No exposure-safety relationships were observed between tovorafenib exposure (maximum plasma concentration [C_{max}], C_{min}, AUC and TAE) and the following reported AEs: elevated blood bilirubin (Grade ≥ 2 or Grade ≥ 3), Grade ≥ 2 nausea and/or vomiting, Grade ≥ 3 anemia, or Grade ≥ 3 fatigue.

Pharmacokinetics-Safety Biomarker

- Separate PK/PD models demonstrated a positive correlation between tovorafenib concentration and AST and CPK. There was a negative correlation between tovorafenib concentration and hemoglobin. No relationship was observed between tovorafenib concentration and ALT.

Table 72.

General Information	
Goal of ER analysis	*To provide E-R relationship analysis characterizing exposure/PK-safety relationships*
Study Included	*Study FIREFLY-1 and Study C28001 (and (b) (4) 205140 for longitudinal safety biomarkers)*
Population Included	*Adult and pediatric patients with cancer; healthy adult subjects were included for longitudinal safety biomarkers*
Endpoint	***Adverse events grouped by CTCAE grades**: fatigue; skin rash; anemia; myalgia; nausea and/or vomiting; ALT elevation; AST elevation; bilirubin elevation; CPK elevation* ***Longitudinal safety biomarkers**: hemoglobin, ALT, AST, CPK*

No. of Patients (total, and with individual PK)		*A total of 287 subjects had available CTCAE graded AE data, of which 263 subjects had corresponding tovorafenib PK exposure data available. A total of 275 subjects had available hemoglobin, AST, and ALT data. A total of 220 subjects had available CPK data.*
Population Characteristics (,)	General	*-Age: median: 17.0 years (range: 1 – 94 years)* *-Weight: median: 59.3 kg (range: 9.20 – 186 kg)* *-n = 141 (53.6%) male* *-n = 196 (74.5%) White; n = 8 (3.0%) Black; n = 11 (4.2%) Asian; n = 3 (1.1%) multiple; n = 9 (3.4%) other; n = 36 (13.7%) unknown*
	Organ impairment	*Refer to population PK analysis for overall number of patients with organ impairment.*
	Pediatrics	*N=3 (1.1%) 1 month - <2 years* *N=27 (10.3%) 2 - <6 years* *N=66 (25.1%) 6 - <12 years* *N=36 (13.7 %) 12 - <18 years*
	Geriatrics	*Not applicable*
[redacted]		(b) (4)
Exposure Metrics Explored		*C_{min}, C_{max}, AUC_{ss}, and TAE*
Covariates Evaluated		*If a statistically significant E-R safety relationship was identified, then potential covariates listed in Table 74 were further investigated*

Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	*Exposure: Grade ≥ 3 skin rash model is provided as an example of an AE of particular clinical interest. Logistic regression describes the relationship between C_{min} and probability of reporting Grade ≥ 3 skin rash*	Yes
Model Parameter Estimates	Table 75 (*Grade ≥ 3 skin rash)*	Parameter estimates of univariate E-R analysis for 9 AEs was supplied by Reviewer (Table 77).
Model Evaluation	*Numerical predictive check of the exposure-skin rash final models was used. For all quartiles of exposure, the observed rate of Grade ≥ 3 skin rash was contained within the 95% CI of the model-predicted rate, showing good agreement between the observed and predicted rates.*	Yes
Covariates and Clinical Relevance	*No covariates were selected in the C_{min}-Grade ≥ 3 skin rash model.*	Yes
Simulation for Specific Population	*Not applicable*	
Visualization of E-R relationships	*Figure 25*	Figure 12, Figure 13, Figure 26 illustrate additional E-R relationships for Gr ≥ 2 or Gr ≥ 3 AEs comprised of the 9 commonly occurring AEs, Gr ≥

		2 or Gr ≥ 3 TEAEs, Gr ≥ 2 skin rash, Gr ≥ 2 CPK/ALT abnormality, Gr ≥ 1 eye events.
Overall Clinical Relevance for ER	(b) (4)	Gr ≥ 2 or Gr ≥ 3 TEAEs, AESI including Gr ≥ 2 skin rash, Gr ≥ 2 CPK/ALT abnormality, Gr ≥ 1 eye events, showed a positive trend with exposures on the linear range of the curve and a steeper slope in pediatric subgroup. Based on the identified ER relationship for safety endpoints, (b) (4) (see 19.4.2.5 for details).
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	Not applicable.	E-R for adverse reactions that are clinically significant was added to the labeling. "Tovorafenib exposure is associated with reduction in height-for-age z-scores in pediatric patients. Reduced height-for-age risk persists during treatment with tovorafenib." "Higher tovorafenib exposure is associated with increased risk of skin rash and, elevated liver enzymes (AST and ALT), and elevated creatinine phosphokinase."

Table 73. Summary of Baseline Continuous Covariates Stratified by Study

Covariate	Statistic	C28001 (N = 125)	FIREFLY-1 (N = 138)	Overall (N = 263)
Age (years)	Mean (SD)	63.4 (11.9)	9.26 (4.58)	35.0 (28.5)
	Median [Range]	65.0 [33.0, 94.0]	9.00 [1.00, 24.0]	17.0 [1.00, 94.0]
Weight (kg)	Mean (SD)	81.3 (20.1)	37.7 (18.8)	58.4 (29.2)
	Median [Range]	79.0 [42.5, 186]	32.9 [9.20, 98.3]	59.3 [9.20, 186]
Body surface area (m^2)	Mean (SD)	1.91 (0.245)	1.17 (0.387)	1.52 (0.496)
	Median [Range]	1.89 [1.38, 2.92]	1.12 [0.440, 2.19]	1.63 [0.440, 2.92]
	Missing	1 (0.8%)	0 (0%)	1 (0.4%)

Covariate	Statistic	C28001 (N = 125)	FIREFLY-1 (N = 138)	Overall (N = 263)
ALT (U/L)	Mean (SD)	31.8 (19.6)	23.7 (15.7)	27.6 (18.1)
	Median [Range]	27.0 [7.00, 127]	20.0 [5.00, 102]	22.0 [5.00, 127]
AST (U/L)	Mean (SD)	30.5 (18.3)	29.4 (10.1)	29.9 (14.6)
	Median [Range]	25.0 [8.00, 123]	28.0 [7.00, 80.0]	27.0 [7.00, 123]
	Missing	0 (0%)	1 (0.7%)	1 (0.4%)
Albumin (g/L)	Mean (SD)	36.8 (4.95)	42.0 (5.08)	39.5 (5.63)
	Median [Range]	37.0 [26.0, 49.0]	42.0 [13.0, 56.0]	40.0 [13.0, 56.0]
ALP (U/L)	Mean (SD)	131 (97.1)	205 (92.4)	170 (102)
	Median [Range]	96.0 [39.0, 689]	198 [54.0, 715]	146 [39.0, 715]
Bilirubin (µmol/L)	Mean (SD)	9.92 (5.20)	6.40 (3.83)	8.07 (4.86)
	Median [Range]	8.55 [3.00, 30.8]	5.13 [1.71, 25.7]	6.84 [1.71, 30.8]
Serum creatinine (µmol/L)	Mean (SD)	80.9 (25.8)	40.6 (15.1)	59.8 (29.0)
	Median [Range]	78.0 [26.5, 168]	38.0 [8.84, 92.8]	55.7 [8.84, 168]
Creatinine clearance (mL/min)	Mean (SD)	95.7 (40.0)	139 (52.4)	118 (51.6)
	Median [Range]	88.8 [25.2, 252]	127 [52.1, 368]	111 [25.2, 368]
eGFR (mL/min/1.73 m^2)	Mean (SD)	87.7 (31.6)	132 (40.1)	111 (42.4)
	Median [Range]	81.9 [35.7, 240]	126 [67.8, 375]	106 [35.7, 375]

Note: eGFR was calculated using the Modification of Diet in Renal Disease equation for adults. In pediatrics, eGFR was calculated using the Schwartz "bedside" equation.

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; N = number of subjects; SD = standard deviation.

Table 74. Summary of Baseline Categorical Covariates Stratified by Study

Covariate	Value	C28001 (N = 125)	FIREFLY-1 (N = 138)	Overall (N = 263)
Age category	Neonates (< 1 month)	0 (0%)	0 (0%)	0 (0%)
	Infants (1 month to < 2 years)	0 (0%)	3 (2.2%)	3 (1.1%)
	Children (2 to <6 years)	0 (0%)	27 (19.6%)	27 (10.3%)
	Children (6 to <12 years)	0 (0%)	66 (47.8%)	66 (25.1%)
	Adolescents (12 to <18 years)	0 (0%)	36 (26.1%)	36 (13.7%)
	Adult (≥ 18 years)	125 (100%)	6 (4.3%)	131 (49.8%)
Sex	Male	68 (54.4%)	73 (52.9%)	141 (53.6%)
	Female	57 (45.6%)	65 (47.1%)	122 (46.4%)
Race	White	117 (93.6%)	79 (57.2%)	196 (74.5%)
	Black	5 (4.0%)	3 (2.2%)	8 (3.0%)
	Asian	1 (0.8%)	10 (7.2%)	11 (4.2%)
	Multiple	0 (0%)	3 (2.2%)	3 (1.1%)
	Other	1 (0.8%)	8 (5.8%)	9 (3.4%)
	Unknown	1 (0.8%)	35 (25.4%)	36 (13.7%)
Ethnicity	Not Hispanic	94 (75.2%)	98 (71.0%)	192 (73.0%)
	Hispanic	15 (12.0%)	5 (3.6%)	20 (7.6%)
	Unknown	16 (12.8%)	35 (25.4%)	51 (19.4%)
Disease type	Relapsed or refractory solid tumors	68 (54.4%)	0 (0%)	68 (25.9%)
	Metastatic melanoma	57 (45.6%)	0 (0%)	57 (21.7%)
	Low-grade glioma	0 (0%)	135 (97.8%)	135 (51.3%)

Covariate	Value	C28001 (N = 125)	FIREFLY-1 (N = 138)	Overall (N = 263)
	Advanced solid tumors	0 (0%)	3 (2.2%)	3 (1.1%)
Prior lines of systemic therapy	One	18 (14.4%)	31 (22.5%)	49 (18.6%)
	Two	19 (15.2%)	32 (23.2%)	51 (19.4%)
	Three	11 (8.8%)	34 (24.6%)	45 (17.1%)
	Four and above	21 (16.8%)	40 (29.0%)	61 (23.2%)
	Unknown	56 (44.8%)	1 (0.7%)	57 (21.7%)

Abbreviations: N=number of subjects.

Table 75. List of Potential E/R Safety Covariates

Covariates	Rationale
PK-safety biomarker	
Regimen	Standard covariate
Disease type	Specific covariate of interest
Sex	Standard covariate
Baseline body weight	Standard covariate
Age	Standard covariate
Race	Standard covariate
PK AE	
Regimen	Standard covariate
Disease type	Specific covariate of interest
Sex	Standard covariate
Baseline body weight	Standard covariate
Age	Standard covariate
Race	Standard covariate
Prior lines of therapy	Specific covariate of interest

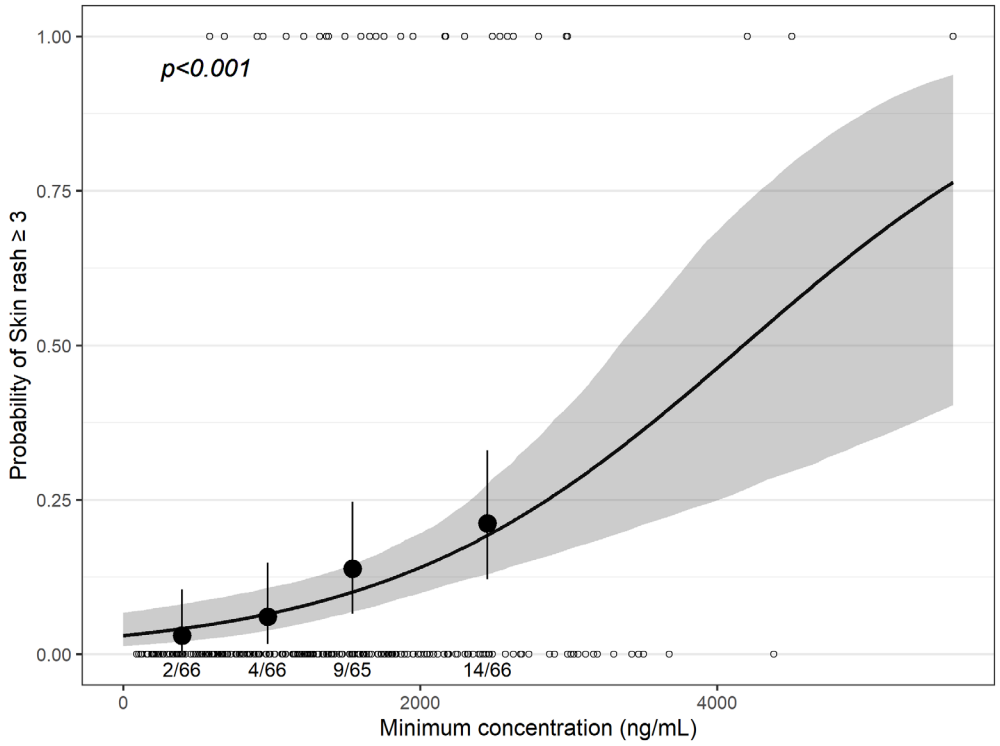
Abbreviations: AE = adverse event; E/R = exposure/response; PK = pharmacokinetic.

Table 76. Parameter Estimates of Exposure - Grade ≥3 Skin Rash Final Models

Grade	Parameter	Parameter Estimate (%RSE)	95% CI
Grade ≥3	Intercept	-3.47 (12.6)	-4.4, -2.67
	Slope of C_{min} (ng/mL)	0.000831 (24.4)	0.000444, 0.00125

Abbreviations: %RSE = percent relative standard error; CI = confidence interval; C_{min} = minimum plasma concentration.

Figure 25. Probability of CTCAE Grade ≥3 Skin Rash Versus Tovorafenib Exposure (Cmin)



Abbreviations: CI = confidence interval; C_{min} = minimum plasma concentration; CTCAE = Common Terminology Criteria for Adverse Events

Notes: Open circles at y = 0 represent subjects without adverse events, and open circles at y = 1 represent subjects with adverse events. Black circles are the observed proportions of adverse events per exposure quartile. Black vertical lines are the 95% CI of the rate of adverse events. The black curved line is the linear logistic regression fit, and the gray shaded region represents the corresponding 95% CI. The numbers above the x-axis represent the number of subjects with adverse events out of the total number of subjects within each exposure quartiles for each age group.

The FDA's Assessment

FDA agrees with the E-R analysis conducted by the Applicant.

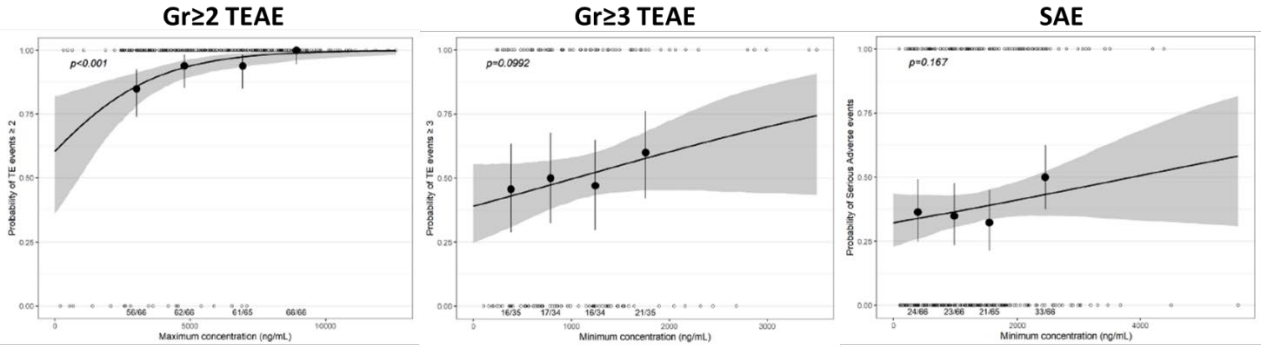
19.4.2.5. ER Review Issues

The FDA's Assessment

FDA considers that the board impact of commonly occurring AEs associated with drug exposure was underrepresented by just exhibiting E-R plot for Gr≥3 skin rash. Statistically significant positive correlations between Cmin,ss or TAE (time-averaged exposure) and the following AEs were identified: Gr≥2 or ≥3 skin rash, Gr≥2 elevated ALT, Gr≥2 or ≥3 elevated AST, Gr≥2 fatigue, Gr≥2 anemia, Gr≥2 or ≥3 CPK, Gr≥2 myalgia, Gr≥1 eye events, Gr≥2 TEAE, and Gr≥3 TEAE. Importantly, age was identified as a significant covariate in E-R models for Gr≥2 skin rash, ALT, and CPK, where younger age was associated with greater odds of these AEs. Additional E-R plots were also included in this review (Figure 12, Figure 13, Figure 26), which indicated that a

modest concentration reduction could improve overall safety. Given the recommended dose of 380 mg/m^2 represents a 10% reduction from (b) (4) 420 mg/m^2, the odds ratio for a reduction of 10% of median exposure was provided for the 9 commonly occurring AEs (Table 77). These odds ratios range from 0.68 to 0.85, indicating a 15% to 32% reduction in odds of experiencing these AEs.

Figure 26. Applicant: Probability of Gr≥2 TEAE, Gr≥3 TEAE, or SAE Versus Steady-State Exposure



Source: Applicant-provided figure.

Abbreviations: SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Additional E-R analysis was requested by FDA to explore a potential benefit in mitigating impact on growth velocity reported in 13% of pediatric patients with growth retardation, growth disorder, and growth failure according to preferred terms in CTCAE. The Applicant developed a PK/PD model that described a consistent and sustained reduction in height-for-age z-scores in pediatric patients while on treatment. Sex and age were identified as significant covariates. This model was applied to evaluate the potential benefit for dosage reduction, and treatment discontinuation on restoration of growth velocity (b) (4) . A dosage of 380 mg/m^2 QW may provide benefit in mitigating the impact on growth in pediatric patients undergoing prolonged treatment, and a dose reduction at the beginning of treatment is likely a more effective strategy compared to modifying the dose in response to significant adverse reactions.

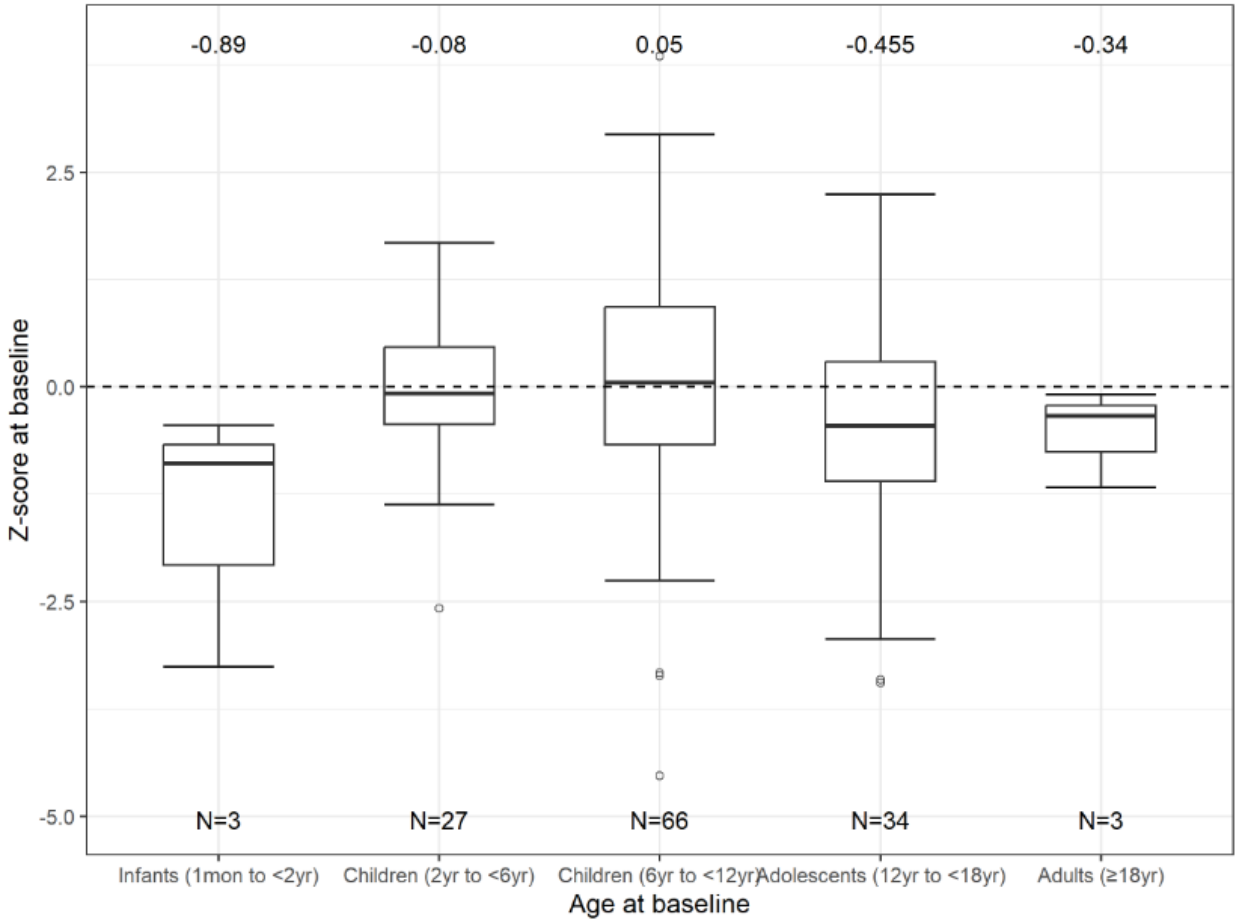
Height-for-Age Z-score PK/PD Model

The z-score PK/PD model was developed by data from 133 patients in FIREFLY-1. This includes 87% and 50% of patients treated for ≥6 months and ≥1 year, respectively. The z-score at baseline mainly distributed around 0 for 5 age subgroups (Figure 27) and showed an age dependent maximum change in z-score where a younger age is associated with a greater reduction (Figure 28).

The z-score was adjusted by adding 10 to ensure all positive values. The adjusted z-score was described by an indirect response model where drug concentration produces an inhibitory

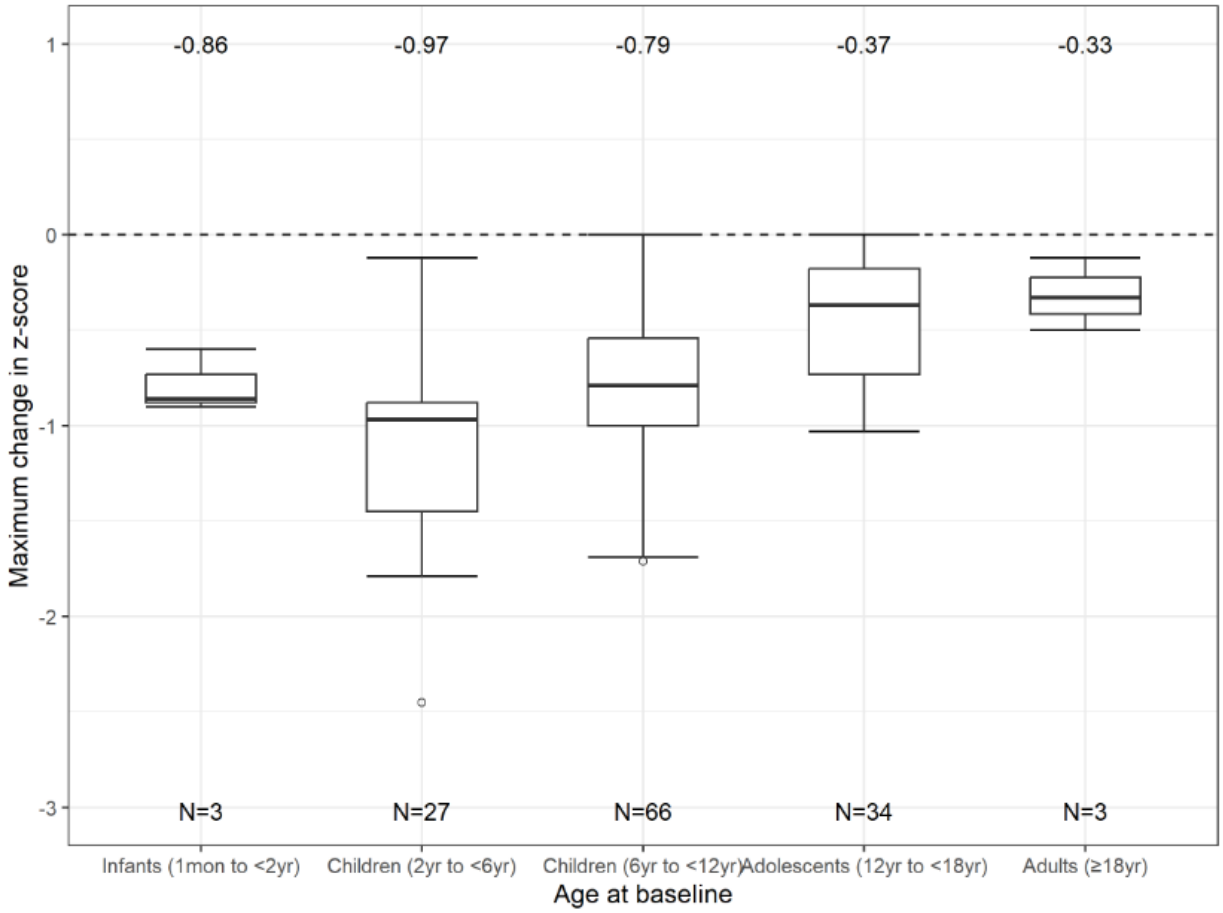
effect on Kin (Table 76). Age and sex were identified as significant covariates that impact drug effect on growth. The model suggests that with a younger age and male sex are associated with a larger decline in z-scores, which is likely attributed to the natural growth trajectory that slows down with age and an early onset of puberty in females. Due to the lack of placebo group, the effect on growth due to natural cause or drug effect could not be differentiated. Based on the goodness-of-fit and VPC plot, the final model described the z-score change over time in the whole population and the central tendency in different age groups reasonably well (Figure 29, Figure 30).

Figure 27. Applicant: Baseline Height-for-Age Z-score by Age Group.



Source: Applicant-provided figure.

Figure 28:Applicant: Maximum Change in Height-for-Age Z-score by Age Group



Source: Applicant-provided figure.

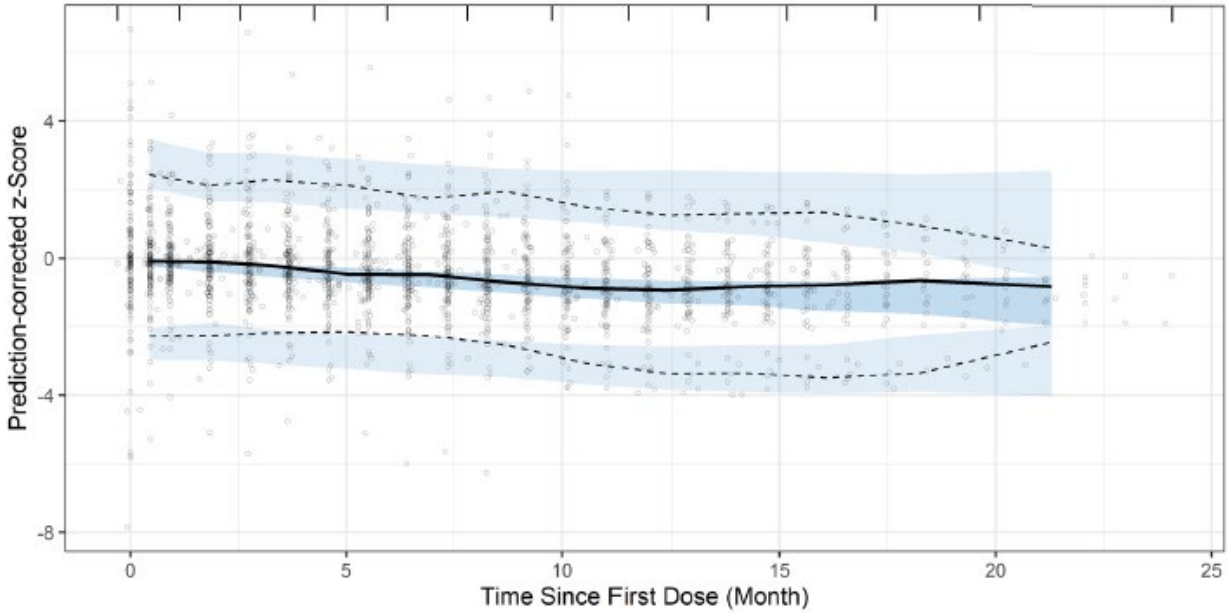
Table 77. Final Model Parameter Estimates for Z-score PK/PD Model

	Estimates	%RSE	95% CI	Shrinkage (%)
Parameters				
BASE*	9.93	1.5	9.638 – 10.222	
Kout (1/1000, hr^{-1})	0.0227	18.4	0.015 – 0.031	
Kd (1/1000)	0.129	14.3	0.093 – 0.165	
AGE on BASE	-0.0565	44.2	-0.106 – -0.007	
AGE on Kd	-0.639	17.1	-0.853 – -0.425	
FEMALE SEX on Kd	-0.278	24.4	-0.411 – -0.145	
Random effects	**Estimates**	**%RSE**	**95 % CI**	**Shrinkage (%)**
IIV on BASE	0.0199	18.7	0.013 – 0.027	0.1
IIV on Kout	0.317	18.3	0.203 – 0.431	10
Residual error	**Estimates**	**%RSE**	**95%CI**	**Shrinkage (%)**
Additive error	0.111	5.6	0.099 – 0.123	6.2

*BASE stands for baseline adjusted z-score (raw z-score+10). Kd: slope of drug effect by drug concentrations. Kout: rate constant for first order reduction in z-score. Kin= BASE*Kout.

Abbreviations: CI = confidence interval; PK/PD = pharmacokinetic/pharmacodynamic; RSE = relative standard error.

Figure 29. Applicant: Prediction-Corrected Visual Predictive Check for the Z-score PK/PD Model

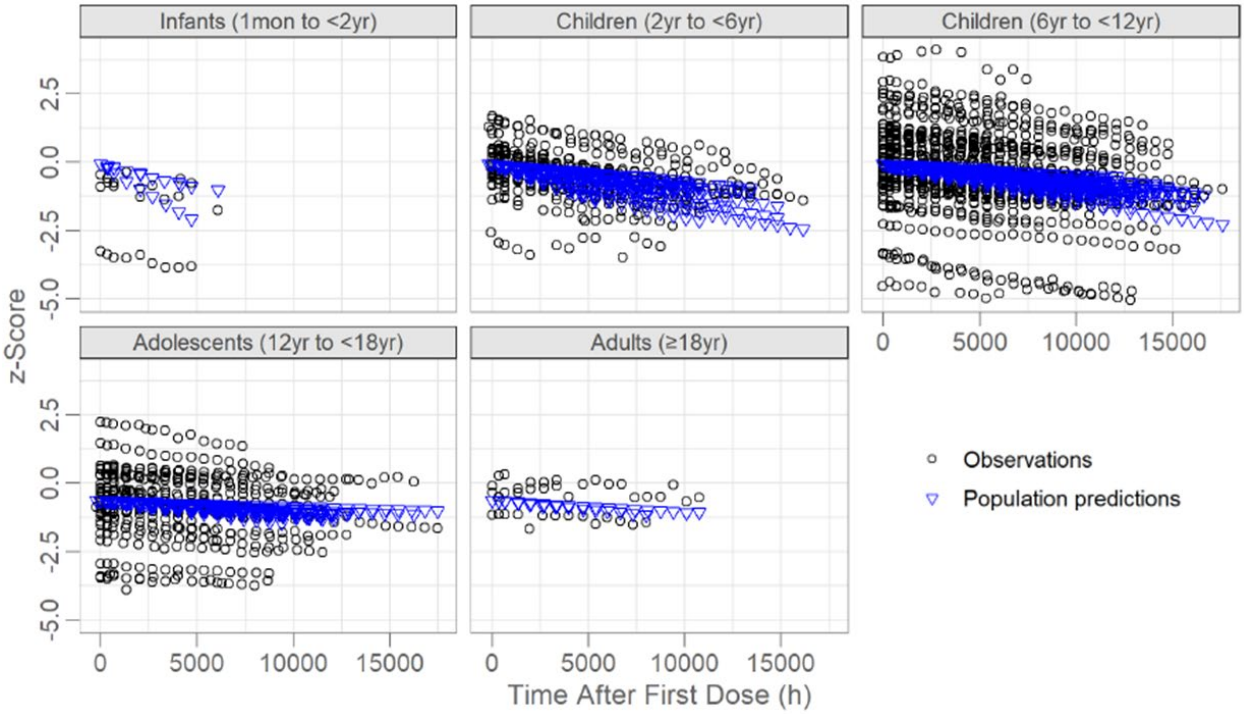


Source: Applicant-provided figure.

Dark blue: 90% CI around the median of the simulations. Light blue: 90% CI around the P5 and P95 of the simulations. Dotted lines: P5 and P95 of the observations. Black lines: median of observations.

Abbreviations: PK/PD = pharmacokinetic/pharmacodynamic.

Figure 30. Applicant: Observed and Model Predicted Z-score Versus Time Profile by Age Group



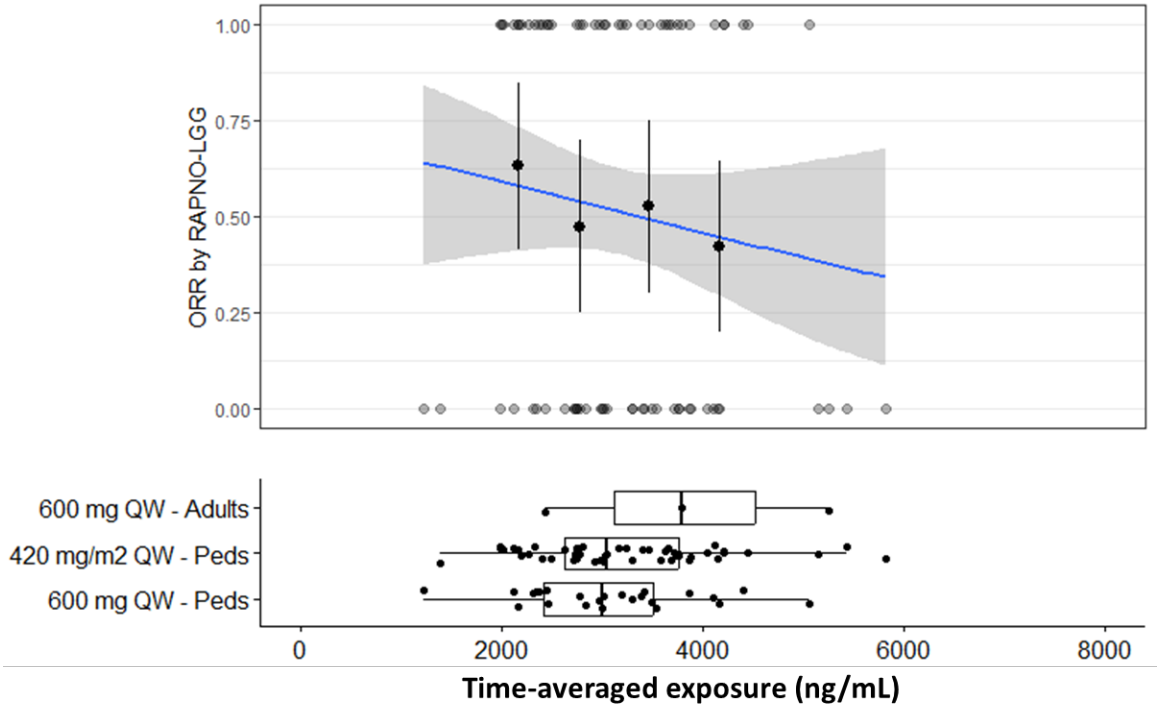
Source: Applicant-provided figure.

19.4.2.6. Reviewer's Independent Analysis

The FDA's Assessment

The following figure and table were generated by the reviewer to further evaluate E-R relationships for efficacy and safety.

Figure 31. E-R Relationship for ORR Based on RAPNO-LGG for Actual Doses Ranging From 290 to 476 mg/m2



Source: Reviewer-generated figure.
Abbreviations: E-R = exposure-response; ORR = overall response rate; QW = once weekly.

Table 78. Odds Ratio for a Reduction of 10% Median Values of Exposure Based on Univariate Logistic Regression Between Exposure Metric and AE

AE	Exposure Metric	TAE (ng/mL)	First week TAE (ng/mL)	First cycle TAE (ng/mL)	AUCss (mg•h/L)	Weekly AUCss (mg•h/L)	Cmin (ng/mL)	Cmax (ng/mL)	DOSE (mg/m2)
Skin Rash	Gr ≥2	**0.83*** **	0.83***	0.87***	0.92**	0.84***	0.96**	0.87***	0.82**
	Gr ≥3	0.82**	0.84**	0.95	0.94	0.82***	**0.92*** **	0.91	0.84
Elevated ALT	Gr ≥2	0.71**	0.75*	0.82	0.83*	**0.73***	0.91*	0.81	0.73
	Gr ≥3	0.68*	0.66*	0.81	**0.69** **	0.68**	0.93	0.68*	0.37
Elevated AST	Gr ≥2	0.84	0.83	0.92	0.93	0.80*	**0.92** **	0.89	0.75
	Gr ≥3	0.86	0.87	0.89	0.99	0.79*	**0.88*** **	0.98	0.83
Anemia	Gr ≥2	**0.85*** **	0.88**	0.87***	0.93*	0.89**	0.98	0.90*	0.79**
	Gr ≥3	0.92	0.97	0.94	1.00	0.95	0.97	1.00	**0.82**
Elevated CPK	Gr ≥2	**0.79*** **	0.81***	0.82***	0.87***	0.85***	1.00	0.80***	0.74**
	Gr ≥3	**0.85***	0.86	0.88	0.90	0.90	1.00	0.87	0.80
Nausea & vomiting	Gr ≥2	0.95	0.94	1.00	**0.95**	0.97	1.01	0.95	0.95
	Gr ≥3	0.75	**0.66***	0.79	0.83	0.84	1.06	0.67	0.60
Fatigue	Gr ≥2	1.00	1.01	1.03	1.04	0.99	**0.97***	1.03	0.96
	Gr ≥3	0.98	0.98	1.03	1.05	0.97	0.96	1.04	**0.76**

AE	Exposure Metric	TAE (ng/mL)	First week TAE (ng/mL)	First cycle TAE (ng/mL)	AUCss (mg•h/L)	Weekly AUCss (mg•h/L)	Cmin (ng/mL)	Cmax (ng/mL)	DOSE (mg/m2)
Myalgia	Gr ≥2	**0.82***	0.81	0.93	0.99	0.87	0.94	0.92	0.68

Source: Reviewer-generated figure.

Median values of TAE (time-averaged exposure), first week TAE, first cycle TAE, AUCss, weekly AUCss, Cmin,ss, Cmax,ss, first dose of FIREFLY-1 in the safety population are: 3116 ng/mL, 2977 ng/mL, 3111 ng/mL, 569 mg*h/L, 569 mg*h/L, 988 ng/mL, 7751 ng/mL, 415 mg/m^2.

*indicates statistical significance where *,**, *** correspond to $p<0.05$, $p<0.01$, $p<0.001$, respectively.

Bold font highlights the exposure metric that produces the lowest AIC among others in the univariate logistic regression for each AE.

Abbreviations: AE = adverse event; AUC = area under the curve; Cmin = minimum plasma concentration; Cmax = peak plasma concentration; TAE = time-averaged exposure.

19.4.2.7. Overall Benefit-Risk Evaluation Based on E-R Analyses

Applicant's Position

No apparent correlation was observed between tovorafenib plasma exposure metrics (ie, C_{min}, AUC_{ss}, C_{max} and TAE) and ORR (RANO-HGG by IRC). Of note, the exposure-ORR analysis was based on systemic plasma exposure. Tovorafenib concentration at the site of action (ie, CNS) in patients was not measured.

Several AEs (eg, skin rash and fatigue) and laboraory abnormalities (eg, decreased hemoglobin, increased AST, and CPK) were associated with tovorafenib plasma exposure (eg, C_{min}). (b) (4)

(b) (4) These results are consistent with the relatively low rate of dose interruptions or reductions and rare study discontinuations due to AEs in the registrational study FIREFLY-1.

The FDA's Assessment

(b) (4) FDA recommends a dosage of 380 mg/m^2 QW for the intended patient population based on the

totality of evidence including efficacy and safety data across actual dose range studied in FIREFLY-1, E-R relationships, and concerns for growth delay in pediatrics (b) (4) (refer to 6.3.2.2 and 19.4.2 for details).

19.4.3. Physiologically Based Pharmacokinetic Modeling Analyses

19.4.3.1. Executive Summary

The FDA's Assessment

The Division of Pharmacometrics has reviewed the PBPK reports (DOTT/1/A-B and DOTT/1/C) and related model summary reports, response to FDA PBPK information requests submitted on 19th December 2023 (seq0021), 25th January 2024 (seq0027), and 31st January 2024 (seq0031), and the modeling supporting files, and concluded that:

- The PBPK analyses are inadequate to predict the effects of CYP2C8 inhibitors or inducers on tovorafenib exposure and support the labeling language because the contribution of CYP2C8 in the model has not been verified using clinical data and cannot be determined from the results of human ADME and in vitro phenotyping studies.
- Tovorafenib was predicted to have weak inhibitory effect on the CYP2C9 substrate tolbutamide, but the predicted effects may be complicated by the potential induction effect of tovorafenib on CYP2C9.
- The magnitude of tovorafenib induction on the exposure of substrates of CYP3A4, CYP2B6, CYP1A2, and CYP2C8 cannot be confidently predicted due to the uncertainties about the induction parameters and methodology. For risk assessment, the simulation results indicate that:
  - Tovorafenib potentially has moderate to strong induction effects on CYP3A substrates in adult patients following oral administration of tovorafenib 600 mg QW.
  - Tovorafenib potentially has weak to moderate induction effects on CYP2C8 substrates in adult patients following oral administration of tovorafenib 600 mg QW.
  - Potential induction effects of tovorafenib on substrates of CYP2B6 and CYP1A2 cannot be ruled out.
- The predicted effects of tovorafenib on the exposure of transporter substrates are considered inadequate because of uncertainties about extrapolating the in vitro inhibition parameters to in vivo, the potential induction effects of tovorafenib, and inadequate verification of the PBPK models of transporter substrates.

19.4.3.2. PBPK Model Development and Verification

Drug's ADME Properties and DDI Potential

Tovorafenib is primarily metabolized by CYP2C8 and aldehyde oxidase (AO) in vitro. The relative contribution was 65%, 23%, 5.3%, 4.3%, and 2.9% for AO, CYP2C8, CYP2C9, CYP2C19, and CYP3A, respectively, based on the in vitro reaction phenotyping studies (Report RPT-01962).

The results from the human ADME study in healthy male adult subjects (DAY101-103), conducted with a single oral dose of 100 mg tovorafenib showed that approximately 95% of the dose administered orally was recovered, in which approximately 29% and 66% of the dose were recovered in the urine and the feces, respectively. Unchanged parent drug in feces represents approximately 8.6% of the dose, indicating that tovorafenib was well absorbed following oral administration of a single 100 mg dose. Approximately 0.15% of the dose was excreted as unchanged drug in the urine, indicating that renal elimination of tovorafenib was minimal. The apparent oral clearance was 1.7 L/h, and the geometric mean renal clearance of tovorafenib was 0.0025 L/h. Tovorafenib is the major circulating component in the plasma and accounted for approximately 79% of total plasma radioactivity exposure. The estimated geometric mean terminal half-life of tovorafenib was approximately 48 hours (DAY101-103).

Based on in vitro studies, tovorafenib is determined to be a reversible inhibitor of CYP3A4, CYP2C8, and CYP2C9 with IC50 values of 41, 7.8 and 47 μM, respectively, but not a time-dependent inhibitor of CYP enzymes (P-024-11-01 and DOT1-DMPK-004). Tovorafenib also inhibited UGT1A1, UGT1A3, UGT1A4, and UGT1A9 with IC50 values of 16, 41, 58, and 54 μM, respectively (DOT1-DMPK-009). Tovorafenib increased mRNA expression of CYP1A2, CYP2B6, CYP2C8, and CYP3A4 in a concentration-dependent manner (DOT1-DMPK-008). Tovorafenib is not a substrate of P-gp, BCRP (DOT-DMPK-012), and OATP1B1 and OATP1B3, (DOT1-DMPK-006), but is an inhibitor of BCRP, OATP1B1, OATP1B3, OAT1, OAT3, and MATE1 with IC50 values of 1.4, 10, 12, 14, 4.9, 5.9 μM, respectively (RPT-02116 and DOT1-DMPK-001). Clinical drug interaction studies with tovorafenib have not been conducted.

The objectives of the Applicant's physiologically based pharmacokinetic (PBPK) analyses are:

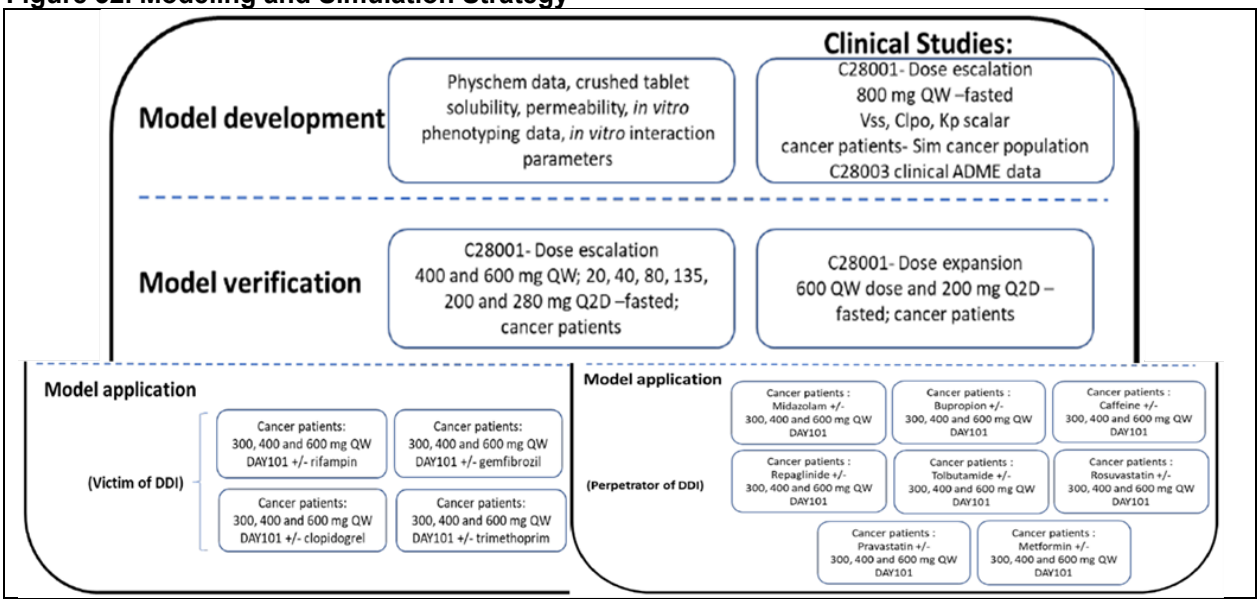
- Evaluate the drug-drug interaction (DDI) potential of tovorafenib as a victim of strong (gemfibrozil), moderate (clopidogrel), and weak (trimethoprim) CYP2C8 inhibitors and CYP2C8 inducer (rifampin) at 300, 400 and 600 mg of tovorafenib
- Evaluate the DDI potential of tovorafenib as a perpetrator of substrates of CYP3A4, CYP2B6, CYP1A2, CYP2C8 and CYP2C9, OATP1Bs, BCRP and MATE1

Applicant's PBPK Modeling and Simulations

All simulations were performed using the PK/PD Profiles mode in the Simcyp® Simulator (Version 20, Certara, Sheffield, UK) unless noted below. Simulations were performed using the default cancer population (sim-Cancer) model. Age, sex, subject number, and dosing regimens were consistent with the actual trial design. Ten trials were simulated for each simulation scenario. Schemes of the PBPK modeling and simulation strategy are shown in Figure 32, which summarizes the studies used for tovorafenib model development and verification, and model applications in predicting DDI of tovorafenib as a victim of CYP2C8 induction or inhibition and as a perpetrator of various transporters and enzymes. The final model input parameters were summarized in Table 78 and Table 79. (b) (4) The tovorafenib PBPK models consist of an Advanced Dissolution, Absorption and Metabolism (ADAM) model for describing drug absorption in each gut segment, a minimal PBPK model (method 1) for distribution, and an enzyme kinetics model for the victim

model and an in vivo clearance model for the perpetrator model. The Simcyp library files gemfibrozil, trimethoprim, rifampin (SV-Rifampicin-MD), caffeine, bupropion, repaglinide, tolbutamide, midazolam, rosuvastatin, pravastatin, and metformin were used without any modification. In addition, a clopidogrel research file (V21R1_RES_Clopidogrel) was used to simulate the effect of a moderate CYP2C8 inhibitor on tovorafenib. Simulations with clopidogrel were performed in Version 21 because the clopidogrel model is only available in this version. The ability of version 21 to reproduce the PK of multiple oral doses of 400, 600 and 800 mg tovorafenib QW in patients with relapsed or refractory solid tumors and 600 mg tovorafenib QW in patients with metastatic melanoma was confirmed.

Figure 32. Modeling and Simulation Strategy



Source: Figure 1 in the PBPK reports DOTT/1/A-B and DOTT/1/C.

Abbreviations: ADME = absorption, distribution, metabolism, excretion; DDI = drug-drug interaction; QW = once weekly; Q2D = once every 2 days.

Table 79. Final Input Parameters in the PBPK Model of Tovorafenib as a Victim

PARAMETER	Value	Reference
Physicochemical and Binding Parameters		
Molecular Weight (g/mol)	506.29	Investigator's Brochure Edition 7
Log P	3.63	Provided by Day One Biopharmaceuticals
Compound type	Neutral	Weak acid with pKa 9.63 - Investigator's Brochure Edition 7. Unionised at physiological pH, hence assumed as neutral
B:P	0.713	Average of blood:plasma concentration ratios range (0.647 to 0.779) observed in phase I mass balance study. Study DAY101-103 CSR
fu	0.025	Average of values measured at 1 and 10 µM using equilibrium dialysis from Report PD09-27
Main binding protein	HSA	Report DOT1-DMPK-003
Absorption model – ADAM model		
fu_{gut}	1	Assumed
Caco-2 P_{app} ($x10^{-6}$ cm/s)	43.6	Report PD09-24
Calibrator P_{app} ($x10^{-6}$ cm/s), Propranolol	19.23	Report PD09-24
Calibrator P_{app} ($x10^{-6}$ cm/s), Atenolol	0.25	Report PD09-24
$P_{eff,man}$ (pred) ($x10^{-4}$ cm/s)	8.51	Predicted using DAY101 P_{app}
fa	1	Predicted
F_G	1	Predicted
Formulation type	Immediate Release Tablet	Clinical Study C28001
Solubility data (mg/mL)	0.1549	IR formulation is (b) (4) (b) (4) Solubility of (b) (4) form

PARAMETER	Value	Reference
		taken from non-sink FaSSIF dissolution experiment of crushed tablet. Report PDCO - 05-EMEA002763-PIP-01-20 Response (b) (4)
Distribution model – minimal PBPK model		
V_{SS} (L/kg)	1.831	Predicted using Method I. Predicted V_{SS} value aligned with the V_z/F estimate from Population PK analysis of plasma PK data at 20 - 280 mg Q2D dose range (Report 2014-EORTC-MLN2480-PKPDAE)
K_p scalar	0.47	Optimised by parameter sensitivity analysis to recover observed plasma concentration-time profile at Day 1 and Day 22 following repeated 800 mg QW dosing of DAY101
Elimination parameters		
CL/F (L/h)	1.1	Optimised input value in retrograde calculations to recover Clinical Study C28001 average CL/F value of 1.8 L/h (20 mg Q2D – 800 mg QW) - produces CL/F of 1.74 L/h
fm_{CYP2C8}	(b) (4)	Calculated using phase I absorption, metabolism, and excretion study data (study DAY101-103 CSR addendum)
fm_{CYP2C9}		
$fm_{CYP2C19}$		
fm_{CYP3A4}		
CYP2C8 CL_{int} (µL/min/pmol)		Calculated using retrograde methodology
CYP2C9 CL_{int} (µL/min/pmol)		
CYP2C19 CL_{int} (µL/min/pmol)		
CYP3A4 CL_{int} (µL/min/pmol)		
HLM CL_{int} (µL/min/mg)	4.356	
fu_{inc}	1	Assumed
CL_R (L/h)	0	Assumed (See Section 3.3.2.1 for details)

Source: Table 9 in the PBPK report DOTT/1/C

Abbreviations: PBPK = physiologically based pharmacokinetic.

Table 80. Final Input Parameters in the PBPK Model of Tovorafenib as a Perpetrator*

PARAMETER	Value	Reference
Elimination parameters		
CL/F (L/h)	1.8	Clinical Study C28001
Interaction parameters		
CYP3A4 K_i (μM)	(b) (4)	Calculated from the IC_{50} values using Cheng-Prusoff equation (See Section 3.5 and Table 8 for details). Report P024-11-01
CYP2C8 K_i (μM)		
CYP2C9 K_i (μM)		
CYP2C19 K_i (μM)		
fu_{mic}		Report DOT1-DMPK-003
CYP1A2 Ind_{max}		Report DOT1-DMPK-008
CYP1A2 $IndC_{50}$ (μM)		Report DOT1-DMPK-008
fu_{inc}		Predicted, Report DOT1-DMPK-008
CYP3A4 Ind_{max}		Report DOT1-DMPK-008
Calibrated CYP3A4 Ind_{max}		Calibrated against positive control (rifampicin). Rifampicin Ind_{max} was 315 at 20 μM - Report DOT1-DMPK-008
CYP3A4 $IndC_{50}$ (μM)		Report DOT1-DMPK-008
fu_{inc}		Predicted, Report DOT1-DMPK-008
CYP2B6 Ind_{max}		Report DOT1-DMPK-008
CYP2B6 $IndC_{50}$ (μM)		Report DOT1-DMPK-008
fu_{inc}		Predicted, Report DOT1-DMPK-008
BCRP K_i (μM)		Calculated from the IC_{50} values and respective transporter probe substrate K_M values and tested concentrations using Cheng-Prusoff equation (See Section 3.5 and Table 9 for details). Report DOT1-DMPK-001 and Report RPT-02116
OATP1B1 K_i (μM)		
OATP1B3 K_i (μM)		
MATE1 K_i (μM)		
fu_{inc}		Assumed

Source: Table 10 in the PBPK report DOTT/1/A-B

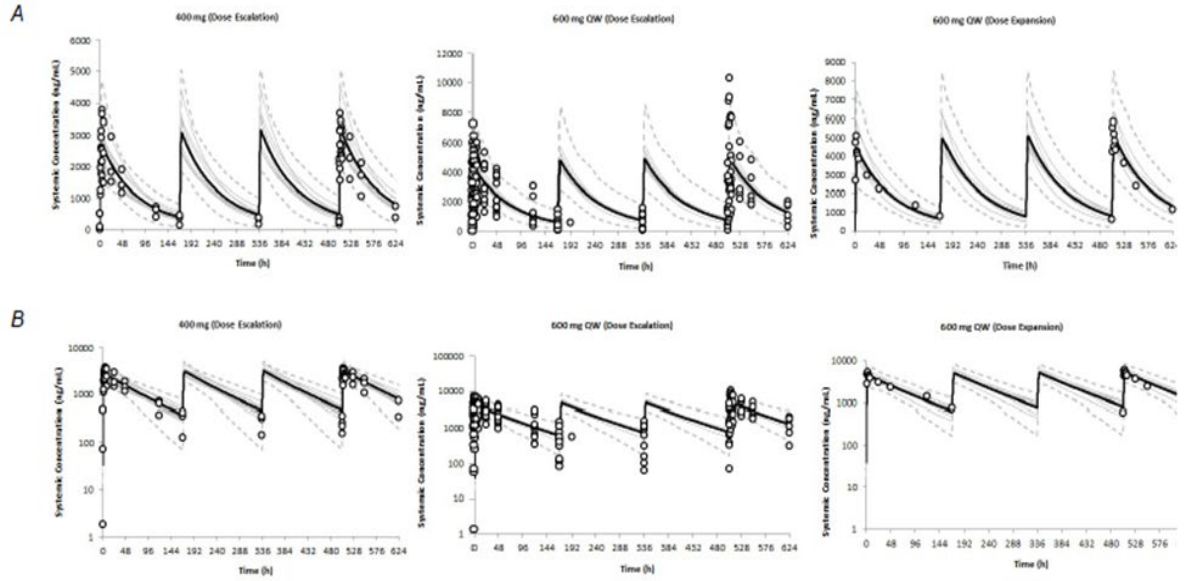
*Only parameters that are different from the victim models are shown. In addition, blood to plasma concentration ratio of (b) (4) and updated solubility data were used in the perpetrator model.

Abbreviations: AUC = area under the curve; GMR = geometric mean ratio; Ind_{max}, the maximum fold induction; $IndC_{50}$, the concentration that gives half maximal fold induction; Ki = inhibitory constant; PBPK = physiologically based pharmacokinetic.

Verification of the Tovorafenib PBPK Model to Simulate PK Profiles of Tovorafenib

Simulated and observed tovorafenib PK profiles and parameters are summarized by FDA reviewer in Figure 33, Figure 34, Table 80 and Table 81.

Figure 33. Simulated and Observed Mean Plasma Concentrations of Tovorafenib on Day 1 and Day 22 Following 400 Mg and 600 Mg Tovorafenib QW in Patients With Relapsed or Refractory Solid Tumors and Following 600 Mg Tovorafenib QW in Patients With Metastatic Melanoma



Source: Figure 9 in the PBPK report (DOTT/1/A-B)

Depicted are simulated (lines) and observed data (circles, Clinical Study C28001). The grey lines represent the mean values of simulated individual trials, the dashed grey lines represent the 5th and 95th percentiles and the solid black line the mean data for the simulated population (n = 10 x10). A. Linear scale; B. Log-linear scale

Abbreviations: QW = once weekly.

Table 81. Simulated and Observed PK Parameters* for Tovorafenib After the First and Multiple Oral Doses of 400 Mg and 600 Mg Tovorafenib QW for 28 Days in Patients With Relapsed or Refractory Solid Tumors (Dose Expansion Cohorts) and in Patients With Metastatic Melanoma (Dose Escalation Cohort)

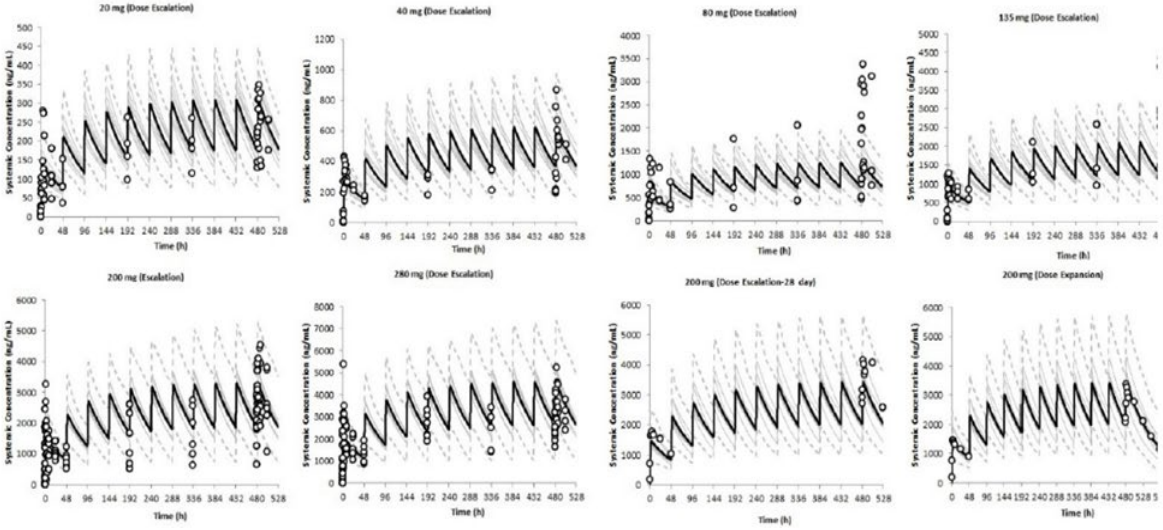
Dosing regimens	Trials	Day 1			Day 22		
		$AUC_{0\text{-}168}$ (h*ng/mL)	C_{max} (ng/mL)	T_{max}	AUC_{tau} (h*ng/mL)	C_{max} (ng/mL)	T_{max}
400 mg QW (Dos Escalation)	Simulated	187039	2557	3.55	223248	3045	3.50
	Observed	180261	2934	4.15	193033	3135	3.15
	S/O	1.04	0.86		1.16	0.97	
600 mg QW (Dose Escalation)	Simulated	290810	3950	4.30	345735	4682	4.25
	Observed	255085	4459	3.15	313087	4740	3.03
	S/O	1.14	0.89		1.10	0.99	
600 mg QW (Dose Expansion)	Simulated	304253	4097	4.25	363570	4881	4.15
	Observed	316984	5531	2.967	313087	4740	3.03
	S/O	0.96	0.74		1.16	1.03	

Source: Table 13 in the PBPK report (DOTT/1/A-B)

* Median values were reported for Tmax, others are geometric means.

Abbreviations: AUC = area under the curve; Cmax = peak plasma concentration; PK = pharmacokinetic; QW = once weekly; S/O = simulated/observed; Tmax = time to peak concentration.

Figure 34. Simulated and Observed Plasma Concentration-Time Profiles After Single and Multiple Oral Doses of Tovorafenib Q2D in Patients With Solid Tumors or Patients With Metastatic Melanoma



Source: Figure 10 in the PBPK report (DOTT/1/A-B)

Depicted are simulated (lines) and observed data (circles, Clinical Study C28001). The grey lines represent the mean values of simulated individual trials, the dashed grey lines represent the 5th and 95th percentiles and the solid black line the mean data for the simulated population (n = 10 x 10)

Abbreviations: Q2D = every 2 days.

Table 82. Simulated and Observed PK Parameters* for Tovorafenib After Single and Multiple Oral Doses of Tovorafenib Q2D in Patients With Solid Tumors

Dosing regimens	Trials	Day 1			Day 22		
		AUC_{0-48} (h*ng/mL)	C_{max} (ng/mL)	T_{max}	AUC_{tau} (h*ng/mL)	C_{max} (ng/mL)	T_{max}
20 mg Q2D (Dose escalation - 21 days)	Simulated	4740	130	2.07	10939	298	1.83
	Observed	4300	140	3.98	10450	302	2.00
	S/O	1.10	0.93		1.05	0.99	
40 mg Q2D (Dose escalation - 21 days)	Simulated	9345	255	2.10	22077	599	1.83
	Observed	11006	393	2.15	20861	760	3.05
	S/O	0.85	0.65		1.06	0.79	
80 mg Q2D (Dose escalation - 21 days)	Simulated	18668	509	2.20	44567	1205	1.95
	Observed	27879	922	2.03	42665	2039	4.05
	S/O	0.67	0.55		1.04	0.59	
135 mg Q2D (Dose escalation - 21 days)	Simulated	31018	845	2.45	74468	2009	2.20
	Observed	35280	1048	3.92	96807	3322	2.00
	S/O	0.88	0.81		0.77	0.61	
200 mg Q2D (Dose escalation - 21 days)	Simulated	50790	1411	2.80	115660	3171	3
	Observed	50094	1934	2.05	117968	3809	2.99
	S/O	0.99	0.73		0.98	0.83	
280 mg Q2D (Dose escalation - 21 days)	Simulated	69930	1940	3.15	161329	4402	2.88
	Observed	76059	2675		155051	4063	2.81
	S/O	0.92	0.73		1.04	1.08	
200 mg Q2D (Dose escalation - 28 days)	Simulated	50438	1373	2.75	121792	3271	2.55
	Observed	66501	2073	4.00	164401	4588	12.79
	S/O	0.76	0.66		0.74	0.71	
200 mg Q2D (Dose Expansion - 28 days)	Simulated	50871	1388		121907	3282	2.55
	Observed	51011	1607	3.11	121961	3549	2.19
	S/O	1.0	0.9		1.0	0.9	

Source: Tables 14-16 in the PBPK report (DOTT/1/A-B)

*Median values were reported for Tmax, others are geometric means.

Abbreviations: AUC = area under the curve; Cmax = peak plasma concentration; PK = pharmacokinetic; Q2D = every 2 days; S/O = simulated/observed; Tmax = time to peak concentration.

The FDA's Assessment

FDA agrees that the Applicant's PBPK model adequately describes the PK profiles of tovorafenib. Clinical PK data that had not been used in model development was used to verify the ability of the tovorafenib PBPK model to describe the PK profiles of tovorafenib. The model could reasonably well describe the plasma concentration-time profiles of tovorafenib following single and multiple oral doses of tovorafenib in patients with cancer. Majority of the model-estimated AUC and C_{max} were within 0.8- and 1.25-fold of the observed values.

19.4.3.3. PBPK Review Issues

19.4.3.3.1. Effects of CYP2C8 Perpetrators on the PK of Tovorafenib.

PBPK analysis was considered inadequate to predict the effects of CYP2C8 inhibitors and inducers on the PK of tovorafenib, because there is uncertainty about the contributions of AO and CYPs to the metabolism of tovorafenib due to the variability of AO activity in the human S9 system, the low turnover rate of tovorafenib, and the potentially overlapping substrate specificity of AO and CYPs. In addition, the contribution of CYP2C8 in the tovorafenib model was not verified using any clinical DDI data. Detailed discussions are as follows:

(b) (4)

1. (b) (4)

2. (b) (4)

3.

Taken together, the uncertainty about the contributions of AO and CYPs in the metabolism of tovorafenib precludes confidently predicting the DDI of tovorafenib as a victim.

19.4.3.3.2. Effects of Tovorafenib on Substrates of Various Cytochrome P450 Enzymes and Transporters

Limitations were identified when using Applicant's PBPK analyses to estimate the effects of tovorafenib on substrates of various cytochrome P450 enzymes and transporters.

Effects of Tovorafenib on the CYP3A Substrate Midazolam

Tovorafenib potentially has moderate to strong induction effects on CYP3A substrates following oral administration of tovorafenib 600 mg QW, but the magnitude of the effect cannot be confidently predicted for the reasons discussed below.

1. (b) (4)

2. [redacted] (b) (4)

Taken together, the interaction between tovorafenib and substrates of CYP3A cannot be ruled out and the predicted induction effect of tovorafenib on CYP3A substrates is inadequate to support dosing recommendation in the labeling.

Table 84. Simulated Effects of Tovorafenib on Midazolam Following Tovorafenib 600 mg QW for 50 Days

Scenario		Geometric Mean Ratio	
Simulated Effects on Midazolam	**Inhibition/Induction Parameters***	**AUC_{0-inf}**	**C_{max}**
CYP3A inhibition only	[redacted] (b) (4)		
CYP3A induction only			
CYP3A induction + inhibition			

Source: Tables 1 in the PBPK report (DOTT/1/A-B) and Table 4 in the response to FDA IR Clinical Pharmacology submitted 19 December 2023 (response-to-fda-ir-2023-11-17, seq0021)

* (b) (4) .

Abbreviations: AUC = area under the curve; (b) (4) .

Induction Effects of Tovorafenib on CYP2B6

The PBPK analysis of the induction effects of tovorafenib on CYP2B6 is considered inadequate because the bupropion PBPK model the applicant used to evaluate the induction effects of tovorafenib on CYP2B6 is not considered verified for predicting DDI with bupropion as a victim, and there is uncertainty about extrapolation of the in vitro induction parameters of CYP2B6. Detailed discussions are provided below.

1. (b) (4)

2.

3.

Induction Effects of Tovorafenib on CYP1A2

The PBPK analysis cannot rule out a potential induction effect of tovorafenib on CYP1A2 substrates for reasons discussed below.

The Applicant evaluated the induction effect of tovorafenib on CYP1A2 using caffeine as a probe substrate. There are limited data on the prediction of CYP1A2 induction using PBPK analysis and induction parameters generated from in vitro hepatocyte induction studies. The Applicant was requested to provide a qualification document to show the predictive performance of drug interactions of various CYP1A2 inducers with drugs that are predominantly metabolized by CYP1A2. The Applicant compared the predicted and observed C_{max} and AUC ratios in the CYP1A2-mediated DDI studies of caffeine, theophylline and tizanidine with rifampin and caffeine with omeprazole (v20-cyp1a2-induction-qualification-nov2023). The extent of induction of 5 out of 7 studies was predicted within the range of 0.8 -1.25-fold of the observed values. (b) (4) [redacted]. Therefore, interaction between tovorafenib and substrates of CYP1A2 cannot be ruled out.

Table 85. Comparison of Model Inputted and Experimentally Measured Induction Parameters of Competitive CYP1A2 Inducers

CYP1A2 Inducers	Model Parameters	In Vitro Parameters Based on mRNA	In Vitro/Model Parameters	In Vitro Data Source	Number of In Vitro Observations
Rifampin	(b) (4) [redacted]			PMID: 17639026 and 21930825	1
Omeprazole				PMID: 29802934; FDA Database	4

Source: response to FDA IR Clinical Pharmacology submitted 19 December 2023(seq0021) and references within the table

* (b) (4) [redacted] (PMID: 21930825);

†mean slope of the line with intercept (PMID: 21930825)

Abbreviations: (b) (4).

Induction Effects of Tovorafenib on CYP2C8

Tovorafenib potentially has weak to moderate induction effects on CYPC8 substrates following oral administration of tovorafenib 600 mg QW, but the effect cannot be confidently predicted for the reasons discussed below.

(b) (4)

(b) (4)

Table 86. CYP2C8 Induction Parameters of Rifampin and Tovorafenib Generated Using Cryopreserved Human Hepatocytes

Hepatocyte donors	Estimated from hepatocyte induction studies		Calibrated to Rifampin*	Induction Potency
	tovorafenib	rifampicin	tovorafenib	$(Ind_{max}-1)/IndC_{50}$
(b) (4)				(b) (4)
mean				
(b) (4)				
mean				

Source: dot1-dmpk-013.pdf and reviewer's analysis

* (b) (4)

Abbreviations: (b) (4)

Table 87. Simulated Effects of Tovorafenib on Repaglinide Following Tovorafenib 600 mg QW for 50 Days

CYP2C8 parameters	(b) (4)	Source
Mean from 3 donors without calibration to rifampin		Applicant's analysis
Mean of calibrated parameters from 3 donors		Reviewer's analysis
Calibrated parameters from 1 donor with highest potency		

Source: Table 2 in IR_update-to-response-to-fda-ir-2023-11-17.pdf and reviewer's analyses

Abbreviations: AUC, area under the concentration-time curve; Cmax, peak plasma concentration; (b) (4) ; QW, once weekly; R, ratio.

Table 88. Predicted and Observed Cmax and AUC Ratios of CYP2C8 Substrates Following Coadministration With 600 mg Rifampin

Study	Substrate	Inducer	Observed		Predicted		Predicted/Observed	
			C_{max} ratio	AUC ratio	C_{max} ratio	AUC ratio	C_{max} ratio	AUC ratio
1	Rosiglitazone (CYP2C8)	Rifampicin	0.73	0.46	(b) (4)			
2	Rosiglitazone (CYP2C8)*	Rifampicin	0.67	0.34				
3	Repaglinide (CYP2C8)	Rifampicin	0.59	0.43				
4	Repaglinide (CYP2C8)&	Rifampicin	0.74	0.68				
5	Repaglinide (CYP2C8)^	Rifampicin	0.21	0.20				
6	Repaglinide (CYP2C8)^	Rifampicin	0.83	0.52				

Predicted values show from simulated trials matching the clinical study design.
**Simulated with healthy volunteer population; & geometric mean; ^ median*

Source: Table 3 in V20_CYP2C8 induction qualification_updated-Jan2024

Abbreviations: AUC, area under the concentration-time curve; Cmax, peak plasma concentration.

Inhibitory Effects of Tovorafenib on CYP2C9 Substrate Tolbutamide

Tovorafenib is expected to have weak inhibitory effect on CYP2C9 substrates in adult and pediatric patients with cancer, but the predicted effects may be complicated by the potential induction effect of tovorafenib on CYP2C9. See detailed discussion below.

(b) (4)

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Table 89. Comparison of Predicted and Observed Interactions of CYP2C9 Substrates With CYP2C9 Inhibitors

Study	Substrates	Inhibitors	Observed		Predicted		Pred/Obs		References
			$C_{max}R$	AUCR	$C_{max}R$	AUCR	$C_{max}R$	AUCR	
1	Tolbutamide	Fluconazole	1.23	1.28					(b) (4) PubMed 2330488
2	Tolbutamide	Fluconazole	1.3	2.09					PubMed 2330488
3	Tolbutamide	Fluvoxamine	NA	1.29					PubMed 11180037
4	Tolbutamide	Fluvoxamine	NA	1.54					PubMed 11180037
5	Tolbutamide	Sulphaphenazole*	1.33	5.28					PubMed 2311340
6	S-Warfarin	Fluconazole	NA	1.35					PubMed 12867493
7	S-Warfarin	Fluconazole	NA	1.86					PubMed 12867493
8	S-Warfarin	Fluconazole	NA	2					PubMed 12867493
9	S-Warfarin	Fluconazole	NA	2.92					PubMed 8801057
10	S-Warfarin	Fluconazole	1.15	2.56					PubMed 20622200
11	Celecoxib	Fluconazole	1.6	2.3					PMID 10749518
12	Flurbiprofen	Fluconazole	1.23	1.81					PubMed 16413247
13	Flurbiprofen	Fluconazole	1.15	1.73					PubMed 22943633
14	Flurbiprofen	Fluconazole	1.47	1.97					PubMed 23047652
15	Flurbiprofen	Fluconazole*	1.37	2.80					PubMed 17054666
16	Phenytoin	Fluconazole	NA	1.33					PubMed 1633070
17	Phenytoin	Sulphaphenazole	NA	3.06					PubMed 284708
18	Tolbutamide	Ketoconazole*	NA	1.77					PubMed 8186066
19	S-Warfarin	Asciminib*	1.08	1.41					PubMed 35293131
20	S-Warfarin	Ceritinib*	1.05	1.54					PubMed 33394101
21	S-Warfarin	Venetoclax*	1.13	1.27					PubMed 27910036

Source: Table 1 in the report (CYP2c9-fda-v20-qualification.pdf) , (b) (4) DDI Database, and reviewer's analysis

* Simulations were performed by the reviewer according to clinical trial design of the clinical DDI studies and the Ki,u values of ketoconazole, and ceritinib were optimized and are shown in Table 8.

Abbreviations: obs, observed; pred, predicted; C_{max}, peak plasma concentration; AUC, area under the concentration-time curve; R, ratio; NA, not available.

The Applicant compared observed and simulated results of 15 clinical DDI studies involving 3 CYP2C9 inhibitors and 5 CYP2C9 substrates including tolbutamide (Table 88) to demonstrate that the CYP2C9 substrate files in Simcyp V20 could predict CYP2C9-mediated DDI. To examine the in vitro to in vivo extrapolation of CYP2C9 inhibition parameters, the reviewer requested the Applicant to summarize the CYP2C9 inhibition parameters of all the inhibitors used in the simulations, specify the sources of the inhibition parameters, and if a parameter is optimized, specify the clinical DDI studies used for the optimization. In addition, the reviewer also searched the (b) (4) DDI Database for lab-to-lab variability of in vitro K_i values of each competitive CYP2C9 inhibitor. The in vitro $K_{i,u}$ values generated in human liver microsomes using tolbutamide or other CYP2C9 probe substrates were compared to the in vivo or optimized K_i values used in the PBPK models of the inhibitors. Table 89 shows that the in vitro $K_{i,u}$ values were approximately (b) (4)-fold greater than those in the PBPK models of CYP2C9 inhibitors. In other words, the in vitro $K_{i,u}$ values of some inhibitors need to be reduced by up to (b) (4)-fold to reproduce the observed effects of these inhibitors on the exposure of CYP2C9 substrates. If only considering the in vitro data generated using tolbutamide as a substrate, the in vitro $K_{i,u}$ values of some inhibitors need to be reduced by up to (b) (4)-fold based on currently available data.

The $f_{u,mic}$ value of tovorafenib at 0.5 mg microsomal protein/mL was 0.387 measured in the in vitro reversible inhibition assay (report P024-11-1, PD09-25). Taking this nonspecific binding into account, tovorafenib is predicted to have no effect on tolbutamide PK by the Applicant. Reducing the in vitro CYP2C9 $K_{i,u}$ (9 μM=$IC50_{,u}$/2, assumed) of tovorafenib by 10-, and 20-fold, tovorafenib increased tolbutamide AUC by 1.25-fold (IR response submitted on 19 December, 2024), and 1.5-fold (reviewer's analysis) when tovorafenib 600 mg QW was co-administered with tolbutamide in adult patients with cancer. Of note, greater than 20% increase in CYP2C9 mRNA at 30-fold of the therapeutic tovorafenib concentration was observed in the hepatocyte induction study (DOT1-DMPK-008). Therefore, the predicted effects may be complicated by the potential induction effect of tovorafenib on CYP2C9, which was not considered in the simulations.

Table 90. Comparison of Model Inputted and Experimentally Measured Inhibition Parameter Ki Values of Competitive CYP2C9 Inhibitors

Inhibitors	Optimized Model Used $K_{i,u}$ (μM)	In Vitro $K_{i,u}$ (tolbutamide) [a] (μM)	In Vitro $K_{i,u}$ (all) [b] (μM)	In Vitro $K_{i,u}$/ Model Used $K_{i,u}$ (tolbutamide)	In Vitro $K_{i,u}$/ Model Used $K_{i,u}$ (all)
Fluconazole	(b) (4)	19.8	2.73-75.2		(b) (4)
Fluvoxamine		2.79	2.73-8.87		
Sulfaphenazole		0.12-0.67	0.06-0.67		
Ketoconazole		2.8	NA		
Asciminib		NA	0.407 [d]		
Ceritinib		NA	0.0701 [d]		
Venetoclax		NA	0.00195 [d]		

Source: Table 5 in FDA IR Clinical Pharmacology PBPK report Response Document submitted on 19 December 2023 (response-to-fda-ir-2023-11-17.pdf), (b) (4) DDI Database, and reviewer's analysis.

In vitro unbound K_i values ($K_{i,u}$) calculated based on K_i values from the (b) (4) DDI Database and free fraction of nonspecific binding in microsomes ($f_{u,mic}$) calculated based on the microsomal protein concentrations used in the studies and measured $f_{u,mic}$. If measured $f_{u,mic}$ is not available, Simcyp predicted values were used.

[a] K_i values were generated using tolbutamide as a CYP2C9 probe substrate.

[b] K_i values were generated using all CYP2C9 substrates in the Certara DDI Database including tolbutamide.

[c] (b) (4)

[d] The in vitro $K_{i,u}$ values were generated using diclofenac as a probe substrate. K_i, inhibition parameter.

Effects of Tovorafenib on OATP1B and BCRP Substrates Rosuvastatin and Pravastatin

The predicted effects of tovorafenib on rosuvastatin and pravastatin were inadequate for reasons detailed below. Drug interaction between tovorafenib and substrates of OATP1B and/or BCRP cannot be ruled out.

There are uncertainties about the translating the in vitro OATP1B or BCRP inhibition parameter (Ki or IC_{50}). An internal analysis conducted by the reviewer showed that drug interactions of pravastatin or rosuvastatin with inhibitors of OATP1B1/3 and/or BCRP were either not predicted or significantly under-predicted even when the lowest in vitro transporter inhibition parameters of these inhibitors in the UW DDI Database (last accessed in June 2020) and the pravastatin and rosuvastatin PBPK models of Simcyp V19, which are the same models as that in V20, were applied in the simulations. The observed interactions with rosuvastatin or pravastatin could only be reproduced, within 25% of clinical observations, when the K_i values of all transporters that are relevant to the disposition of pravastatin or rosuvastatin were simultaneously reduced 10- to 100-fold. (b) (4) Therefore, the inhibitory effect of tovorafenib on rosuvastatin may potentially be underpredicted.

It should be noted that strong and moderate CYP3A inducers (such as rifampin and efavirenz) could reduce the exposure of rosuvastatin and pravastatin though the exact mechanisms are

unclear (PMID: 32460379). Given the potential induction effect of tovorafenib on CYP3A, its potential to reduce the exposure of rosuvastatin and pravastatin cannot be ruled out. Taken together, the predicted effects of tovorafenib on rosuvastatin and pravastatin were considered inadequate due to the uncertainties about the translating the in vitro OATP1B or BCRP inhibition parameter and potential complex interaction with rosuvastatin and pravastatin with a potential CYP3A inducer. Drug interaction between tovorafenib and substrates of OATP1B and/or BCRP cannot be ruled out.

Effects of Tovorafenib on MATE1 Substrate Metformin

The ability of the metformin model to predict MATE1 inhibition has not been well verified because the in vitro to in vivo extrapolation of MATEs/OCTs inhibition parameter K_i value has not been established. Three inhibitors of MATEs cimetidine, pyrimethamine and trimethoprim were reported to increase metformin exposure, and data from clinical DDI studies of metformin with these inhibitors were used to verify the metformin model (Simcyp metformin summary report). Although the simulated effects of these inhibitors on metformin exposure were within (b) (4)-fold of the observed effects, the K_i value of MATEs in the cimetidine model was (b) (4)-fold lower than its IC_{50} values of MATE1 in the (b) (4) DDI database and (b) (4)-fold lower than its IC_{50} values of MATE-2K published in the database. For OCT2, the in vitro K_i values reported in the database were equal to or (b) (4)-fold lower than that in the cimetidine model, approximately (b) (4) fold lower than that in the pyrimethamine model, and (b) (4) fold higher than that in the trimethoprim model. It should be noted that, if metformin efficacy is of concern, evaluating metformin plasma exposure alone may be insufficient to inform the metformin dosing (PMID: 29761830). Overall, the PBPK analysis of tovorafenib interaction with metformin is considered inadequate.

19.4.4. Summary of Bioanalytical Method Validation and Performance

The FDA's Assessment

Plasma concentrations of tovorafenib were determined with method (Method #96-1116) at (b) (4) for studies FIREFLY-1, (b) (4) 20140, C28001, and C28002 (Table 90). Plasma concentrations of tovorafenib were determined with method (Method #8470257) at (b) (4) for study Day101-003 (Table 91).

Table 91. Summary of Bioanalytical Method Performance ((b) (4) 96-1116)

Method description	Tovorafenib (also referred to as BIIB024 or MLN2480 in the BMV report) in K2EDTA plasma was evaluated using LC-MS/MS. The method involved protein precipitation extraction of tovorafenib and its stable labeled internal standard (IS) ([^{13}C] [M+5] DAY101) from human plasma, followed by LC-MS/MS with positive ionization
Materials used for calibration curve & concentration	Tovorafenib (Lot#10-03870-S2 and 102019): 0.5, 1, 4, 10, 40, 100, 400, 1500, 3000, and 3500 ng/mL. Calibration standards were prepared in human plasma.
Validated assay range	Initially, was 0.5 to 3500 ng/mL. On 4/2022, changed to 3.0 to 3500 ng/mL.

Material used for QCs & concentration	Tovorafenib (Lot#10-03870-S2 and 102019): 0.5, 1.5, 40, 500, and 2800 ng/mL		
Minimum required dilutions (MRDs)	Not applicable		
Source & lot of reagents	Tovorafenib (i.e., BIIB024, MLN2480) (b) (4), Lot 10-03870-S2, expiration date 22 Apr 2012 Biogen IDEC MA Inc., Lot 102019, expiration date 31 Mar 2013 Internal standard: [^{13}C] [M+5] MLN2480 (b) (4), Lot 63651-1-19A, expiration date 19 Mar 2013		
Regression model & weighting	Linear, $1/x^2$ weighted		
Validation parameters	**Method validation summary**		**Acceptability**
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	10	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-3.2 to 4.3%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 11.3%	Yes
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs	-1.3 to 1.4%	Yes
	Inter-batch %CV	≤ 9.5%	Yes
	Percent total error (TE)	N/A	
Selectivity & matrix effect	Selectivity 6 lots tested; ≤20% LLOQ for analyte signal. ≤ 5% for IS signal. Spike-selectivity was tested at 0.5 ng/mL in 6 lots of human plasma; observed bias: -3.8%. Matrix effect Matrix effect was determined in human plasma at 3 concentrations (1, 60, and 3500 ng/mL, n=5) and results met acceptance criteria.		Yes
Interference & specificity	No significant interferences observed.		Yes
Hemolysis effect	Two concentrations (1.5 and 2800 ng/mL) of tovorafenib were prepared in 2% and 5% hemolyzed human plasma. Bias ranged from -3.9 to 4.8%.		Yes
Lipemic effect	Not determined		Yes
Dilution linearity & hook effect	10,000 ng/mL diluted 20-fold. Bias was -2.2%.		Yes
Bench-top/process stability	21 Hours at Room Temperature for plasma; 239 hours at 4°C for processed samples		Yes
Freeze-Thaw stability	4 Cycles at -20°C and -70°C		Yes
Long-term storage	420 days at -20°C and -70°C		Yes
Parallelism	Not applicable		Yes
Carry over	Overall ≤ 20% of LLOQ for analyte. The exception was in Run 14, in which injection carryover was 26.6% for tovorafenib.		Yes

Method performance in study FIREFLY-1 (3488-2001)		
Assay passing rate	13 out of 14 analytical runs were accepted. Incurred sample re-analysis passing rate: 96.6%	Yes
Standard curve performance	Original assay range (0.5 to 3500 ng/mL) • Cumulative bias range: -3.3 to 4% • Cumulative precision: ≤9.7% CV Adjusted assay range (3 to 3500 ng/mL) • Cumulative bias range: -2.7 to 5.7% • Cumulative precision: ≤6.1% CV	Yes
QC performance	Original assay range (0.5 to 3500 ng/mL) • Cumulative bias range: -0.7 to 6.4% • Cumulative precision: ≤14.3% CV Adjusted assay range (3 to 3500 ng/mL) • Cumulative bias range: -5.8 to -0.7% • Cumulative precision: ≤8.1% CV	Yes
Method reproducibility	Incurred sample reanalysis was performed in 9.8% (91/865) of samples, and 96.6% of the samples met the pre-specified criteria.	Yes
Study sample analysis/ stability	All samples were analyzed within 420 days at −20°C, which is within the established time frame for long-term stability.	Yes
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ: 0.5, 1, 4, 10, 40, 100, 400, 1500, 3000 and 3500 ng/mL, by 06 April 2022. 3, 6, 30, 120, 300, 1500, 3150 and 3500 ng/mL, after 06 April 2022.	
Method performance in study C28001 (96-1128A)		
Assay passing rate	36 out of 40 analytical runs were accepted. Incurred sample re-analysis passing rate: 95.9%	Yes
Standard curve performance	Cumulative bias range: -2.0 to 3.0% Cumulative precision: ≤ 9.1% CV	Yes
QC performance	Cumulative bias range: -2.5 to 3.3% Cumulative precision: ≤ 18.3% CV	Yes
Method reproducibility	Incurred sample re-analysis was performed in 10% for the initial 1000 samples and at least 5% of the remaining analyzed samples (148/1878).	Yes
Study sample analysis/ stability	With the exception of 5 plasma samples generated in C28001 study, samples were analyzed within 420 days at -20°C or -70°C.	Yes
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ: 0.5, 1, 4, 10, 40, 100, 400, 1500, 3000, and 3500 ng/mL	
Method performance in study C28002 (96-1420)		
Assay passing rate	12 out of 15 analytical runs were accepted. Incurred sample re-analysis passing rate: 93.3%	Yes
Standard curve performance	Cumulative bias range: -5.1 to 4.5% Cumulative precision: ≤ 12.6% CV	Yes
QC performance	Cumulative bias range: -3.2 to 1.1% Cumulative precision: ≤ 12.8% CV	Yes
Method reproducibility	Incurred sample re-analysis was performed in 10% of study samples (60/592).	Yes

Study sample analysis/ stability	With the exception of 6 plasma samples generated in C28002 study, samples were analyzed within 420 days at -20°C and -70°C	Yes
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ: 0.5, 1, 4, 10, 40, 100, 400, 1500, 3000, and 3500 ng/mL	
Method performance in study (b) (4) 205140 (3488-2101)		
Assay passing rate	7 out of 7 analytical runs were accepted. Incurred sample re-analysis passing rate: 100%	Yes
Standard curve performance	Cumulative bias range: -3.8 to 4.0% Cumulative precision: ≤ 5.6% CV	Yes
QC performance	Cumulative bias range: -2.0 to 3.6% Cumulative precision: ≤ 4.9% CV	Yes
Method reproducibility	Incurred sample re-analysis was performed in 19% of study samples (75/400).	Yes
Study sample analysis/ stability	All samples were analyzed within 420 days at -20°C and -70°C	Yes
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ: 0.5, 1, 4, 10, 40, 100, 400, 1500, 3000, and 3500 ng/mL	

Table 92. Summary of Bioanalytical Method Performance (8470257)

Method description	Tovorafenib (also referred to as BIIB024 or MLN2480 in the BMV report) in K2EDTA plasma was evaluated using LC-MS/MS. The method involved protein precipitation extraction of tovorafenib and its stable labeled internal standard (IS) ([^{13}C] [M+5] DAY101) from human plasma, followed by LC-MS/MS with positive ionization.		
Materials used for calibration curve & concentration	DAY101 (Lot#224538): 5, 10, 40, 150, 600, 2250, 4500, and 5000 ng/mL		
Validated assay range	5.00 to 5000 ng/mL		
Material used for QCs & concentration	DAY101 (Lot#224538): 5, 15, 200, 2500, and 4000 ng/mL		
Minimum required dilutions (MRDs)	Not applicable		
Source & lot of reagents	Tovorafenib (i.e., DAY101): (b) (4), Lot #224538, Retest date (b) (4) [^{13}C] [M+5] DAY101 (b) (4) PGS-110-24, Retest date (b) (4)		
Regression model & weighting	Linear, $1/x^2$ weighted		
Validation parameters	**Method validation summary**		**Acceptability**
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	8	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-4.4 to 4.7%	Yes

	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 7.6%	Yes
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs	-11.2 to 8.5%	Yes
	Inter-batch %CV	≤ 19.7%	Yes
	Percent total error (TE)	N/A	Yes
Selectivity & matrix effect	Total of 6 different lots tested. Observed bias from -5.4 to 15.2%.		Yes
Interference & specificity	No significant interferences observed. No interference with 40,000 ng/mL of Ibuprofen.		Yes
Hemolysis effect	Two concentrations (15 and 4000 ng/mL of tovorafenib) were prepared in plasma containing 2% lysed whole blood. Observed bias from -6.0 to 8.0%.		Yes
Lipemic effect	Two concentrations (15 and 4000 ng/mL of tovorafenib) were prepared in plasma with a natural high lipid content. Observed bias from -18.7 to 2.7%.		Yes
Dilution linearity & hook effect	80,000 ng/mL diluted 100-fold. Observed bias 0.1% to 7.8%.		Yes
Bench-top/process stability	42 hours at room temperature for plasma. 174 hours at 2 to 8°C for processed samples.		Yes
Freeze-Thaw stability	5 cycles at -10 to -30°C. 5 cycles at -60 to -80°C.		Yes
Long-term storage	50 days at -10 to -30°C. 143 days at -60 to -80°C.		Yes
Parallelism	Not applicable		Yes
Carry over	Overall ≤ 20% of LLOQ for analyte, except for Runs 5, 7, and 10. Carryover impacts were reviewed and no impact to the integrity of data generated.		Yes
Method performance in study DAY101-103 (8470254)			
Assay passing rate	4 out of 4 analytical runs in plasma were accepted. Incurred sample re-analysis passing rate: 100%		Yes
Standard curve performance	Cumulative bias range: -3.1 to 2.7%. Cumulative precision: ≤ 7.5% CV.		Yes
QC performance	Cumulative bias range: -2.4 to 2.0%. Cumulative precision: ≤ 7.7% CV		Yes
Method reproducibility	Incurred sample re-analysis was performed in 13% of study samples (24/180).		Yes
Study sample analysis/ stability	All study samples were analyzed within 143 days at -60 to -80°C.		Yes
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ: 5, 10, 40, 150, 600, 2250, 4500, and 5000 ng/mL		

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment

Refer to Section 8.2 for FDA's assessment of safety.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/	AUTHORED/ APPROV
Clinical Reviewer and Co-Cross Disciplinary Team Lead(CDTL)	Sonia Singh, M.D.	CDER/OOD/DO2	Sections: All	**Select one:** _X_ Authored _X_ Approved
	Signature: Sonia Singh -S Digitally signed by Sonia Singh -S Date: 2024.04.22 12:57:42 -04'00'			
Clinical Team Lead/Co-CDTL	Diana Bradford, M.D.	CDER/OOD/DO2	Sections: All	**Select one:** __X_ Authored __X_ Approved
	Signature: See Cross-Disciplinary Team Lead			
Statistical Reviewer	Somak Chatterjee, Ph.D.	CDER/OTS/DBV	Sections: 8	**Select one:** _X_ Authored _____ Approved
	Signature: Somak Chatterjee -S Digitally signed by Somak Chatterjee -S Date: 2024.04.22 09:48:02 -04'00'			
Statistical Team Lead	Xiaoxue Li, Ph.D.	CDER/OTS/DBV	Sections: 8	**Select one:** _X_ Authored _X_ Approved
	Signature: Xiaoxue Li -S Digitally signed by Xiaoxue Li -S Date: 2024.04.22 10:02:25 -04'00'			
Division Director (OB/DBV)	Shenghi Tang, Ph.D.	CDER/OTS/DBV	Sections: 8	**Select one:** ___ Authored _X__ Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S Date: 2024.04.22 10:07:11 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHO	AUTHORED/ APPROVE
Nonclinical Reviewer	Stephanie L. Aungst, Ph.D.	CDER/OND/OOD/DHOT	Sections: 5	**Select one:** _X__Authored _X__ Approved
	Signature: Stephanie L. Aungst -S Digitally signed by Stephanie L. Aungst -S Date: 2024.04.22 08:42:26 -04'00'			
Nonclinical Reviewer	Amy Skinner, Ph.D.	CDER/OND/OOD/DHOT	Sections: 5	**Select one:** _X__Authored _X__ Approved
	Signature: Amy M. Skinner -S Digitally signed by Amy M. Skinner -S Date: 2024.04.22 08:46:04 -04'00'			
Nonclinical Supervisor	Claudia P. Miller, Ph.D.	CDER/OND/OOD/DHOT	Sections: 5	**Select one:** _X_Authored _X_Approved
	Signature: Claudia Miller -S Digitally signed by Claudia Miller -S Date: 2024.04.22 09:03:19 -04'00'			
Nonclinical Division Director (Acting)	Haleh Saber, Ph.D.	CDER/OND/OOD/DHOT	Sections: 5	**Select one:** ___Authored _X__ Approved
	Signature: Haleh Saber -S Digitally signed by Haleh Saber -S Date: 2024.04.22 09:09:44 -04'00'			
Clinical Pharmacology Reviewer	Sarah Kim, Pharm.D., Ph.D.	CDER/OTS/OCP/DCPII	Sections: 6, 19.4.4	**Select one:** X___ Authored X Approve
	Signature: Sarah Kim -S Digitally signed by Sarah Kim -S Date: 2024.04.22 10:14:44 -04'00'			
Pharmacometrics Reviewer	Ye Xiong, Ph.D.,	CDER/OTS/OCP/DPM	Sections: 6, 19.4.1, 19.4.2	**Select one:** _X_Authored ___Approved
	Signature: Ye Xiong -S Digitally signed by Ye Xiong -S Date: 2024.04.22 10:18:11 -04'00'			

Pharmacometrics Team Lead	Youwei Bi, Ph.D.,	CDER/OTS/OCP/ DPM	Sections: 6, 19.4.1, 19.4.2	**Select one:** _X_ Authored _X_ Approved
	Signature: Youwei Bi -S Digitally signed by Youwei Bi -S Date: 2024.04.22 10:23:27 -04'00'			
PBPK Modeling Reviewer	Ying-Hong Wang, Ph.D	CDER/OTS/OCP/ DPM	Sections: 19.4.3	**Select one:** _X___ Authored ___Approved
	Signature: Ying-hong Wang -S Digitally signed by Ying-hong Wang -S Date: 2024.04.22 11:35:27 -04'00'			
PBPK Modeling Team Lead	Yuching Yang, Ph.D.	CDER/OTS/OCP/ DPM	Sections: 19.4.3	**Select one:** ___ Authored _X_ Approved
	Signature: Yuching Yang -S Digitally signed by Yuching Yang -S Date: 2024.04.22 11:41:28 -04'00'			
Genomics Reviewer	Jielin Sun, Ph.D.	CDER/OTS/OCP/ DTPM	Sections: 6	**Select one:** __X___ Authored __Approved
	Signature: Jielin Sun -S Digitally signed by Jielin Sun -S Date: 2024.04.22 11:48:22 -04'00'			
Genomics Team Lead	Jeffrey Kraft, Ph.D.	CDER/OTS/OCP/ DTPM	Sections: 6	**Select one:** __X___ Authored _X_ Approved
	Signature: Jeffrey B. Kraft Jr -S Digitally signed by Jeffrey B. Kraft Jr -S Date: 2024.04.22 12:21:21 -04'00'			
Master Pharmacokineticist	Jeanne Fourie Zirkelbach, Ph.D.	CDER/OTS/OCP/ DCPII	Sections: 6, 19.4	**Select one:** x Authored xApproved

	Signature: Jeanne Fourie Zirkelbach -S Digitally signed by Jeanne Fourie Zirkelbach -S Date: 2024.04.22 12:14:44 -04'00'			
Clinical Pharmacology Deputy Division Director	Stacy Shord, Pharm.D.	CDER/OTS/OCP/ DCP II	Sections: 6, 19.4	**Select one:** ___ Authored _x_Approved
	Signature: Stacy Shord -S Digitally signed by Stacy Shord -S Date: 2024.04.22 12:26:14 -04'00'			
Associate Director for Labeling (ADL)	Barbara Scepura, M.S.N., C.R.N.P.	CDER/OND/OOD/ DOII	Sections: 11	**Select one:** _ x_Authored ___ Approved
	Signature: Barbara A. Scepura -S Digitally signed by Barbara A. Scepura -S Date: 2024.04.22 12:52:58 -04'00'			
Cross-Disciplinary Team Lead (CDTL)	Diana Bradford, M.D.	CDER/OOD/DO2	Sections: All	Select one: __X__Authored __X__Approved
	Signature: See Signature Page			
Deputy Division Director (Signatory)	Nicole Drezner, M.D.	CDER/OOD/DO2	Sections: All	**Select one:** ___ Authored __x_Approved
	Signature: See Signature Page			

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/

DIANA L BRADFORD
04/23/2024 11:59:49 AM

NICOLE L DREZNER
04/23/2024 12:01:32 PM

MARTHA B DONOGHUE
04/23/2024 12:13:02 PM